American Association of Neuropathologists

2025 101st AANP Annual Meeting Abstract Book

Overview: Scientific Sessions
Friday June 20, 2025 &
Saturday June 21, 2025

All abstracts of the papers presented in this program are published in the June 2025 issue of the *Journal of Neuropathology and Experimental Neurology*.

FRIDAY PLATFORMS 1 & 2

	Platform Session 1: *Tumors: Glial 1* Great Lakes Ballroom B/C	Platform Session 2: *Neurodegenerative: Alzheimer* Great Lakes A1-A3
8:00 am - 8:15 am	**1** **Persistent Proliferative Progenitor Cell States and CDK4/6 Expression in Treatment-Resistant H3 G34-Mutant Diffuse Hemispheric Glioma** J Chiang, Q Zhang, X Li	**9** **PSEN1-mutant Early Onset Alzheimer Disease – The Northwestern Brain Brank Cases** H Smith, M Mejia-Bautista, P Jamshidi, J Ahrendsen, L Jennings, R Castellani
8:15 am- 8:30 am	**2** **Unraveling the miRNA-EMT-Stemness Interplay in Fusion-Positive Supratentorial Ependymomas: Identifying Therapeutic Vulnerabilities"** A Sharma, S Chauhan, R Kulshrestha, A Kumar, R Malik, M Sharma, V Suri	**10** **Identification of SERPINA3High Astrocytes subtypes as a potential modulator of amyloid pathology in Alzheimer's disease** M Taga, D Bennett, L Duquesne, B Karaahmet, H Klein, A Kroshilina, A Sigalov, C Yung, Y Zhang
8:30 am- 8:45 am	**3** **Methylation Profiling Limitations for High Grade Brain Tumors** M Milani, C Chen, L Chen	**11** **Characterization of the ischemic penumbra using MRI and 3D histology: Proof-of-principle case analysis** R Nanjappa, A Ayyappan, R Verma, J Jayakumar, K Ram, R Rangaswami, M Sen, R James, A Manesh, G Varghese, D Nauen, R Folkerth, M Sivaprakasam
8:45 am- 9:00 am	**4** **Isolated activation of the PI3K/AKT pathway characterizes a novel group of indolent diffuse gliomas in adults** D Meredith, R Masi	**12** **Spatial proteomic and plasma biomarker analyses in mixed pathology cases**. J Walker, A Ehrenberg, E Daoud, P Shang, C De Sanctis, V Flores Almazan, K Laborc, E Thorn, S McQuillan, L Chiu, Q Hossain, J Parker-Garza, M Gonzales, C White, T Richardson, T Kautz
9:00 am- 9:15 am	**5** **Clinically applicable deep learning model for robust classification of central nervous system tumors from histopathology images** C Dampier, H Lalchungnunga, D Hoang, E Shulman, Z Abdullaev, B Li, Z Luo, O Singh, Z Wu, T Pearce, C Horbinski, C Lucas, P Cimino, M Nasrallah, M Quezado, H Chung, S Brandner, E Ruppin, K Aldape	**13** **Idiotypic-susceptible: a clinically relevant, neurofibrillary tangle subtype of Alzheimer's disease**. J Robinson, H Cai, D Irwin, E Lee, N Loh, D Ohm, J Phillips
9:15 am- 9:30 am	**6** **Molecular features of primary gliosarcoma with evidence for a distinct transcriptomic profile in mesenchymal components** M Wood, G Zangirolani, J Lee, T Neff, C Beadling, C Corless	**14** **Uncovering cell-type specific miRNAs in Alzheimer's Disease brains to refine plasma miRNAs candidate AD biomarkers** G Kureli, N Umesh Ganesh, U Coşkun, Y Lee, S Burkhardt, A Schütz, D Krüger, S Liu, T Park, R Pradhan, F Sananbenesi, Y Huang, S Risacher, Y Wan, L Shaw, A Krunic, T Mellott, J Blusztajn, A Saykin, K Nho, A DeStefano, H Lin, Q Yang, T Pena-Centeno, A Fischer, I Delalle
9:30 am- 9:45 am	**7** **Translation control in neuron-cancer cross talk drives glioblastoma progression** E Guney, A Dabrowska, N Magee, R Phua, L Wang, D Baker, K Lee, C Cadwell, C Escoubas, D Ruggero, W Weiss	**15** **Neurons accumulate disease-specific somatic deletion mutations across tau pathologic states in Alzheimer's disease** M Miller, B Jin, K Brown, D Smirnov, S Naik, S Kirkham, E Hennessey, M Frosch, D Oakley, B Hyman, A Huang
9:45 am- 10:00 am	**8** **Infiltrative margin biology in high-grade gliomas defined through spatial multi-omics** N Tsankova, B Pai, S Ramos, W Cheng, E Ozen, T Silva-Hurtado, L Kulumani Mahadevan, R Yong, E Zaslavsky	**16** **Histological and single cell analysis of human iPSC-derived APPV717I neurons after long-term engraftment in the mouse brain** G Hargus, P Gaur, J McInvale, C Ayers, R Kang, P Upadhyayula, A Sproul, P deJager, P Canoll, V Menon

FRIDAY PLATFORMS 3 & 4

	Platform Session 3: *Tumors: Glial 2* Great Lakes Ballroom B/C	Platform Session 4: *Neurodegenerative: Alzheimer, other* Great Lakes A1-A3
1:30 pm - 1:45 pm	**17** **The clinical value of histopathological and molecular metrics in pediatric ependymoma - data from the ACNS0831 trial** D Ellison, A Onar-Thomas, J Dalton, S Lensing, R Tatevossian, N Chambwe, P Blackburn, N Foreman, A Smith	**25** **Harnessing Spatially Distinct Microglial Subpopulations as a Novel Approach to Alzheimer's Disease Treatment.** A Ardura-Fabregat
1:45 pm- 2:00 pm	**18** **Mapping the transcriptional landscape of glioblastoma in spatial context at single cell resolution** C Mount, D Gerovasilis, A Greenwald, S Kovatsis, J Lu, M Suva, I Tirosh, Z Wen	**26** **Machine Learning Quantification of Amyloid-β Deposits in Frontal, Temporal, and Parietal Cortices in a Diverse Cohort with Alzheimer Disease** D Garcia, S Rai Sharma, N Saito, L Beckett, C DeCarli, D Gutman, J Vizcarra, D Coughlin, A Teich, L Garcia, D Mungas, C Chuah, B Dugger
2:00 pm- 2:15 pm	**19** **Observation of SOX2 expressing tumor cells invading within the corpus callosum at autopsy in glioblastoma patients** A Winiarz, S Bobholz, A Lowman, S Duenweg, B Nath, B Chao, F Kyereme, M Mirzaei, D Kim, J Connelly, E Cochran, J Jacobsohn, E Mrachek, P LaViolette	**27** **Factors underlying rapid progression and resilience in patients with high-level Alzheimer disease neuropathologic change** T Richardson, F Almeida, S Rohde, L Canbeldek, S Hiya, C Maldonado-Diaz, J Samanamud, K Clare, C Slocum, L Kulumani Mahadevan, L Chiu, K Farrell, J Crary, E Daoud, C White, III, M Gonzales, T Oliveira [2], J Walker
2:15 pm- 2:30 pm	**20** **Loss of Rb immunoreactivity correlates with RB1 mutation status across central nervous system neoplasms** S Rajan, K Pham, C Dampier, T Zaikos, C Eberhart, D Nauen, M Morris, C Ho, R Xian, J Dudley, C Gocke, J Eshleman, M Lin, Y Zou, D Kamson, D Mukherjee, V Croog, C Bettegowda, M Holdoff, S Sahebjam, J Rincon-Torroella, M Sherief, K Schreck, C Lucas	**28** **Factors influencing the spread of early tau pathology in the brain** R Rodriguez Reyes, M Morris, H Guo
2:30 pm- 2:45 pm	**21** **MTAP Outperforms p16 as Surrogate Marker for CDKN2A Status in IDH-mutant Astrocytomas** R Multz, M Sukhanova, M Mejia Bautista, H Smith, P Jamshidi, C Horbinksi, J Ahrendsen	**29** **Relationship between histologic neuropathology and RT-QuIC seeding in neurodegenerative and normal brain** A Hiniker, D Browne, I Peng, H Zamore, D Smirnov, C Shin, D Coughlin, M Avina, D Pizzo, A Unapanta, A Kraus
2:45 pm- 3:00 pm	**22** **Histopathological and Molecular Heterogeneity of Novel Adult High-Grade IDH-wildtype Glioma Subgroups (HGG_B, HGG_E, and HGG_F)** Y Wang, J Serrano, C Schroff, M Snuderl	**30** **Spatial Transcriptomic Insights into Neurodegeneration: pTDP-43, Synuclein Gamma, and Immune Modulation** A Gonzalez, S Kazempour Dehkordi, C Corbett, K Clarke, M Dopler, B Danner, S Babu, J Parker-Garza, A Ghaseminejad-Bandpey, M Keating, M Alhneif, K Bieniek, S Seshadri, S Etemadmoghadam, H Zare, M Flanagan
3:00 pm- 3:15 pm	**23** **Second-line treatment duration associated with remote SOX2 positivity in glioblastoma pateints at autopsy** S Bobholz, A Winiarz, B Chao, A Lowman, D Kim, M Mizraei, B Nath, S Duenweg, M Barrett, F Kyereme, J Connelly, K Mrachek, J Jacobsohn, E Cochran, M Krucoff, P LaViolette	**31** **Determining the spatiotemporal pattern of T cell infiltrates during the course of Alzheimer's Disease** Y Cheng, M Taga, V Marshe, Y Zhang, W Cao, S Engel, M Fujita, T Lama, P De Jager
3:15 pm- 3:30 pm	**24** **Two cases of Glioneuronal Tumor Kinase-Fused (GNT_KinF_A) from a Single-Center Experience** E Pai, A Viaene, M Li, M Nasrallah, M Santi	**32** **Chronic Traumatic Encephalopathy Neuropathologic Change in Military Personnel: Continued Assessment from the DoD/USU Brain Tissue Repository** D Priemer, S Abdallah, P Smith, D Perl

FRIDAY POSTERS #1-#20

Friday June 20, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 4:30 pm	**1**	**Combinatorial targeting of avapritinib-driven MAPK activation in high-grade glioma** K Schwark, S Kong, M Miclea, T Patel, A Stanczak, B Lau, R Cartaxo, D Messinger, R Doherty, S Ji, J Wadden, M Clausen, F Momen, T Adam, K Wink, A Hutchinson, M Niculcea, H Serhan, N Merrill, L Mayr, S Neyazi, D Muñoz, N Nuechterlein, E Fernandez, J Pavisic, D Klawinski, S Merajver, A Beck, M Filbin, J Coppé, C Koschmann
	2	**Clinical relevance of EGFR amplification in IDH-mutant astrocytoma** C Slocum, P Nguyen, M Vij, D Hambardzumyan, J Walker, M Umphlett, N Tsankova, T Richardson
	3	**Improving glioblastoma survival by combining YAP-TEAD inhibitors with surgical resection in preclinical xenograft models** T Silva Hurtado, B Pai, R Yong, T Tang, N Tsankova
	4	**High-Grade Astrocytoma with Piloid Features is a Histologically and Molecularly Heterogenous Group With Poor Survival** S Belakhoua, J Wu, E Freitag, C Schroff, N Dhasmana, J Serrano, V Vasudevaraja, M Snuderl
	5	**High-Throughput Screening Reveals K784-6195 as a Selective Therapeutic Candidate for NF1-Associated High-Grade Gliomas with ATRX Deficiency** F Rodriguez, S Dubey, S Rai, S Aung, F Guillen, M Yuan, C Eberhart
	6	**Assessing Nectin and Nestin Expression in Adult and Pediatric Diffuse Midline Gliomas: A Step Toward HSV-Based Oncolytic Viral Immunotherapy** A Santos, F Repetto, S Alexandrescu, I Solomon
	7	**Cellular Deconvolution of the Tumor Microenvironment in Pleomorphic Xanthoastrocytoma** G Pinto, V Zschernack, V Dreschmann, T Goschzik, E Dörner, M Toma, T Pietsch
	8	**Pediatric H3 G34-Mutant Diffuse Hemispheric Glioma: Unique Biology and Clinical Behavior** J Chiang, D Tlais, Q Zhang, J Roach, C Tinkle, T Lin, X Li, A Mostafa, D Moreira, R McNall-Knapp, S Rush, B Le, S Sinno, A Agarwal, K Ginn, R Green, S Partap, A Onar-Thomas, L Furtado, A Bag
	9	**Integrative Molecular Analysis for Enhanced Ependymoma Classification** M Sharma, R Malik, A Sharma, V Suri
	10	**Unveiling the Spread: Molecularly Defined Oligodendroglioma with Osseous Metastases** E Pai, Y Matsumoto, D Dou, S Nelluri, P Devi, S Priori, N Amankulor, M Alonso-Basanta, O Singh, Z Abdullaev, K Aldape, A Desai, S Mohan, M Nasrallah
	11	**Methylation Profiling Limitations for High Grade Brain Tumors** M Milani, C Chen, L Chen
	12	**Pituicytomas with unusually high-grade features: a series of two cases** R Landvater, E Pinarbasi, N Becker, S Stone, P Jamshidi, K Conway
	13	**S.T.A.G.: Spatial Transcriptomics on Angiocentric Gliomas** M Bui, A Dunnon, S Guzman, A Toland
	14	**Posterior fossa high grade glioma with MYB::QKI fusion** M Ospina-Romero, S Powell, M Gubbiotti
	15	**High-grade astrocytoma with pleomorphic and pseudopapillary features (HPAP) – expanding the clinicopathologic spectrum of an emerging entity** H Smith, D Meredith, K Conway, S Venneti, R Castellani, P Jamshidi, X Lu, M Sukhanova, B Nezami, L Jennings, D Duckett, L Santana-Santos, J Ahrendsen
	16	**Evaluating SOX2 Immunohistochemistry for Tumor Specificity in Gliomas** D Kim, S Bobholz, M Mirzaei, B Nath, S Duenweg, A Lowman, B Chao, A Winiarz, M Barrett, F Kyereme, J Connelly, E Cochran, J Jacobsohn, E Mrachek, M Krucoff, P LaViolette
	17	**Perivascular Invasion in Glioma: Characterization and Treatment Associations Using SOX2 Immunohistochemistry** D Kim, S Bobholz, B Nath, A Lowman, S Duenweg, B Chao, A Winiarz, M Mirzaei, M Barrett, F Kyereme, J Connelly, E Cochran, J Jacobsohn, E Mrachek, M Krucoff, P LaViolette
	18	**DNA Methylation Profiling of Adult High-Grade Gliomas** A Gilani , A Denney
	19	**Next generation sequencing and methylation profiling of a composite pleomorphic xanthoastrocytoma-ganglioglioma** M Ospina-Romero A Haws, L Prasannan, M Lee, M Quezado, K Aldape, D Lopez-Terrada, J Gastier-Foster, A Roy, K Fisher, C Mohila
	20	**A Rare Case of Spinal Metastasis in an Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted** A Aksionau , A Felpel , M Abedalthagafi

Posters are not offered for CME credit

FRIDAY POSTERS #21-#40

Friday June 20, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 4:30 pm	**21**	**Dysembryoplastic neuroepithelial tumor with malignant transformation following radiation** Y Zhu, C Ida, C Zepeda-Mendoza, A Vizcaino Villalobos, R Vaubel, A Raghunathan, J Schwartz, K Miller, C Giannini
	22	**Spectrum of Paediatric Diffuse High-Grade Gliomas** G Chacko, E Kurien, R Jeyachandran, R Pai, R John, K Prabhu, R Moorthy , V Joseph, S B
	23	**Still multiforme: transdifferentiation in molecularly characterized glioblastoma** K Pham, C Dampier, S Rajan, M Holdhoff, S Sahebjam, Y Comair, J Weingart, C Bettegowda, J Dudley, M Lin, J Eshleman, C Ho, M Morris, C Eberhart, C Lucas
	24	**Low-grade Oligodendroglioma With Sarcomatous Transformation While On A Novel IDH Inhibitor.** L Evans, V Venur, S Emerson, K Galbraith
	25	**Sporadic Subependymal Giant Cell Astrocytomas: An Institutional Review of 5 Cases** R Revia, S Guzman, A Toland
	26	**Glial neoplasm with myogenic differentiation and BRAF V600E mutation: a novel entity?** M Elnagdy, C Cai, E Daoud, K Hatanpaa
	27	**Rare Intronic BRAF Gene Fusion in a Recurrent Parietal Pleomorphic Xanthoastrocytoma: A Case Report** D Mansour, L Chen, P Singh
	28	**Ganglioglioma with KCTD8-NTRK2 Chromosomal Rearrangement** A Krbanjevic, B Mobley, P Paueksakon
	29	**Ultra-hypermutant Astrocytoma with IDH1 Mutation and Epigenetic Features of High-grade Astrocytoma with Piloid Features (HGAP) – A Case Report** H Smith, M Mejia-Bautista, E Adams, J Ahrendsen, D Duckett, B Nezami, L Santana-Santos, M Sukhanova, L Jennings, C Horbinski, D Brat, R Castellani, K Conway, P Jamshidi
	30	**Novel ZFTA fusion partner in supratentorial ependymoma arising in the midbrain and basal ganglia** s ahuja, M Edelman, M Atlas, S Rodgers, A Johnson
	31	**Ependymoma-like Tumor with Mesenchymal Differentiation (ELTMD) with ZFTA fusion: a Case Report and Literature Review** D Lombardo, A Tannenbaum, M Gurney, J Helgager, K Han
	32	**Rare posterior fossa high-grade astrocytoma with unique dot-like H3k27me3 attenuation and varied histopathologic features** M Milani, C Chen, R Lall, E Neil, G Fitzpatrick
	33	**Novel case of ependymoma with clear cell features and IDH2 mutation in a patient with Maffucci syndrome** D BeDell, C Ozutemiz, A Venteicher, G Fitzpatrick
	34	**Diagnostic challenges and longitudinal genomic analysis of a highly recurrent MN1:BEND2 fusion tumor lacking classical astroblastoma features** A Huttner, M Aboian, T Klug
	35	**Identification of MYO5A::NTRK3 Gene Fusion in a Recurrent IDH1 R132G-Mutant Astrocytoma: Implications for Targeted Therapy** A Aksionau, S Neill, M Abedalthagafi
	36	**Histological and Immunohistochemical Assessment of Cellular Heterogeneity in Pediatric Ependymomas** M Alturkustani
	37	**The need of integrated diagnosis in spinal ependymomas. A report of 2 cases** P Loreto Palacio, A Blitz, M Cohen, M Couce, T Hodges
	38	**Histologic and molecular characterization of a MAZ::NCOA2 fusion-positive intracranial glial neoplasm** E Stalter, O Lopes Abath Neto, C Voyles
	39	**Insulinoma-Associated Protein 1 as a Marker for Glioblastoma with Primitive Neuronal Component** G Wakeman, J DeWitt
	40	**SLC44A1::PRKCA fusion in tumor lacking papillary glioneuronal tumor morphology** V Huynh, A Raghunathan, J Hardcastle, S Smoley, M Isaacson, M Gandham, S Dasari, Z Abdullaev, K Aldape, M Quezado, D Pratt, P Cimino, C Ida

Posters are not offered for CME credit

FRIDAY POSTERS #41-#60

Friday June 20, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 4:30 pm	**41**	**Glioblastoma Whole Mount Tissue Immunohistochemical Staining of SOX2 and Ki67, Alignment, and Analysis** B Chao, S Duenweg, S Bobholz, M Barrett, A Winiarz, B Nath, A Lowman, F Kyreme, J Connelly, M Krucoff, P LaViolette
	42	**An Institutional Experience with the DNA Methylation Class High Grade Glioma with Pleomorphic and Pseudopapillary Features** R Alfattal, S Weathers, P Dasgupta, L Ballester, M Gubbiotti
	43	**Glioblastomas with composite primitive neuronal and sarcomatous components** M Chung, K Aldape, Y Comair, C Dampier, C Eberhart, M Holdhoff, S Lin, C Lucas, B Ozer, M Quezado
	44	**High-Grade Glioma with Pleomorphic and Pseudopapillary Features (HPAP): A Case Report on a Rare Entity** A Nobee, J Dailey, J Donahue
	45	**Pediatric Diffuse Midline Glioma with ACVR1 mutation and subsequent EZHIP overexpression** E Smith, D Ellison, K Jones
	46	**Metastatic Melanoma Involving a Glioblastoma: a Potentially Tricky Diagnosis Confirmed with Individual Genotypic Profiles** S Cain, J Crow, M Haeri, S Hyter, W Zhang, N Lakis
	47	**Circumscribed astrocytoma with VGLL-fused: A Case Report** Z Piao, A Mhoyan, S Kirschbaum, P Kim, R Guzman-Marin, R Green, F Torres, P Gabikian, V Chhabra, D Wang, Y Mao, M Ghassemi
	48	**Neuropathology of NCI, MCI, clinical Alzheimer's dementia, and cognitive decline in community-dwelling elders who die as centenarians** P Mojdeganlou, S Agrawal, D Bennett, J Schneider, L Yu
	49	**Common Neuropathological changes from Hispanics and Non-Hispanics enrolled in multiple Alzheimer's Disease Research Centers** G Serrano, S Aslam, J Walker, C Borja, I Lorenzini, M Mariner, T Beach
	50	**Spatially Mapping Insulin/PI3K/AKT/mTOR Dysregulations in Down Syndrome with Alzheimer's Disease Human Hippocampi** A Wohlfert, K Jones, S Guzman, A Granholm
	51	**Understanding the role of TDP-43 in Alzheimer's disease via cellular characterization** G Uruk, R Gatto, K Joseph, R Reichard, J Whitwell
	52	**The interaction of depression and Alzheimer's disease** S Hiya, L Canbeldek, S Qin, J Walker, T Richardson
	53	**Investigation of human amyloid pathology with perimortem stable isotope labeling** K Roberts, S Koutarapu, J Ge, M Dulewicz, C Guillermier, G Strout, J Hou, S Mukherjee, A Upadhyay, J Savas, R Bateman, J Hanrieder, K Schwetye
	54	**Association of CNS Corpora Amylacea with Aging and Alzheimer's disease pathology** A Tuzzolo, J Vaillareal, E Medina-Parrilla, T Bathe, A de la Rosa, R Sharma, J Phillips, S Prokop
	55	**Alzheimer's Disease Pathology in patients with Down Syndrome: Insights from 19 Adult Cases** M Mejia-Bautista, H Smith, P Jamshidi, J Ahrendsen, R Castellani
	56	**Leveraging machine learning and digital pathology to understand microglial activation in atypical Alzheimer's disease** S Dunlop, M Rutledge, B Boon, A Wood, D Rothberg, I Velez Uribe, J Gondrez, R Duara, N Graff-Radford, D Dickson, G Day, M Murray
	57	**Biochemical characterization of Aβ extracted from vascular and parenchymal plaques using mass spectrometry** S Koutarapu, K Roberts, R Coyle, J Mehla, C Sato, G Zipfel, R Bateman, K Schwetye, S Mukherjee
	58	**Evaluating Pre-Trained Deep Learning Models for Detection of Alzheimer's Disease in Histopathological Images: A Retrospective Study** F Vaibhav, A Duhan, S Shahi, V Kaliraman
	59	**Insights into the Anatomical Vulnerability Associated with the PSEN1 L381F Mutation** M Majeed, H Garringer, K Newell, R Vidal, M Jacobsen, J Bonnin, J Mokry, P Moretti, B Ghetti
	60	**Hippocampal CA1: Early Site of Tau Tangles Associated with Amyloid Aggregates in a Young Population** R Rodriguez Reyes, M Morris, L Gomez-Isaza, M Luongo

Posters are not offered for CME credit

FRIDAY POSTERS #61-#80

Friday June 20, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 4:30 pm	**61**	**Multiple neuropathologies underly hippocampal atrophy and hypometabolism in a case with a slowly progressive amnestic syndrome** H Youssef, R Gatto, N Pham, D Jones, R Petersen, M Machulda, J Whitwell, K Josephs
	62	**Postmortem Evaluation of Mineralized Blood Vessels in Hispanic and Non-Hispanic White Decedents with Alzheimer Disease** S Tamizharasu, D Garcia, N Saito, M Luu, L Beckett, L Honig, C DeCarli, R Rissman, A Teich, D Mungas, L Jin, B Dugger
	63	**Alzheimer's disease Brain Banking at Mayo Clinic in Florida** D Dickson, M Murray
	64	**Mapping Cell Type and Transcriptomic changes associated with TDP-43 Pathology in LATE-NC and FTLD-TDP** E Pinarbasi, R Sudharshan, A Rao, S Barmada
	65	**Evaluation of LATE-NC based on pTDP-43 immunoreacitive structure density** A Arakawa, A Uchino, M Hara, T Matsubara, S Murayama, Y Saito
	66	**GFAP+ astrogliosis in the striatum of Huntington's disease mice is spatially related to secondary motor cortex axonal bundles** T Brown, E Reid, J VanTreeck, M Thayer, R Gomez-Pastor
	67	**Neurodegenerative Disorders Among Older Community-Dwelling Subjects Who Die by Suicide: A Comparative Study Against Natural Deaths** M Elnagdy, E DAOUD, C WHITE, J RAISANEN, D BURNS, B EVERS, J BERNARD, T DANIELSEN, C HAUCH
	68	**Comorbid Chronic Traumatic Encephalopathy and Progressive Supranuclear Palsy** D Kirsch, B Abdolmohammadi, M Alosco, V Alvarez, J Cherry, J Crary, A McKee, J Mez, R Nicks, T Stein
	69	**Neuropathology in the LifeAfter90 Study: 2025 update on an Ethnically Diverse Cohort Study of Oldest-Old** B Dugger, V Patel, L Jin, M Luu, M Martinez Pamatz, C DeCarli, P Gilsanz, D Mungas, C Kawas, M Corrada, R Whitmer
	70	**Comprehensive Mapping of Hypoxia/Ischemia-Associated β-Amyloid Deposition Patterns in the Human Central Nervous System** E Karlovich, C Rhodes, D Premier, D Perl, K Tanji, J Goldman
	71	**A Rare Case of Neurodegeneration with Brain Iron Accumulation and Genetic Characterization** L GOMEZ-ISAZA, J Redding-Ochoa, S Scholz, A Ray, J Troncoso
	72	**AI-based prediction of neuropathologic diagnoses from macroscopic findings** S Koga, D Ono, D Dickson
	73	**Development of a Human Brain Matrix through Advanced Digital Fabrication and 3D Scanning** M Dastmalchi, A Goli, M Haeri
	74	**The Interplay Between Cerebrovascular Disease, TMEM106B, and TDP-43 Pathology** M Dopler, C Corbett, A Gonzalez, A Ghaseminejad-Bandpey, S Etemadmoghadam, M Keating, M Smith, B Danner, J Parker-Garza, M Alhneif, O Ogunbona, K Bieniek, S Seshadri, M Flanagan
	75	**Thiophene-Based Ligand HS-84 Binding in Human PrP Proteinopathies** M Jacobsen, N Maynard, L Cracco, K Newell, R Vidal, T Klingstedt, P Nilsson, B Ghetti
	76	**Neuropathologic Findings in a Rare Case of Alpers-Huttenlocher Syndrome at Autopsy** L Robinson, J Suddock, E Abreo
	77	**Histopathological Features Associated with Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS)** J Opara, M Davis, M Weiss, T Bird, D Child, C Latimer
	78	**Microglial Heterogeneity in Alzheimer's Disease, Dementia with Lewy bodies, and LATE-NC** R Shahidehpour, A Bachstetter, P Nelson
	79	**Prolonged Survival in Cerebellar Variant Multiple System Atrophy with Parkinsonian Features and Co-Existing Lewy Body Disease** S Etemadmoghadam, A Ghaseminejad-Bandpey, M Keating, C Gaona, A Gonzalez, C Corbett, O Ogunbona, M Dopler, K Clarke, K Li, J Parker-Garza, B Danner, M Alhneif, M Habes, K Bieniek, S Seshadri, M Flanagan
	80	**Isolated Astrocytic Tau Pathology at Cortical Sulcal Depths: Is it "AR"TAG?** D Priemer, G Kovacs, D Perl

Posters are not offered for CME credit

FRIDAY POSTERS #81-#100

Friday June 20, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 4:30 pm	**81**	**Feasibility Assessment for Evaluation of Cerebellar Pathology in Huntington Disease** J Opara, A Sayyadi, D Child
	82	**A case of rapidly progressing limb-onset ALS with an intermediate ATXN2 repeat expansion** T Brown, L Chen
	83	**Neuroinflammatory and Vascular Changes in Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD)** G Uruk, F Mu Hui, R Gatto, R Reichard, J Whitwell, K Josephs
	84	**Adult polyglucosan body disease neurodegeneration with associated liver disease: an autopsy study** K Jones, F Weaver, P Kishnani, R Koch
	85	**The Brain Bank for Aging Research (BBAR) protocol for amyotrophic lateral sclerosis (ALS)** S Murayama, Y Saito
	86	**Neuropathologic and Ocular Vascular Anomalies in Advanced Ataxia-Telangiectasia** D Smirnov, L Kozanno, A Stemmer-Rachamimov, M Frosch
	87	**Neuropathology of micro- and nano-plastics in brain** E Bearer, M Garcia, N Adolphi, A Caprihan, M Campen, G Rosenberg
	88	**Lipid metabolism during normal aging and age-associated neurodegenerative disease** A Ahamad, S Ge
	89	**Interface astroglial scarring and an unclassified tauopathy with features of progressive supranuclear palsy and corticobasal degeneration** S Hasan, K Bharani, R Sobel
	90	**C9orf72 Mutation in a Patient with Amyotrophic Lateral Sclerosis** **E Salari, S Schwartz**
	91	**Jamestown Canyon virus meningoencephalitis in a lymphoma patient following rituximab therapy with biopsy findings** D BeDell, M Folkertsma, A Venteicher, G Fitzpatrick
	92	**A case of cerebral immune reconstitution inflammatory syndrome (IRIS) in an HIV-positive patient** M Gulfo, S Kurt, S Qi Huang, F Sheikh, J Hua-fang Lin, R Fecher, R Yokoda, S Chin
	93	**A Tumor by Any Other Name: A Case of Pott's Puffy Tumor Caused by Frontal Sinus Fungal Ball** A Sandoval, F Stone, C Lucas, J Chiu, A Campbell, C Eberhart
	94	**A fatal case of Acanthamoeba encephalitis** D Guptil, J DeWitt
	95	**No findings of neurodegenerative disease in a long COVID patient** C Hayes, S Rajan, M Morris, D Nauen, C Ho
	96	**Neuropathology of a Necrotizing Brain Abscess with Dematiaceous Mold: A Case Report of Cerebral Phaeohyphomycosis** J Dailey, M Punsoni
	97	**Fatal Eastern Equine Encephalitis in a Medically Complex Patient: A Case Report and Literature Review** H Qiu, S Hoseini, V Chaturvedi, E Borys, G Kleinman
	98	**An Unusual Fungus In A Neurosurgical Specimen** H Qiu, S Hoseini, V Chaturvedi, E Borys, G Kleinman
	99	**Utilization of Process Record Slide (PRS) technology to facilitate harmonization of immunohistochemical reactions between laboratories.** G Fernandes, J Otero, J
	100	**Instituting a Brain Biopsy Protocol for Tissue Conservation at the University of North Carolina: How Effective Has It Been?** E Price, B Cho

Posters are not offered for CME credit

SATURDAY PLATFORMS 5 & 6

	Platform Session 5: *Tumors: Nonglial* Great Lakes Ballroom B/C	Platform Session 6: *Neurodegenerative: FTLD/Lewy body/Parkinson, Vascular, Trauma* Great Lakes A1-A3
8:00 am - 8:15 am	**33** **WNT signaling regulates melanoma brain invasion and colonization** K Zhang, D Balandin, V Wang, M Ramos Rocha, F Huang, C Palm, A Carey, E Black, E Harper, R Koya, E Kumah, J Rincon-Torroella, C Eberhart, C Lucas, A Weeraratna	**41** **A diagnostic rubric to differentiate LATE-NC Stage 3 from FTLD-TDP** P Nelson, R Shahidehpour, Y Katsumata, D Dickson, N Ghayal, K Aung, X Wu, P Phe, G Jicha, A Neltner, J Archer, M Corrada, C Kawas, S Sajjadi, D Woodworth, S Bukhar, T Montine, D Fardo
8:15 am- 8:30 am	**34** **RNA Sequencing Reveals Novel SYN2::PPARG Fusion in a Subset of Gonadotroph Pituitary Neuroendocrine Tumors (PitNETs)** S Belakhoua, G Shen, S Subramaniyam, D Jones, M Snuderl	**42** **MAPT mutations P301L and R406W are associated with two distinct tau filament folds** B Ghetti, M Schweighauser, C Qi, Y Shi, S Lovestam, J Murrell, A Murzin, H Garringer, R Vidal, S Peak-Chew, C Franco, S Scheres, M Goedert
8:30 am- 8:45 am	**35** **Brain Invasion and Other Histological Grade 2 Features in Whorling-Sclerosing Meningiomas** J Houpt, A Ahmed, I Balki, L Ang	**43** **Annexin A11 proteinopathy in frontotemporal degeneration and amyotrophic lateral sclerosis** N Ghayal, G Sachdeva, R Crook, S Roemer, A Jain, W de Coster, H Sekiya, M DeTure, K Josephs, R Rademakers, M van Blitterswijk, D Dickson
8:45 am- 9:00 am	**36** **Benign Notochordal Cell Tumors with Atypical Features** Z Temerit Kumm, M Whisman, M Gokden	**44** **Age-Related Prevalences of Parkinson Disease Neuropathological Comorbidities in Comparison to Non-Demented, Non-Parkinsonian Subjects** T Beach, C Adler, H Shill, A Atri, I Lorenzini, L Sue, G Serrano
9:00 am- 9:15 am	**37** **Improved molecular pathology for assays in meningioma with NICO Myriad system device** G Fernandes, O Uchechi, K Shade, E Kurtz, M Franco, M Abreu, M McDermott, K Wu, J Otero, D Prevedello	**45** **Florbetapir positron emission tomography with autopsy comparison in patients presenting with primary progressive aphasia** P Kakodkar, P Jamshidi, D Mashoudy, D Gutstein, T Gefen, T Parrish, M Mesulam, R Castellani
9:15 am- 9:30 am	**38** **Survival analysis of brain-invasive otherwise benign meningiomas at a single institution cohort** C Voyles, A Bellizzi, O Lopes Abath Neto	**46** **Hypertensive and diabetic pathologic changes in the kidney are associated with specific cerebrovascular changes** E Higginson, J Persons, R Tashjian, N Becker, P Jamshidi, E Pinarbasi, M Gosse, P Rastogi, K Conway
9:30 am- 9:45 am	**39** **Concordance of Molecular Testing for Evaluation of High-Risk Molecular Features in Meningiomas** B Crumley, E Russler-Germain, S Dahiya	**47** **The ENRICH Study: Investigating Neuroinflammatory Signatures of Cognitive and Psychological Health in Traumatic brain Injury** J Opara, K Sytsma, S Husarik, J Jang, L Travis, T Louangrath, B Edlow, C MacDonald, K Dams-o'connor, C Keene, A Nolan
9:45 am- 10:00 am	**40** **Embryonal Tumor with Multilayered Rosettes: A Single Institution Series of Six Cases** C Takahashi, M Majeed, D Jackson, H Harmsen, W Bell	**48** **Associations of cardiovascular risk factors with select neuropathologies in a diverse cohort with Alzheimer disease** B Dugger, H Wang, N Saito, L Beckett, L Honig, C DeCarli, R Rissman, A Teich, D Mungas, L Jin

SATURDAY PLATFORMS 7 & 8

	Platform Session 7: *Developmental/pediatric, Methodologies* Great Lakes Ballroom B/C	Platform Session 8: *Demyelinating/inflammatory, Peripheral Nerve/Muscle* Great Lakes A1-A3
2:00 pm - 2:15 pm	**49** **Stillbirth: Associations Between Major Patterns of Placental Pathology and Acquired Neuropathology** A Viaene, J Steele, R Linn	**57** **Neuropathologic findings in cases of Stiff Person Syndrome and Progressive Encephalomyelitis with Rigidity and Myoclonus** A Denney, A Wohlfert, A Granholm-Bentley, A Piquet, S Guzman;
2:15 pm- 2:30 pm	**50** **Patterns of Non-Acute Fetal Ischemic CNS Injury** Y Fisher, P Shannon	**58** **Uncovering Novel Extracellular Matrix Transcriptome Alterations in Lesions of Multiple Sclerosis** E Stephenson, R Jain, S Ghorbani, R Gorter, C D'Mello, V Yong
2:30 pm- 2:45 pm	**51** **Generation of a temporal and spatial transcriptomic atlas for motor neuron development** M Rose, N Shirooni, V Padisetti, P Sureshkumar, X Yang, J Li, K Kermani, I Whedon, A Barroga, F Munawar, L Nguyen, S Thayer, A Tenney, A Gelber, D Creighton, F Chen, E Engle	**59** **Immune-Mediated Necrotizing Myopathy (IMNM): An Underdiagnosed Entity** M Sharma, N Rajput, B Jassal, A Dhall, V Suri, V Vishnu, R Bhatia, S Jain
2:45 pm- 3:00 pm	**52** **White matter injury in the term stillbirth** S Beldick, P Shannon, Y Fisher	**60** **Exploring the Connection Between MAST Cells and Symptomatic Pineal Cysts** C Allen, T Baker, R Norris, S Patel, C Welsh
3:00 pm- 3:15 pm	**53** **Congenital syphilis with overwhelming leptomeningeal growth of Treponema pallidum** M Del Bigio, E Ferreira, S Kosteniuk, P Rahaman	**61** **Severe neurotoxic syndrome in six post-solid organ transplant patients on calcineurin inhibitors: Clinical and histopathological features** M Vizcaino, D Tajfirouz, A Sharma, A Madhavan, L Eckel, S McCarter, E Flanagan, Y Guo, M Toledano, A McKeon, I Carabenciov, D Dubey, A Orandi, M Bhatti, C Schinstock, C Kennedy, M Leise, B Boilson, J Chen, D Salomao, C Giannini, R Vaubel
3:15 pm- 3:30 pm	**54** **SlideRelabeler: a user-friendly, stand-alone open-source software application for creating deidentified whole-slide images** A Rosado, D Gutman, T Pearce	**62** **Epineurial perivascular inflammation in peripheral nerve biopsies: a clinicopathologic evaluation** N Becker, B Becker, J Persons, P Jamshidi, D Manthei, S Stone, K Conway
3:30 pm- 3:45 pm	**55** **Multicompartment neuroanatomic segmentation of autopsy brain tissue sections using deep learning methodologies** T Pearce, L Nadeesha, A Neltner, M Klusty, C Ti, M Gokmen, J Vizcarra, C Cadano, N Jaafari, S Cheung, Q Gu, A Tafti, C Ozcan, C Bumgardner, P Nelson, D Gutman	**63** **Molecular and Clinical Insights into Calpainopathy (LGMDR1) in India: A single centre experience**. A Dhall, B Jassal, M Faruq, U Shamim, R Bhatia, V Vishnu, V Suri, M Sharma
3:45 pm- 4:00 pm	**56** **3D scanning and printing to improve brain tissue sampling and research** K Bieniek, M Smith, E Ochoa, M Keating, N Honnorat, M Mojtabai, M Flanagan, M Habes, S Seshadri	**64** **Spectrum of Peripheral and Autonomic Neuropathies in Patients with wtATTR Amyloidosis and Response to Patisiran Therapy** H Hashim, Y Hussain, E Hmedat, J Numan

SATURDAY POSTERS #101-#120

Saturday June 21, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 5:00 pm	**101**	**"Ectopic" Embryonal Neoplasms of the Central Nervous System: Two Cases at a Single Tertiary Care Center** E Price, G Chamberlin, B Cho, D Trembath
	102	**The First Reported Case of CNS Collision Tumor Comprising of Malignant Meningioma and Malignant Peripheral Nerve Sheath Tumor** A Khalili-Toosi, D Zieba, M Snuderl, R Pulinthanathu, J K Liu, A Baisre-De Leon, M Movahed-Ezazi
	103	**Carcinoma Metastasizing to Meningioma: A Case Series and Pathologic Insights** P Nguyen, C Slocum, M Umphlett, J Walker, N Tsankova, J Crary, T Richardson
	104	**A rare case of intracranial ALK-Positive Histiocytosis with DCTN1-ALK fusion originally diagnosed as a meningioma** R Colbourn, A Banihashemi
	105	**Intracranial solitary fibrous tumor with myxoid features: a rare presentation** A Jones, M Lopes, S Patel , A Asthagiri, Z Abdullaev, K Aldape, C Fadul, M McCord
	106	**BCOR Expression In A High-grade Neuroepithelial Tumor With MN1::BEND2 fusion: A Diagnostic Pitfall** P Nisarga, B Rathore, P Hodjat, A Mishra, B Derinkuyu, R Graham, P de Blank, J Skoch, S Roy, D Leino, K Gupta
	107	**Extracranial Intracranial Mesenchymal Tumor with FET-CREB fusion: two case reports.** S Patel, T Pearce, D Marker
	108	**Loss of CDKN2A in a rare case of metastatic pituitary neuroendocrine tumor** J Peck, S Cathcart, A Yuil-Valdes, J Chen
	109	**A rare congenital case of HMGA2::NCOR2-positive giant cell tumor of cranial bone; acquired histologic features to diagnostic KPGCT/XGET.** P Nisarga, K Gupta, B Turpin, R Redline, S Szabo
	110	**Pineal melanocytic neuroectodermal tumor of infancy (MNTI)/ anlage tumor (PAT): a diagnostic challenge** E Guney, I Caliskan, V Tang, K Mirchia, M Pekmezci, S Cha, K Aldape, A Bollen, A Perry, P Samghabadi
	111	**Adult medulloblastoma: pleural metastasis following 10 years of remission in a 39-year-old male patient** A Kollasch-McGarvey, J Persons, K Eschbacher
	112	**Case report of KRAS mutation in pituitary adenoma: a marker of aggressive behavior?** C Chen, M Milani, C Ozutemiz, P Mroz, N Godse, M Sharma, G Fitzpatrick
	113	**Fourth Ventricular Choroid Plexus Adenoma with Atypical Hemorrhagic Presentation: A Histopathologic and Diagnostic Review** H Qiu, G Kleinman
	114	**An unusual high-grade intracranial sarcoma harboring EWSR1::CREM fusion** V Huynh, B Ebner, C Ida, A Raghunathan, J Jebastin Thangaiah, R Batiste, C Giannini A Folpe, M Vizcaino Villalobos
	115	**A Rare Pediatric CNS Embryonal Tumor with ATM Germline Mutation and Concomitant CUX1-RAF1 Fusion** T Alkayyali, L Klesse, D Swift, A Sengupta, V Singh, V Rajaram
	116	**An Unusual Case of a Chordoma Arising in the Cavernous Sinus** S Schwartz, S Gargano
	117	**Single Health System Experience with Hormone Receptor Expression in Meningiomas** D Jackson, M Majeed, K Shiue, N Gatson, H Harmsen, W Bell
	118	**Sarcomatoid primary CNS neoplasms with GLI1 alteration** S Stone, R Landvater, N Becker, K Conway, D Rottmann, S Camelo-Piragua
	119	**Molecular characteristics of metastatic meningioma: A case report in the era of cIMPACT-NOW Update 8** L Evans, K Galbraith, R Yoda
	120	**Large cell/anaplastic Medulloblastoma with Marked Neuronal Differentiation in a Patient with PTPN11 Mutation** D Jackson, M Majeed, R Qaiser, A Lion, T Tihan, W Bell

Posters are not offered for CME credit

SATURDAY POSTERS #121-#140

Saturday June 21, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 5:00 pm	**121**	**Two Cases of Metastatic Urothelial Carcinoma Involving Posterior Fossa** D Jackson, M Majeed, M Pease, A Acosta, B Mobley, W Bell
	122	**Therapeutic effects of 40Hz light stimulation in 3xTg-AD mice by modulating cellular autophagy** Z Gu, Y Fu, H Cao, Y Huang, C Zuo, Y Song, X Chen, F Wang
	123	**Histologic, immunophenotypic, and molecular characterization of CNS Neuroblastoma, FOXR2-activated, in a 5-year-old male patient** F Ogaban, K Eschbacher
	124	**The monocyte-macrophage marker CD163 is highly expressed by meningioma** A Kollasch-McGarvey, A Bellizzi, O Lopes Abath Neto
	125	**A slow progressive neuroepithelial tumor with a MN1-PATZ1 fusion in a young adult** J Redding-Ochoa, L Chen
	126	**Intrasellar Plasma Cell Neoplasms** R Cecchi, K Conway, R Landvater
	127	**Mesenchymal Chondrosarcoma with Extensive Intracranial Involvement** J Persons, M Tanas, M Samuelson, K Eschbacher
	128	**Central Nervous System Presentation of Classic Hodgkin Lymphoma: A Two Case Series** A Schmidt, C Syposs
	129	**Anaplastic Meningioma with Sarcomatous Transformation and Extracranial Metastasis** L Kulumani Mahadevan, L Canbeldek, C Slocum, N Tsankova, T Richardson, J Walker, M Gupta, J Crary, W Fan, M Umphlett
	130	**Morphological and Immunohistochemical Diagnosis in a Case of Metastatic Meningioma to the Lung** M Bouthim, M Curtis, S Schwartz
	131	**A Rare Case of Xanthomatous Meningioma in a 47-Year-Old Female** A Schurr, S Schwartz
	132	**The Brain is a Big Place: A Ventricular Mass with Important Lessons** W Humphrey, J Rechberger
	133	**TERT promoter mutation in Metastatic Papillary Thyroid Carcinoma Presenting as a Dural-Based Mass** M Majeed, D Jackson, C Takahashi, M Pease, N Gatson, H Harmsen, W Bell
	134	**Malignant Peripheral Nerve Sheath Tumor with Osteosarcomatous Differentiation in a Vestibular Schwannoma: A Case Report** D Lombardo, D Buehler, Z Morris, K Aldape, J Helgager
	135	**An ATRT in a 75 yo female** J Fullmer, C Schukow, J LLenos
	136	**CAPNON: A Rare Case with Long-term Follow-up** T Auen, J Boxerman, C Yu, D Cielo, D Anthony
	137	**Histologic, immunophenotypic, and molecular characterization of a case of chondroid synoviocytic neoplasm** K Higham-Kessler, M Tanas, A Isaacson, K Eschbacher
	138	**Meningioangiomatosis versus intraparenchymal meningioma with meningioangiomatosis-like growth pattern** I Caliskan, S Perez, A Putnam, G Chamyan, K Mirchia, J Van Ziffle, A Perry
	139	**Uncommon Cutaneous Presentation of a CNS Tumor** J Eberle-Singh, R Thomas
	140	**Cystic Choroid Plexus Papilloma in an Adult: A Diagnostic Challenge on Frozen Section: Case Report and Literature Review** A Cuevas Ocampo, C Soto Davila, O Arevalo Espejo, B Hartman, C Giannini

Posters are not offered for CME credit

SATURDAY POSTERS #141-#160

Saturday June 21, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 5:00 pm	**141**	**Meningioma: The Good, the Bad, and the Proliferative.** J Dailey, A Nobee, M Punsoni
	142	**Calcifying pseudoneoplasms of the neuraxis (CAPNON) associated with Meningioangiomatosis in a Pediatric Patient. A Case Report** D Zieba, A Baisre de Leon, M Brady, C Guerrieri, M Movahed-Ezazi, L Tomycz
	143	**Intradiploic epidermoid cysts of the skull: Case report.** A Alkhotani, A Alkhotani
	144	**Schwannoma with Extensive Xanthomatous Changes: A Case Report** A Alkhotani, A Alkhotani
	145	**Distant metastases of an atypical meningioma presenting 14 years later after primary tumor resection: a case report and review of the literature** K Firde, I Akhtar, L Barry, A Bombonati, Y Rong
	146	**EBV+ Primary Central Nervous System Lymphoma in an Immunocompetent Patient** A Kenyon, L Kenyon, G Uppal
	147	**Intracranial solitary fibrous tumor with myxoid features: a rare presentation** A Jones, M Lopes, S Patel, A Asthagiri, Z Abdullaev, K Aldape, C Fadul, M McCord
	148	**Intradural Extraosseous Ewing Sarcoma in an Older Adult: A Case Report** H Ellsworth, H Bayne, H Ellsworth, E Karlovich, O Al Dalahmah, V Tikhomirov
	149	**Metastatic thymoma to brain parenchyma** J Fullmer, J Blumberg
	150	**Atypical meningiomas with diverse variants of unknown significance: a report of three cases.** S Sharma, M Toscano, E Shaver
	151	**An unusual case of late recurrence of atypical choroid plexus papilloma with intracranial and spine metastases in an elderly patient** O Tetteh, J Singh, R Ber, C Mau, B Donahue, T Daniels, B Cooper, J Zeng
	152	**Clinicopathological characterization of vacuolar tauopathy associated with VCP D395G** R WATANABE, J Papatriantafyllou, K Maeda, G Aguirre, M Ando, B Benoit, M Grossman, D Irwin, B Kim, L Massimo, C McMillan, S Papageorgiou, T Shiraishi, Y Sugihara, E Suh, H Takashima, C Toro, V Van Deerlin, I Nasrallah, E Lee
	153	**Alpha-Synuclein Oligomers and Visual Hallucinations in Dementia with Lewy Bodies: A Clinicopathological Study** H Sekiya, L Franke, D Ono, G Day, C Lachner, N Graff-Radford, P McLean, T Ferman, D Dickson
	154	**Prevalence of Chronic Traumatic Encephalopathy Pathology in Lewy Body Disease** L GOMEZ-ISAZA, M Luongo, M Morris, J Troncoso, T Zaikos
	155	**TDP-43 Proteomics of the Frontal Cortex in Lower Motor Neuron Disease and Frontotemporal Dementia** L Cracco, E Doud, R Rademakers, H Garringer, M Jacobsen, E Buratti, B Ghetti, K Newell
	156	**RNA sequencing of amygdala in Parkinson's disease** C Tremblay, G Frosi, S Aslam, J Walker, A Intorcia, I Lorenzini, P Choudhury, C Adler, e Driver-Dunckley, S Mehta, H Shill, A Atri, Y Zeighami, T Beach, G Serrano
	157	**Late-Onset Frontotemporal Lobar Degeneration TDP-43 Type A with Lewy Body Pathology and Protein Colocalization** A Ghaseminejad-Bandpey [1], S Etemadmoghadam, C Corbett, M Keating, A Gonzalez, O Ogunbona, M Dopler, K Clarke, J Parker-Garza, B Danner, M Alhneif, K Bieniek, S Seshadri, M Flanagan
	158	**Investigating Optic Nerve Alterations in Parkinson's Disease: A Histological and Protein Analysis Study** I Lorenzini, A Gonzalez, A Intorcia, A Shull, Z Wermager, J Walker, S Qiji, S Beh, R Arce, C Borja, M Cline, A Krupp, R McHattie, M Mariner, T Beach, G Serrano
	159	**Asymmetric, Limbic-Predominant 4 Repeat Tauopathy with Pick body-like Inclusions discovered incidentally at autopsy – A Case Report** H Smith, M Mejia-Bautista, P Jamshidi, J Ahrendsen, R Castellani
	160	**Contribution of TAR DNA-binding protein 43 (TDP-43) and Anexin A11 in Frontotemporal Lobar Degeneration's Limbic Tau-PET Signal** R Gatto, G Uruk, H Youssef, R Reichard, V Lowe, J Whitwell, K Josephs

Posters are not offered for CME credit

SATURDAY POSTERS #161-#180

Saturday June 21, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 5:00 pm	**161**	**Corticospinal tract degeneration in frontotemporal lobar degeneration associated with phospho-TDP43 proteinopathy** R Castellani, D Mashoudy, T Gefen, M Mesulam, P Jamshidi
	162	**Early-Onset Sporadic Lower Motor Neuron Disease and Frontotemporal Dementia Associated with a TDP-43 Proteinopathy of Unknown Etiology** K Newell, D Clark, F Unverzagt, M Jacobsen, M Majeed, L Cracco, R Vidal, H Garringer, R Rademakers, B Ghetti
	163	**Asymmetric Frontotemporal Lobar Degeneration (FTLD)-TDP-43 with concurrent FTLD-tau, Corticobasal Degeneration Subtype** K Wysong, W Pendlebury, J DeWitt
	164	**Examining Sex Differences in Neuroinflammation Associated with Traumatic Brain Injury** L Chung, K Sytsma, A Feichtenbiner, J Opara, R Mittenzwei, C Keene, A Nolan
	165	**Two cases of unusual sulcal phosphorylated tau aggregates in donors with a remote history of traumatic brain injury** A Penev, J Opara, R Mittenzwei, D Child, C Latimer, D Keene, A Nolan
	166	**Characterization of the ischemic penumbra using MRI and 3D histology: Proof-of-principle case analysis** R Nanjappa, A Ayyappan, R Verma, J Jayakumar, K Ram, R Rangaswami, M Sen, R James, A Manesh, G Varghese, D Nauen, R Folkerth, M Sivaprakasam ***NOTE:*** Moved to a platform presentation.
	167	**Distinct patterns of vascular smooth muscle degeneration in cerebral small vessel diseases: A large-scale 3D structural analysis** R Saito, K Tainaka, H Hayashi, M Ozawa, O Onodeara, A Kakita
	168	**Diffuse Cerebral, Brainstem, and Cerebellar Fat Emboli Occurring in the Context of Abdominal Compartment Syndrome and Soft Tissue Injury** J Houpt, Y Li, E Tugaleva, R Jacques, L Ang
	169	**Neuropathologic findings in a case of GAD65+ Autoimmune Epilepsy with mechanistic insights from HD Visium Spatial Transcriptomics** A Denney, A Wohlfert, A Granholm-Bentley, A Piquet, K Jones, A Toland, S Guzman
	170	**Consecutive brain biopsies illustrate the histological evolution of acute hemorrhagic leukoencephalitis** E Pai, F Jones, A Banihashemi, J Orthmann-Murphy, E Lee
	171	**Amyotrophic lateral sclerosis in a patient with a 30-year history of multiple sclerosis** E Russler-Germain, R Schmidt, S Smith, A Cross, S Dahiya
	172	**20-Year-Old Male with X-linked Adrenoleukodystrophy: A Case Report with Postmortem Findings** D Mack, S Chen, S Moore
	173	**Insights in underlying pathophysiology of brain malformations associated with VRK1-related syndrome derived from fetal neuropathology** S Brock, A Tessier, O Monestier, V Benoit, F Debray, L Ghassemi, K Van Berkel, F Vauthier
	174	**Histopathologic Characterization of Focal Cortical Dysplasia in DEPDC5-Related Epilepsy** J Newman, A Toland, S Guzman, H Vogel
	175	**Exome Sequencing in a Grey Matter Heterotopia Cohort Identifies Novel Roles for Neurodevelopmental Genes.** M Lukacs, D Harris, C Prasad, C Walsh, J Neil
	176	**A Practical Atlas of the Developing Human Brain for the Neuropathologist** R Risgaard, M Duran, K Han, S Salamat
	177	**Brain-restricted chromosome 1q gains underlies focal epilepsy with hyaline astrocytic inclusions** H Adle-Biassette, A DE MEULEMEESTER, M Scopin, S Lina, R Checri, C Nava, L El Khattabi, M DOLADILHE, S FERRAND SORBETS, G DORFMULLER, M CHIPAUX, S BALDASSARI, S BAULAC
	178	**Multimodal single-cell analyses of the early postnatal Down Syndrome brain** R Risgaard
	179	**Friedreich ataxia is a hypoplastic and neurodegenerative disease** A Koeppen, J Mazurkiewicz, S Pelech, J Qian, C Sutter, P Feustel
	180	**Atypical Histopathology in a Surgical Case of Epilepsy Associated with Sturge-Weber Syndrome Complicated with Developmental Venous Anomaly** H Miyata, J Abe, R Honda, T Ono, S Miura, M Ito

Posters are not offered for CME credit

SATURDAY POSTERS #181-#200

Saturday June 21, 2025		
Time:	**Poster #:**	**Boundary Waters Ballroom**
8:00 am – 5:00 pm	**181**	**Caudal Pontomedullary Dysplasia (Brainstem Disconnection Syndrome) in a Term Neonate** S Belakhoua, S Karathanasis, F Dekio, M Snuderl, R Folkerth
	182	**An autopsy case of hyaline protoplasmic astrocytopathy in a 17-year-old epileptic patient status post remote functional hemispherectomy** C Voyles, E Stalter, M Blessing, O Lopes Abath Neto
	183	**Congenital Brainstem Tumor: Novel Molecular Insights from a Fetal Case** Y Fisher, S Shinar, C Hawkins, E Miller, P Shannon
	184	**Optic Pathway Glioblastoma/Malignant Optic Nerve Glioma (MONG) with Molecular Characterization in an Adult** H Highfield, K Sinicrope, D Sun, C Davidson
	185	**CNS-like Ocular Tumors, A Series** A Gilani, A Toland
	186	**A MICU1 mutation leading to adult-onset myopathy and cerebellar ataxia with unique pathologic and ultrastructural features** R Geyer, J Imitola, Q Wu
	187	**Mitochondrial changes in muscle biopsies of patients with antisynthetase syndrome and other idiopathic inflammatory myopathies** A Murphy, G Mak, K Gordon, G Grafham, J Provias, M Tarnopolsky, J Lu
	188	**Intracellular Amyloidosis in Peripheral Nerve and Skeletal Muscle Biopsies** G Grafham, G Mak, S Grant, A Murphy, S Baker, M Tarnopolsky, J Lu
	189	**A complex diagnosis of nemaline myopathy requiring genetic testing and muscle biopsy correlation** A Jones, A Jones, V Smith, J Mandell
	190	**Concurrent inclusion body myositis and sarcoid myopathy in a young patient** C Lee, K Quigg, A Stino, N Becker, K Conway
	191	**Congenital Myasthenia with Unexpected Cytochemical, Immunohistochemical, and Electron Microscopic Findings** R Rebbe, K Moradi, S Beydoun, L Darki, A Mathew, K Hurth
	192	**Limb girdle muscular dystrophy R28 in an infant. Expanding the spectrum of pathology** H Vogel, A Johnson, J Newman
	193	**Muscle building injection induced myositis** K Arkun, H Hamid
	194	**Pediatric Neurooncology Postmortem Research and the Children's Brain Tumor Network: Impact and Neuropathology Perspectives** M Blessing, B Frenkel, J Lilly, P Gustafson, J Stevens, K Yao, C Kopsidas, M Williams, T Torrescano, A Liljensten, C Campbell, A Backlund, N Diarra, D Dupal, J Mason, T Patton, C Stamy, M Frazer, M Hefti, A Resnick, K Eschbacher, M Santi-Vicini, M Koptyra , A Viaene
	195	**Neuropathological Findings in Bongkrekic Acid Intoxication: A Case Series of Six Autopsies** K Chang, W Lin, Y Wang, T Weng
	196	**Creating an AI-Driven Morphological Landscape of Meningiomas** M Ayad, K McCortney, C Horbinski, L Cooper
	197	**Development of Neuropathology-Specific Entrustable Professional Activities (EPAs)** R Multz, K Conway, J Ahrendsen, R Castellani, P Jamshidi
	198	**Applying machine learning to assist in the quantitative assessment of brain arteriolosclerosis through automation** J Lou, P Chang, K Nava, C Chantaduly, H Wang, W Yong, V Patel, A Chaudhari, E Monuki, E Head, H Vinters, S Magaki, D Harvey, C Chuah, C DeCarli, C Williams, M Keiser, B Dugger
	199	**Nonspecific localized amyloid deposition in a patient with hereditary peripheral neuropathy mimicking ATTR amyloidosis** M Milani, C Chen, Y Koksel, A Venteicher, G Fitzpatrick
	200	**The role of histopathology and molecular analysis in the grading and management of spinal meningiomas-an institutional experience** A Koziol, Q Wu

Posters are not offered for CME credit

PLATFORM 1: Tumors: Glial

1

Persistent Proliferative Progenitor Cell States and CDK4/6 Expression in Treatment-Resistant H3 G34-Mutant Diffuse Hemispheric Glioma

J Chiang [1], Q Zhang [2], X Li [2]; [1] St. Jude Children's Research Hospital, [2] St. Jude Children's Research Hospital

Background: H3 G34-mutant diffuse hemispheric glioma is a highly aggressive tumor with a grim prognosis. Effective therapies and mechanisms of treatment resistance remain unknown. Recent studies have identified a GABAergic interneuron developmental hierarchy within these tumors, offering a unique opportunity to identify therapeutic vulnerabilities.

Methods: We performed high-resolution spatial whole-transcriptomic profiling on 18 regions of matching pre-therapy (n=9) and post-therapy progressive (n=9) G34-mutant diffuse hemispheric glioma samples to identify therapy-induced changes in cell states and therapeutic targets with immunohistochemistry validation. Treatments received included focal or craniospinal radiation, with or without temozolomide, pembrolizumab, or B7-H3 CAR T-cells. The median post-therapy interval was 65 days (range 35-92 days).

Results: We analyzed 23,309 pre-therapy and 14,214 post-therapy tumor cells. After therapy, there was a significant expansion of SOX2+ radial glia-like cells (41.5±1.7% vs. 69.8±0.3%, p=1.9x10^-5), PAX6+ progenitor-like cells (19.3±0.2% vs. 30.5±1.1%, p=0.0114), FOXG1+ interneuron progenitor-like cells (17.1±0.2% vs. 39.0±4.7% p=0.0095), and GAD1+ early interneuron-like cells (7.1±0.1% vs. 13.0±0.3%, p=0.0157), accompanied by marked increases in proliferating cells (31.3±0.2% vs. 77.9±15.0%, p=0.0025). Conversely, more differentiated neuronal progenitor-like cells, including Nestin+ (30.8±0.7% vs. 21.0±0.1%, p=0.0036), DCX+ (17.4±1.0% vs. 3.1±0.0%, p=0.0007), DLX2+ (6.3±0.0% vs. 3.8±0.0%, p=0.0075), DLX5+ (4.7±0.1% vs. 2.1±0.0%, p=0.0227), and GAD2+ (1.8±0.0% vs. 0.1±0.0%, p=0.0017) populations, along with AQP4+ astrocyte-like cells (10.3±0.1% vs. 6.1±0.1%, p=0.0200), were significantly depleted post-therapy. MGMT+ tumor cells increased significantly (0.7±0.0% vs. 3.0±0.0%, p=2.4x10^-5) post-therapy, while CDK4/6 expression remained unchanged in 88.7±14.7% of tumor cells pre- and post-therapy.

Conclusions: Our findings reveal that tumor cells in specific proliferative progenitor-like states persist after therapies, acting as the principal tumor-propagating population. In contrast, those in more differentiated states are significantly reduced. These persistent progenitor-like cells present a unique therapeutic opportunity. Our data support the development of CDK4/6-directed therapy for H3 G34-mutant diffuse hemispheric glioma, while the post-therapy increase in MGMT expression suggests a mechanism of temozolomide resistance.

2

"Unraveling the miRNA-EMT-Stemness Interplay in Fusion-Positive Supratentorial Ependymomas: Identifying Therapeutic Vulnerabilities"

A Sharma [1], S Chauhan [2], R Kulshrestha [3], A Kumar [2], R Malik [2], M Sharma [2], V Suri [2]; [1] AIIMS, [2] All India Institute of Medical Sciences, [3] Indian Institute of Technology

Background: Ependymomas, particularly those arising in the supratentorial region, pose a significant clinical challenge due to their molecular heterogeneity and resistance to therapy. Among these, ZFTA-RELA fusion has emerged as a defining genetic alteration in supratentorial ependymomas, yet the underlying regulatory mechanisms driving tumor progression remain poorly understood. Increasing evidence suggests that epithelial-mesenchymal transition (EMT) and stemness acquisition contribute to tumor aggressiveness and recurrence. However, the role of miRNA-mediated regulation in these processes remains largely unexplored. We present a novel miRNA profiling study identifying key miRNA regulators associated with EMT, stemness, and tumor progression in supratentorial ependymomas.

Methods: We employed small RNA sequencing, bioinformatics target prediction, and experimental validation through qRT-PCR and immunohistochemistry (IHC). miRNA profiling was performed using small RNA sequencing, followed by differential expression analysis and validation through qRT-PCR. Fusion subtyping was determined via RT-PCR and sanger sequencing, while immunohistochemistry assessed EMT and stemness markers. Bioinformatics analysis employing DIANA tools, network analysis, mirNEt, mirDB, Cancermine identified miRNA targets and enriched pathways, with survival analysis performed using Kaplan-Meier curves.

Results: Comparative miRNA analysis identified 3021 dysregulated miRNAs in ZFTA RELA fusion-positive and 3059 in ZFTA RELA fusion-negative ependymomas, with significant overlaps. Validation via qRT-PCR confirmed upregulation of hsa-miR-138-5p and downregulation of hsa-miR-216a-3p and hsa-miR-135b-5p in fusion-positive tumors. Target genes TERT, YAP1, and RELA were significantly expressed in fusion-positive tumors, with TP53 showing a 3.9-fold increase. Pathway analysis revealed enrichment in NF-kB and NOTCH pathways. EMT markers SNAIL, SLUG, and Nestin were elevated in fusion-positive tumors, supporting aggressive tumor behavior. Fusion-positive tumors exhibited shorter progression-free survival, with SNAIL and SLUG correlating with poorer outcomes.

Conclusions: Interplay between fusion status, miRNA, EMT and stemness emphasize the complexity and context-specific nature of miRNA-mediated regulation in supratentorial ependymomas. Future studies are needed to explore regulatory networks leading to the development of targeted therapeutic strategies for aggressive ependymomas.

3

Methylation Profiling Limitations for High Grade Brain Tumors

M Milani [1], C Chen [2], L Chen [1]; [1] University of Minnesota, [2] University of Minnesota Medical School

Background: DNA methylation profiling has revolutionized the subclassification of central nervous system (CNS) tumors, providing insights into tumor prognosis, recurrence, and personalized treatments. Despite its utility, challenges persist in classifying rare or poorly understood high-grade gliomas (HGGs) that fail to match existing methylation data. This study evaluates the clinical, histopathological, and molecular characteristics of four such cases, emphasizing room for improvement of methylation profiling in refining diagnoses and treatment.

Methods: We retrospectively analyzed data from four adult patients with HGGs unclassified by methylation profiling. Clinical features, imaging, histopathology, and next-generation sequencing results were reviewed. Methylation profiling was performed by the NIH. Cases were evaluated for histopathological features, molecular markers, and survival outcomes.

Results: All patients exhibited diverse clinical presentations, with MRI and histopathological findings confirming high-grade gliomas. Histopathological analysis revealed varied features across the cases including bizarre multinucleated giant cells and deeply infiltrating small round blue cells. Immunohistochemical markers highlighted GFAP positivity and ATRX retention across cases, with TP53 mutations identified in three cases. Methylation profiling failed to yield clear matches for any known class. Instead, profiling suggested a high-grade epithelioid neoplasm for Case 1, while Cases 2-4 were deemed indeterminate IDH-wildtype neoplasms with aggressive clinical courses. Despite treatment, two patients experienced disease progression and died, while the remaining two showed stable disease on follow-up.

Conclusions: This study highlights the diagnostic challenges of unclassifiable CNS tumors in the context of DNA methylation profiling, reflecting the need for expanded reference datasets. While profiling has transformed the field of tumor diagnostics, its limitations still exist. Enhanced collaboration and data sharing to broaden diagnostic categories is essential to improving methylation profiling. Until then, integration of clinical, histological, and molecular findings are imperative to optimize patient management, improve classification accuracy, and increase positive therapeutic outcomes.

4

Isolated activation of the PI3K/AKT pathway characterizes a novel group of indolent diffuse gliomas in adults

D Meredith [1], R Masi [2]; [1] Brigham and Women's Hospital, [2] Harvard Medical School

Background: Despite widespread genetic definitions for many tumors in the 5th CNS WHO, large-scale molecular profiling efforts continue to identify subclasses of gliomas with distinct clinicopathologic features. During routine clinical practice, we encountered an adult diffuse glioma with low-grade histology harboring only a gain-of-function PIK3CA variant and unusual copy number profile that failed to match existing methylation classes. We therefore aimed to identify and characterize similar examples of this novel IDH-wildtype low-grade adult diffuse glioma.

Methods: Diffuse low-grade gliomas harboring oncogenic PI3K/AKT pathway alterations were identified from both the TCGA and our institutional sequencing databases. Tumors showing definitional mutations or copy changes for existing WHO entities were excluded (e.g. +7/-10, IDH1/2 mutations, EGFR amplification, TERT promoter variants, etc.). Detailed clinical information, pathologic features, methylation class, and genomic profiles were collected for the resulting cohort of five patients.

Results: Median age at time of diagnosis was 50 years (range: 35-68 years). The location of tumors included temporal lobe (n=4) and hypothalamus (n=1). All tumors showed bland diffuse astrocytoma morphology without microvascular proliferation or necrosis. Rare mitoses were observed in a single case, and the Ki67 index was approximately 1% or less in all cases. One case exhibited rare Rosenthal fibers. Four cases contained mutations in PIK3CA (p.G366R, p.C420R x 2, p.K711N), while one harbored a loss-of-function in-frame deletion in PIK3R1 (p.E451_Y452del). No additional driver mutations, rearrangements, or recurrent copy changes were observed. Methylation profiling was successfully performed for 4 cases; none showed a high confidence match to existing methylation clusters. Additionally, tumors did not cluster together. All five patients received gross total resections and showed no evidence of disease recurrence at follow up (median: 30 months, range: 9-151 months).

Conclusions: Here we describe a novel cohort of IDH-wildtype low-grade adult diffuse gliomas whose unifying feature is activation of the PI3K/AKT pathway.

5

Clinically applicable deep learning model for robust classification of central nervous system tumors from histopathology images

C Dampier [1], H Lalchungnunga [2], D Hoang [2], E Shulman [2], Z Abdullaev [2], B Li [2], Z Luo [2], O Singh [2], Z Wu [2], T Pearce [3], C Horbinski [4], C Lucas [5], P Cimino [6], M Nasrallah [7], M Quezado [2], H Chung [2], S Brandner [8], E Ruppin [2], K Aldape [2]; [1] NCI-JHH, [2] NIH/NCI, [3] UPMC, [4] Northwestern Medicine, [5] Johns Hopkins University, [6] NIH/NINDS, [7] University of Pennsylvania, [8] UCL Queen Square Institute of Neurology

Background: We have previously shown that DNA methylation levels can be predicted from digital whole slide images (WSIs) and used to accurately classify CNS tumors into broad categories. Here, we incorporate this approach into a novel deep learning framework that combines a state-of-the-art vision transformer with an additional molecular modality (gene expression) and a hierarchical design to predict WHO tumor categories from WSIs.

Methods: We trained a deep learning model to integrate predictions of DNA methylation and RNA expression with classifications based on image representations and patient demographics. We utilized nested classifier tiers, each optimized independently, to predict tumor types among nine tumor families and then 52 WHO-based tumor classes. We trained our model on 5,882 WSIs from 5,715 patients, of which 2,988 had paired DNA methylation profiling and 848 had paired RNA-sequencing. We tested our model on an independent, multi-institutional cohort of 5,257 samples. Confidence scores above tier-specific thresholds tuned to maximize Youden indices (mean 0.80, range 0.59-0.93) were considered 'high.'

Results: Our model returned high-confidence, class-level predictions for half (49%, 2,592/5,257) of samples with accuracy of 98% (2,540/2,592). With a fixed confidence score threshold of 0.5, our model returned predictions for 87% (4,553/5,257) of samples with accuracy of 82% (3,733/4,553). In a 'pathologist vs. machine' experiment in which four neuropathologists completed an identical classification task for 96 tumors chosen to represent a range of pediatric- and adult-type glial and non-glial tumors, our model (without confidence score thresholds) correctly classified 80% (77/96), while the most accurate neuropathologist correctly classified 76% (73/96), and the neuropathologist average was 57% (55/96). Among high-confidence predictions, model accuracy was 97% (29/30), and highest neuropathologist accuracy was 83% (25/30).

Conclusions: Our model, utilizing inferred DNA methylation and gene expression, can classify CNS tumors with high accuracy and could aid human neuropathologists in their clinical evaluation of CNS tumors.

6

Molecular features of primary gliosarcoma with evidence for a distinct transcriptomic profile in mesenchymal components

M Wood [1], G Zangirolani [2], J Lee [2], T Neff [2], C Beadling [2], C Corless [2]; [1] Oregon Health & Science University, [2] Knight Cancer Institute

Background: Gliosarcoma (GSC) is a subtype of glioblastoma, IDH-wildtype (GBM) defined by biphasic morphology with interdigitating malignant mesenchymal and glial/astrocytic components, and accounts for ~2% of GBM cases. The mesenchymal component may be present at initial diagnosis (primary GSC) or at GBM recurrence/progression (secondary GSC).

Methods: We assembled an institutional cohort of 37 adult primary GSC and compared clinical and genetic features to a 2-to-1 matched cohort of adult primary GBM. Next-generation sequencing data were obtained for 25 GSC cases. Digital spatial transcriptomic profiling was performed on four GSC cases to identify differentially expressed transcripts within the mesenchymal elements of these tumors.

Results: The GSC cohort included 24 male and 13 female patients with median age of 65 years (range 34-87). The GBM cohort included 43 male and 32 female patients with median age 66 years (range 44-87). Thirty-five GSC tumors with available location were 51% temporal, 26% frontal, 9% parietal, 6% occipital, or 8% involving multiple brain lobes. Overall survival was similar in 28 GSC and 75 GBM cases with clinical follow-up. Next-generation sequencing of GSC showed a higher rate of NF1 mutation compared to GBM (48% vs. 9%; $p< 0.001$) and a lower rate of EGFR alterations (12% vs. 47%; $p< 0.01$). Spatial RNA-based transcriptomic analysis of GSC mesenchymal and glial regions showed distinct transcriptomic profiles in tumor elements with upregulation of collagen, smooth muscle, and extracellular matrix protein transcripts in the mesenchymal regions and higher expression of astrocytic identity transcripts in glial regions.

Conclusions: This study adds evidence for a distinct genetic profile in primary GSC characterized by frequent NF1 inactivation and low rate of EGFR activating alterations. Digital spatial methodologies are feasible for studying differential gene expression with potential to inform future studies on the origin of mesenchymal elements in GSC.

7

Translation control in neuron-cancer cross talk drives glioblastoma progression

E Guney, A Dabrowska, N Magee, R Phua, L Wang, D Baker, K Lee, C Cadwell, C Escoubas, D Ruggero, W Weiss; University of California, San Francisco

Background: While neuron-tumor cross talk plays a critical role in tumorigenesis, underlying mechanisms enabling both neuron-tumor interactions and therapeutic opportunities are poorly understood. The effect of neurons on cancer cells has been assessed largely through RNA-seq analyses. Importantly, levels of mRNA correlate poorly with the abundance of proteins. Since electrical discharges occur in milliseconds, translation control represents the fastest way neurons can direct cancer cells to reshape their proteome.

Methods: To decipher mechanisms by which neuronal signaling regulates translation control in glioblastoma (GBM), we established coculture models, screening 24 primary mouse cortical neurons with either cell lines or short-term cultures of human patient-derived xenografts.

Results: Among these, six led to increased neuronal firing. For example, GBM26 cells drove increased firing in neurons starting at day 3 of coculture (PCC3) compared to neuron-only conditions. PCC3 co-cultures (compared to GBM26 monocultures) showed increased proliferation in vitro, as well as shortened latency and increased burden in vivo in orthotopic xenografts. PCC3 co-cultures, compared to GBM26 monocultures, showed significantly increased de novo protein synthesis as well as increased expression of key translation initiation factors, including the major cap-binding protein eIF4E, which controls the translation of specific oncogenic mRNAs.

Conclusions: Our findings suggest that neuronal signaling impacts translation control in GBM cells, driving progression. We hypothesize that PCC2 represents the earliest timepoint at which neuron-tumor signaling starts to reshape the GBM translatome. Ongoing ribosome profiling in neurons and GBM cells as monoculture and coculture will allow us to 1). Decipher unique neuronal and cancer cell translatomes underlying neuron-cancer interactions, and 2). Identify developmental and neuromodulatory targets established by an oncogenic translational program.

8

Infiltrative margin biology in high-grade gliomas defined through spatial multi-omics

N Tsankova [1], B Pai [1], S Ramos [1], W Cheng [1], E Ozen [2], T Silva-Hurtado [1], L Kulumani Mahadevan [1], R Yong [1], E Zaslavsky [1]; [1] Icahn School of Medicine at Mount Sinai, [2] Columbia University

Background: Despite genomic heterogeneity, most high-grade gliomas (HGG), including IDH-wildtype glioblastoma, display infiltrative growth, which impedes complete surgical resection and leads to inevitable recurrence. Our understanding of HGG biology comes predominantly from studies using resected "core" tissue. Paradoxically, chemoradiation targets residual disease biology at the resection margin, which remains poorly defined.

Methods: To better characterize HGG biology near the resection margin, we generated high-throughput single-nucleus (sn)RNA-seq and snATAC-seq multi-omic data from matching "core" and "margin" dissections in four distinct WHO grade 4 HGG (EGFR-amplified, NF1-mutant, FGFR3-TACC3 fused, IDH1-mutant; n= 36,811 snRNA-seq and 30,705 snATAC-seq nuclei after filtering) and combined it with new spatial transcriptomics data from two additional samples (EGFR-amplified, CDK4-amplifed) to further evaluate "core-to-margin" transition. Computational analyses included data integration, inference of copy number alterations to annotate tumor cells, reconstruction of core-to-margin transition using RNA velocity and pseudotime, and differential analyses in "core" vs. "margin" cell types or regions-of-interest for genes, open chromatin peaks, cell-cell interaction pairs, transcription factor motif activity and associated regulon targets.

Results: By contrasting tumor-specific biology in "core" vs. "margin", we defined unique, shared "glioma infiltration" transcriptomic and chromatin accessibility signatures near the margin. Infiltrative margin tumor cells differentially overexpressed genes related to Notch, WNT, EGFR, and MAPK signaling, gliogenesis, cell adhesion, and axon guidance. By correlating histology to tumor-enriched spots in spatial transcriptomics data, we further defined upregulated genes within structures of Scherer, such as subpial spread and perineuronal satellitosis, many of which related to synaptic neurotransmission.

Conclusions: Tumor biology at the margin has unique and potentially targetable vulnerabilities, shared among samples with different genomic drivers, understanding which can result in more accurate drug design and preclinical modeling. This multi-omic dataset enables further studies into tumor and microenvironment biology in the context of residual disease in adult glioblastoma and other high-grade gliomas.

PLATFORM 2: Neurodegenerative: Alzheimer

9

PSEN1-mutant Early Onset Alzheimer Disease – The Northwestern Brain Brank Cases
H Smith, M Mejia-Bautista, P Jamshidi, J Ahrendsen, L Jennings, R Castellani; Northwestern Memorial Hospital

Background: Genetic Alzheimer's disease (AD) syndromes comprise the primary line of evidence in favor of the amyloid cascade hypothesis in sporadic AD. Mutations in PSEN1, although rare, are the most common cause of autosomal dominant Alzheimer's disease. To understand the genotype-phenotype correlations and extent to which familial cases inform sporadic disease, we reviewed the genetic information, clinical findings, and neuropathology in all PSEN1-mutant cases in the Northwestern University ADRC brain bank.

Methods: We compiled a series of fourteen autopsy specimens from patients with confirmed PSEN1 mutations. Collected data include PSEN1 variant, clinical course, and neuropathology, including interrogation for Aβ, tau, TDP-43, and synuclein.

Results: PSEN1 mutations included A431E (N=5), G206A (N=4), H163R (N=1), P88L (N=2), and P267A (N=1). The age of onset was youngest for A431E (mean 41), oldest for P88L (mean 65), and intermediate for the remaining variants. Cotton wool plaques were prominent in A431E and G206A variants, absent in P88L and P267A cases. Amyloid and tau burdens were most pronounced in A431E cases and exceeded that in sporadic AD, particularly apparent in the cerebellum. Diffuse plaques in the dentate nucleus were exclusive to A431E. Cerebral amyloid angiopathy was variable in G206A variants but moderate to severe in all other variants. Glial tau was inconspicuous. Lewy bodies were present in both P88L cases (amygdala) and one A431E case (diffuse neocortical). Amygdala and hippocampal TDP-43 were noted in one P88L case.

Conclusions: This series demonstrates heterogeneity in pathological phenotype, from inseparable from sporadic AD to unique. A431E differs both qualitatively and quantitatively with sporadic AD. The extent to which PSEN1-mutant familial AD informs the pathogenesis of sporadic AD appears to differ as a function of mutation.

10

Identification of SERPINA3High Astrocytes subtypes as a potential modulator of amyloid pathology in Alzheimer's disease

M Taga [1], D Bennett [2], L Duquesne [1], B Karaahmet [1], H Klein [1], A Kroshilina [1], A Sigalov [1], C Yung [1], Y Zhang [1]; [1] Columbia University Irving Medical Center, [2] Rush University

Background: To address the need for identifying specific targets to modulate the progression of Alzheimer's disease pathology (AD), it is essential to characterize genes that are not only expressed by particular cellular subtypes but are also physically associated with the pathology. In this study, we employed various spatial techniques in different systems such as human post-mortem tissue and zebrafish models to identify potential target genes involved in the progression of amyloid pathology.

Methods: Spatial transcriptomics combined with immunofluorescence was performed on the dorsolateral prefrontal cortex of 15 AD and two non-AD subjects to characterize cellular signatures in the neuritic plaque microenvironment. The identified targets were validated at single-cell resolution at the protein level through immunofluorescence staining by segmenting 64,753 astrocytes across 20 AD subjects. Their association with amyloid pathology was further validated in CSF (n= 259 and n=800).

Results: Within the 263 neuritic plaques detected, a total of 182 plaque-associated genes were identified within a 150 µm radius of the neuritic plaques. GFAP and SERPINA3 were both upregulated within the neuritic plaque niche. These findings were validated at the protein level using immunohistochemistry with an automated segmentation pipeline in whole brain sections revealing an increase of SERPINA3High GFAPHigh astrocytes near the neuritic plaques. The increase in SERPINA3 expressed was observed in the CSF in association with Aβ1-42, and in AD individuals. Elevated SERPINA3 expression by astrocytes was also detected near amyloid deposits in the zebrafish model.

Conclusions: We identified SERPINA3High GFAPHigh astrocyte subpopulation as a potential contributor to the formation of the neurotoxic microenvironment using unbiased approaches. Its association with pathology was validated across various systems. This is a crucial step in understanding cellular networks and designing targeted therapeutic approaches.

11

Characterization of the ischemic penumbra using MRI and 3D histology: Proof-of-principle case analysis

R Nanjappa [1], A Ayyappan [2], R Verma [2], J Jayakumar [2], K Ram [2], R Rangaswami [3], M Sen [4], R James [4], A Manesh [4], G Varghese [4], D Nauen [5], R Folkerth [6], M Sivaprakasam [7]; [1] Sudha Gopalakrishnan Brain Center, Indian Institute of Technology, Madras, [2] Sudha Gopalakrishnan Brain Centre, Indian Institute of Technology, Madras, India, [3] Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India, [4] Christian Medical College, Vellore, Tamil Nadu, India, [5] Johns Hopkins University School of Medicine, Baltimore, MD, USA, [6] Icahn School of Medicine at Mount Sinai, New York, USA, [7] Indian Institute of Technology, Madras, Chennai, India

Background: Ischemic stroke remains a significant cause of morbidity and mortality, with limited rational therapeutic options, despite extensive modelling in experimental animals. Translational progress will require better cellular characterization directly in human tissue, particularly of the ischemic penumbra as potentially "salvageable" in the acute and subacute clinical setting. In this study, we present a comprehensive multimodal approach employing premortem and postmortem MRI for definition of the ischemic core and penumbra, followed by whole brain histology.

Methods: The specimen (69-year-old man with COVID-19 and a 20-day course of multiple strokes) was fixed, cryoprotected in graded sucrose, and sectioned at 20 µm, with serial standard stains and immunohistochemistry for HIF1α, fibrinogen, CD68, GFAP, collagen 4, and CD34.

Results: Based on gross examination, block face imaging and H&E staining, different regions of interest were identified for comparative analysis: (a) cortical region with subacute ischemic infarct core and penumbra (confirmed on MRI), with focal reperfusion haemorrhage; (b) focus of cortical region with spongiosis and acute neuronal changes; and (c) cortical regions without apparent ischemia. Digital 3D reconstruction of scanned histological sections enabled mapping of cellular changes across neuroanatomical regions. For the subacute infarct, the core was devoid of intact neurons and GFAP+ glia, and of CD34+ and collagen 4+ microvessels, but was densely infiltrated by CD68+ macrophages, as anticipated. In the peri-infarct (penumbral) regions, clasmatodendrosis (fragmented glial processes) accompanied perivascular fibrinogen deposition (blood-brain barrier insufficiency). The subacute infarct penumbra, the acutely ischemic occipital cortex, and, surprisingly, some "normal-appearing" cortical regions were notable for clear HIF1α immunoreactivity of neurons, glia, and even vascular wall cells.

Conclusions: We propose that our multimodal-multiscale approach bridges neuroimaging with neuropathology, offering novel insights into the spatial and temporal progression of ischemic stroke including the penumbra and "normal-appearing" areas, potentially amenable to therapeutic intervention. Additional cases are currently in process in our laboratory.

12

Spatial proteomic and plasma biomarker analyses in mixed pathology cases.

J Walker [1], A Ehrenberg [2], E Daoud [3], P Shang [3], C De Sanctis [1], V Flores Almazan [1], K Laborc [1], E Thorn [1], S McQuillan [1], L Chiu [1], Q Hossain [1], J Parker-Garza [4], M Gonzales [5], C White [3], T Richardson [1], T Kautz [4]; [1] Icahn School of Medicine at Mt. Sinai, [2] UC San Francisco, Berkeley, [3] UT Southwestern, [4] UT Health San Antonio, [5] Cedars-Sinai Medical Center

Background: Alzheimer's disease (AD) and primary age-related tauopathy (PART) commonly display co-pathologies, such as cerebrovascular disease (CVD), Lewy body disease (LBD), and limbic-predominant age-related TDP-43 encephalopathy (LATE). Texas Alzheimer's Research and Care Consortium (TARCC) participant post-mortem tissue and ante-mortem plasma were analyzed to assess the correlation between various pathologic changes and plasma biomarkers. Spatial proteomics was also performed to investigate the proteomic profiles of these pathologies and how comorbidities may affect the proteome.

Methods: Using the Quanterix HD-X platform, plasma levels of p-tau T181, p-tau T217, NfL, GFAP, Aβ-40, and Aβ-42 were measured in TARCC participants with AD, PART, LBD, LATE, CVD and combinations of these pathologies (n=16). P-tau burden in the tissue was quantified using Aperio ImageScope. NanoString's GeoMx Digital Spatial Profiling (DSP) was utilized to examine protein expression in and around neurons, neurofibrillary tangles, and TDP-43+ inclusions in the frontal neocortex, hippocampus and locus coeruleus, as well as in and around diffuse and neuritic plaques in the neocortex.

Results: Analyses demonstrated a significant correlation between CERAD neuritic plaque score and plasma p-tau217 levels ($p=0.025$, $r=0.573$). Plasma p-tau217 levels, however, did not correlate with the Braak stage, Thal phase or overall p-tau burden in the frontal neocortex or hippocampus. Spatial proteomics revealed multiple significant protein expression differences between diseases, as well as between inclusion type and region of the brain. These included higher levels of Park5, VPS35 and MAP2 in PART, a positive correlation between P2RX7 and LATE stage ($p< 0.0001$, $r=0.4656$), and an inverse correlation between LC3B and CERAD NP score ($p< 0.0001$. $r=-0.3660$).

Conclusions: In conclusion, we observed differences in proteostasis, neuroinflammation, and autophagy pathways across various disease stages and comorbid conditions. We also found a strong correlation between plasma p-tau217 levels and CERAD neuritic plaque score, but no significant correlation between plasma p-tau217 and Braak stage or Thal phase.

13

Idiotypic-susceptible: a clinically relevant, neurofibrillary tangle subtype of Alzheimer's disease

J Robinson, H Cai, D Irwin, E Lee, N Loh, D Ohm, J Phillips; University of Pennsylvania

Background: Neurofibrillary tangles in Alzheimer's disease (AD) stereotypically spread from the hippocampus to association cortices and then to idiotypic cortices (i.e. primary motor, somatosensory, and visual). Previous studies have reported variable and clinically relevant tangle densities across hippocampus and association cortices, but idiotypic tangle burden is understudied.

Methods: 87 cases with a high level of AD neuropathologic change including amnestic AD (n=37), behavioral variant AD (BV, n=18), corticobasal syndrome (CBS, n=19), and posterior cortical atrophy (PCA, n=13) were assessed for tangle density by digital tau immunohistochemistry in the three idiotypic cortices, three association cortices (middle-frontal, superior-temporal, and inferior-parietal), and two hippocampal sectors (CA1 and subiculum). Using previously reported criteria, interquartile ranges of mean association:hippocampus and idiotypic:association tangle ratios algorithmically assigned cases to mutually exclusive subtypes: hippocampal-sparing, limbic-predominant, idiotypic-susceptible, or typical Braak (remaining cases).

Results: In typical Braak, the hippocampus, association cortex and idiotypic cortex tangle densities were 100±58/mm2 (mean±stdev), 51±31, and 17±9, respectively. Densities in hippocampal-sparing cases were lower in hippocampus (64±33), and higher in association cortex (83±11), while densities in limbic-predominant cases were higher in the hippocampus (136±20) and lower in association cortex (27±8). In idiotypic-susceptible cases, both hippocampus (59±19) and association cortex (25±23) densities were lower, whereas idiotypic cortex densities were higher (24±10). Tangle subtype prevalence differed by clinical phenotype. Typical Braak, hippocampal-sparing, limbic-predominant, and idiotypic-susceptible were 65/11/14/11% in amnestic AD, while BV had more hippocampal-sparing cases with a 50/33/11/6% distribution (Fisher's exact, p=0.06). CBS was commonly idiotypic-susceptible with a 26/5/16/53% distribution (p=0.004), as was PCA with a 31/0/0/69% distribution (p=0.002). Age, disease duration, and sex also differed between tau subtypes.

Conclusions: We report on a novel pathologic subtype of AD. Our results indicate that the idiotypic-susceptible subtype is quantitatively different from the limbic-predominant and hippocampal-sparing subtypes and may have clinicopathological relevance in AD.

14

Uncovering cell-type specific miRNAs in Alzheimer's Disease brains to refine plasma miRNAs candidate AD biomarkers

G Kureli [1], N Umesh Ganesh [2], U Coşkun [3], Y Lee [2], S Burkhardt [3], A Schütz [3], D Krüger [3], S Liu [4], T Park [4], R Pradhan [3], F Sananbenesi [3], Y Huang [4], S Risacher [4], Y Wan [5], L Shaw [5], A Krunic [2], T Mellott [2], J Blusztajn [2], A Saykin [4], K Nho [4], A DeStefano [6], H Lin [7], Q Yang [6], T Pena-Centeno [3], A Fischer [3], I Delalle [2]; [1] Boston University Pathology & Laboratory Medicine, [2] Department of Pathology & Laboratory Medicine, Boston University Chobanian & Avedisian School of Medicine, [3] Department for Epigenetics and Systems Medicine in Neurodegenerative Diseases, German Center for Neurodegenerative Diseases (DZNE), [4] Department of Radiology and Imaging Sciences and the Indiana Alzheimer's Disease Research Center, Indiana University School of Medicine,, [5] Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, [6] Department of Biostatistics, Boston University School of Public Health, [7] Department of Medicine, UMass Chan Medical School

Background: MicroRNAs (miRNAs) are short non-coding RNAs that regulate proteostasis at the systems level and are emerging as potential prognostic and diagnostic biomarkers for Alzheimer's disease (AD). Small RNA sequencing of plasma samples collected at baseline from 847 participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI) revealed miRNAs with changes in the level of expression that correlated with AD diagnosis and helped predict the conversion from early mild cognitive impairment (MCI) to AD. Additionally, some miRNA levels were significantly associated with A/T/N positivity. Pathway enrichment analysis of genes targeted by miRNAs associated with the conversion of MCI to AD revealed involvement of synaptic function, lipid metabolism, and stress response pathways.

Methods: To validate candidate miRNA biomarkers and explore the relationship between brain and plasma miRNA signatures, small RNA sequencing was performed on 3-5 longitudinal plasma samples, before and after AD diagnosis, and on cortical cells obtained from postmortem brains of 23 individuals from the Framingham Heart Study (FHS). They comprised 12 "true controls", i.e. brains without pathological changes associated with any of the neurodegenerative diseases (NDs), and 11 "pure" AD cases, Braak stages 3 – 6, without other NDs pathologies present. Small RNAs including miRNAs were extracted from ~ 4,000 cortical cells (per cell-type), individually dissected from cryosections of prefrontal and hippocampal cortices via laser capture microscopy.

Results: This approach allows for correlative FHS phenotypic analyses and the validation of AD miRNA signatures obtained in ADNI samples, as inherent differences between cell types and cortical regions may differentially contribute to miRNAs expression changes during AD progression.

Conclusions: By integrating cortical cell type-specific miRNA signatures with small RNA

sequencing of plasma samples, this study provides a comprehensive characterization of miRNA profiles during AD progression while offering insights into yet-unknown pathogenetic mechanisms critical for the development of disease-modifying therapies.

15

Neurons accumulate disease-specific somatic deletion mutations across tau pathologic states in Alzheimer's disease

M Miller [1], B Jin [2], K Brown [2], D Smirnov [2], S Naik [2], S Kirkham [3], E Hennessey [2], M Frosch [4], D Oakley [4], B Hyman [4], A Huang [3]; [1] Brigham and Women's Hospital, Harvard Medical School, [2] Brigham and Women's Hospital, Harvard Medical School, [3] Boston Children's Hospital, [4] Massachusetts General Hospital

Background: Tau deposition in neurons marks Alzheimer's disease (AD) neuropathology and progression, suggesting that tau may directly damage cells and drive cell death. In advanced AD, somatic mutations accumulate in the genomes of neurons, with features that suggest deleterious effects on cellular function.

Methods: To examine the relationship between tau deposition and genomic somatic mutation within individual cells, we developed a method to isolate single neurons according to tau pathology, based on hyperphosphorylated tau (P-tau). We then performed single-cell whole-genome sequencing (scWGS) on P-tau+, P-tau-, and tau-agnostic neuronal nuclei from 7 individuals with AD, as well as nuclei from 15 neurotypical control individuals. We also evaluated regional protein deposition with immunohistochemistry (IHC).

Results: We found that both P-tau+ and P-tau- neurons accumulate somatic single-nucleotide variants (SNVs) in AD, above neurotypical controls, commensurate with tau-agnostic AD neurons. Mutational signature analysis showed that each group of AD neurons exhibited accumulation of AD-related Signature C, indicating common upstream mutagenic mechanisms. Evaluating for somatic insertion and deletion (Indel) mutations, we observed a novel pattern in AD neurons, a pronounced increase in somatic Indels over the levels present in control neurons, primarily comprised of two-basepair deletions. AD neurons of all three groups accumulated two-basepair deletions at substantially elevated rates, regardless of P-tau accumulation. Finally, IHC showed that AD neuronal somatic mutation rates are associated with global pathology, in contrast to single-cell tau pathology.

Conclusions: Our results suggest that tau pathology, the most prominent hallmark of AD, occurs independently of somatic mutation. Tangle-free neurons are as susceptible as tangle-bearing neurons in AD brain to somatic mutations. Nonetheless, somatic mutation accumulation correlated with global pathologic patterns in AD, indicating that other non-tangle actors drive somatic mutation, while tangles may not be inherently genotoxic. We also discovered a novel somatic deletion pattern, which is shared across multiple neurodegenerative diseases.

16

Histological and single cell analysis of human iPSC-derived APPV717I neurons after long-term engraftment in the mouse brain

G Hargus, P Gaur, J McInvale, C Ayers, R Kang, P Upadhyayula, A Sproul, P deJager, P Canoll, V Menon; Columbia University

Background: Alzheimer's disease (AD) is the most frequent form of dementia affecting millions of people without a cure, and disease mechanisms are still not fully understood.

Methods: Here, we applied a human-to-mouse xenotransplantation approach to assess histological alterations and changes in gene expression in human induced pluripotent stem cell (iPSC)-derived AD neurons at 2 and 12 months post injection into the mouse forebrain in comparison to transplanted control neurons.

Results: We differentiated human iPSCs carrying the familial AD APPV717I mutation into neurons, which demonstrated enhanced Aβ42 production, elevated phospho-tau, and impaired neurite outgrowth in vitro. After injection into the forebrain of immunocompromised mice, APPV717I and isogenic control neural progenitor cells differentiated into NeuN-positive neurons representing about 90% of cells in both APPV717I and control grafts at 2 months post injection. 12 months after injection however, APPV717I grafts were significantly smaller and contained an increased number of phospho-tau-positive neurons. We performed comparative single-nucleus RNA-sequencing of microdissected APPV717I and control grafts at 2 and 12 months post injection, and found shifts in the cellular composition of grafts with an enrichment of cell death pathways in APPV717I neurons at 12 months post injection, which were not seen in control neurons at that time point or in APPV717I neurons 2 months after injection.

Conclusions: These data give important insights into transcriptional dysregulation in human APPV717I neurons linked to cellular vulnerability in vivo and provide a unique opportunity to study potentially beneficial effects of therapeutic compounds in this xenograft disease model.

PLATFORM 3: Tumors: Glial 2

17

The clinical value of histopathological and molecular metrics in pediatric ependymoma - data from the ACNS0831 trial

D Ellison [1], A Onar-Thomas [2], J Dalton [2], S Lensing [2], R Tatevossian [2], N Chambwe [2], P Blackburn [2], N Foreman [3], A Smith [4]; [1] St. Jude Children's Research Hospital, [2] St. Jude Children's Research Hospital, [3] Children's Hospital Colorado, [4] Orlando Health-Arnold Palmer Hospital

Background: The ACNS0831 Children's Oncology Group clinical trial enrolled patients from 2010 to 2019 with the primary aim of determining whether post-irradiation chemotherapy offers a survival benefit to children with ependymoma.

Methods: Histopathological metrics to inform grade were collected from tumors of 449 eligible patients, 283 (63%) with a posterior fossa (PF) ependymoma, and 166 (37%) with a supratentorial (ST) ependymoma. A retrospective analysis of molecular group (ZFTA, YAP1, PFA, PFB), H3K27-trimethylation status (PF tumors), and CNVs on chromosomes 1q and 6q (PF tumors) and at the CDKN2A locus (ST tumors) was undertaken using methylation profiling, fluorescence in situ hybridization, and immunohistochemistry. Outcome data were used to assess the prognostic value of histopathological and molecular variables.

Results: Of ST and PF ependymomas, 75% and 54% were WHO grade 3, respectively. The rest were WHO grade 2 ependymomas; there were no subependymomas. Grade was significantly ($p < 0.01$) associated with event-free and overall survival in all patients with a gross total resection. Molecular group was established in 422/449 (94%) of cases. Most ependymomas were classified by methylation profiling as PFA (59%), followed by ZFTA (31%), PFB (8%), and YAP1 (2%). A relatively good outcome was associated with PFB tumors, when compared to ZFTA and PFA tumors. Gain of 1q and loss of 6q were associated with a worse outcome among PF and PFA tumors, but homozygous deletion of CDKN2A was not an adverse prognostic factor among ST tumors. Utilizing the histopathological and molecular variables of PF ependymomas, it was possible to create tumor risk-groups with significantly different outcomes. However, ST ependymoma molecular markers did not carry prognostic value.

Conclusions: This is the first clinical trial of new therapeutic approaches for intracranial ependymoma that has prospectively collected tissue for molecular analysis. Data suggest that histopathological and molecular variables can be used in future trials for therapeutic stratification.

18

Mapping the transcriptional landscape of glioblastoma in spatial context at single cell resolution

C Mount [1], D Gerovasilis [1], A Greenwald [2], S Kovatsis [1], J Lu [1], M Suva [1], I Tirosh [2], Z Wen [2];
[1] Massachusetts General Hospital, [2] Weizmann Institute

Background: The diffusely infiltrative growth pattern of glioblastoma (GBM) is a major obstacle to effective therapy. The many patterns of invasion that have been recognized histologically in GBM are influenced by a complex, heterogeneous local microenvironment. While single cell RNA sequencing has reshaped our understanding of GBM heterogeneity and uncovered phenotypes of many cellular populations in these tumors, the spatial context of this heterogeneity could not be assessed with earlier technologies. By contrast, spatial transcriptomics platforms have the potential to map this transcriptome-wide information in preserved spatial context.

Methods: We recently reported the use of spatial transcriptomics to uncover global architecture in GBM and showed that hypoxia represents a key organizing feature of GBM heterogeneity. However, the limited resolution of this platform precluded assessment of whole-transcriptome features at truly cellular resolution. In this work, we now present our findings utilizing the next generation of this technology and showcase the ability to map whole transcriptome data in spatial context at true single cell resolution in primary patient GBM samples.

Results: We explore heterogeneous GBM phenotypes in the context of GBM spatial microarchitecture. Using copy number inference, we demonstrate the ability to assess clonal heterogeneity in spatial context and map the pattern of invasion of unique GBM clones. Finally, we discuss our progress to discover organizing principles guiding the patterns of GBM cell invasion.

Conclusions: Taken together, we demonstrate the potential of single cell spatial transcriptomics to advance our understanding of the GBM microenvironment and uncover the biology driving the aggressive infiltrative growth of this disease.

19

Observation of SOX2 expressing tumor cells invading within the corpus callosum at autopsy in glioblastoma patients

A Winiarz, S Bobholz, A Lowman, S Duenweg, B Nath, B Chao, F Kyereme, M Mirzaei, D Kim, J Connelly, E Cochran, J Jacobsohn, E Mrachek, P LaViolette; Medical College of Wisconsin

Background: Sex-determining region Y-box 2 (SOX2) is a transcription factor that regulates pluripotency and is highly expressed in glioblastoma (GBM). GBM is highly invasive and spreads along white matter tracts, including the corpus callosum (CC). Magnetic resonance imaging (MRI) is used to monitor GBM, but recent studies suggest that contrast enhancement (CE) fails to accurately depict true tumor extent, as GBM cells infiltrate well beyond seen on conventional scans.

Methods: This study investigated the hypothesis that non-enhancing GBM spread across the CC would be present and visualizable as SOX2-positive cells (SOX2+) in autopsy samples from GBM. Inclusion criteria required patients to have an MRI within 30 days of death. Large-format tissue samples were collected from pathologically confirmed GBM patients that underwent standard of care (n=8). Samples were paraffin-embedded, stained with H&E and SOX2 immunohistochemistry, and digitized at 40x. ROIs were manually drawn on T1C to define the corpus callosum. SOX2 tissue samples were non-linearly warped to MR space and compared to regions of contrast enhancement (CE) on T1C and FLAIR hyperintensity.

Results: SOX2+ were identified in all patients within the CC. Three patients had CE in the CC seen on T1C, while five did not. Interestingly, SOX2+ cells were present regardless of CE. Additionally, visualized FLAIR hyperintensity varied within the CC, with two patients showing no hyperintensity, three with some hyperintensity, and three with hyperintensity within the whole CC.

Conclusions: Future studies will quantify the distance and direction of SOX2 expressing stained cells from the CC to determine tumor extent. Additional samples from surrounding areas could provide more insights into cell migration patterns, taking note of whether tumor spread occurs along white matter tracts. SOX2 has the potential to serve as a histological marker for tumor cell invasion, however, further investigation is warranted to determine its reliability.

20

Loss of Rb immunoreactivity correlates with RB1 mutation status across central nervous system neoplasms

S Rajan [1], K Pham [2], C Dampier [1], T Zaikos [3], C Eberhart [2], D Nauen [2], M Morris [2], C Ho [2], R Xian [2], J Dudley [2], C Gocke [2], J Eshleman [2], M Lin [2], Y zou [2], D Kamson [2], D Mukherjee [2], V Croog [2], C Bettegowda [2], M Holdoff [2], S Sahebjam [2], J Rincon-Torroella [2], M Sherief [2], K Schreck [2], C Lucas [2]; [1] Johns Hopkins Hospital/ National Institutes of Health, [2] Johns Hopkins Hospital, [3] UC Irvine

Background: CDK4/6-RB pathway alterations are implicated in high-grade nervous system tumor proliferation and progression, and approximately 10% of glioblastomas are associated with inactivating RB1 alteration. A subset of other nervous system neoplasms harbor inactivating RB1 alterations as oncogenic drivers, including retinoblastoma, pineoblastoma, and the newly proposed entity high-grade glioma with pleomorphic and pseudopapillary features (i.e. HPAP). While molecular assays including next-generation sequencing can detect these alterations, Rb immunohistochemistry may serve as a potential surrogate in the initial workup of diagnostically challenging cases and across countries where access to molecular testing is limited. We hypothesize that Rb protein expression will be reduced in cases harboring inactivating RB1 mutations.

Methods: Immunohistochemistry was performed on formalin fixed paraffin embedded sections. Next-generation sequencing analysis was performed on all cases. Nuclear expression of Rb was assessed and scored as either retained or lost, and the extent of loss was also correlated with RB1 mutant allele frequency.

Results: We identified 8 cases of central nervous system neoplasms with RB1 alterations. These included 1 high grade glioma NOS, 1 IDH-mutant astrocytoma, and 6 IDH-wildtype glioblastoma (4 of which interestingly harbored a primitive neuronal component). Of the 7 cases harboring a nonsense mutation, 7/7 (100%) demonstrated loss of Rb immunoreactivity in a proportion of tumor cells roughly equivalent to the RB1 mutant allele frequency. The one IDH-mutant astrocytoma with retained Rb immunoreactivity harbored a VUS RB1 p.K63_D68delinsN mutation. For comparison, we identified 14 central nervous system neoplasms with intact RB1 alleles, and all 14 cases demonstrated retained Rb immunoreactivity.

Conclusions: Rb immunohistochemistry can potentially be used across central nervous system neoplasms to prospectively identify cases harboring RB1 truncating mutations. This information may be helpful in generating a differential diagnosis for cases where RB1 status is diagnostically relevant. Further validation in a larger cohort of central nervous system tumor types is in process.

21

MTAP Outperforms p16 as Surrogate Marker for CDKN2A Status in IDH-mutant Astrocytomas

R Multz, M Sukhanova, M Mejia Bautista, H Smith, P Jamshidi, C Horbinksi, J Ahrendsen; Northwestern University, Feinberg School of Medicine

Background: The 2021 WHO Classification of Tumors of the Central Nervous System integrates histology and ancillary molecular/cytogenetic testing into its grading schemes. Homozygous deletion of cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B) is sufficient to increase the WHO grade of IDH-mutant astrocytomas to WHO Grade 4, irrespective of histologic findings. We hypothesize that immunohistochemistry (IHC) for p16 (the conditionally expressed product of CDKN2A) and/or MTAP, a constitutively expressed gene adjacent to CDKN2A, could serve as reliable surrogates for CDKN2A/B status in IDH-mutant astrocytomas.

Methods: A cohort of 121 IDH-mutant, 1p/19q-intact astrocytomas with confirmed CDKN2A status by chromosomal microarray (OncoScan) was stained with IHC for p16 and MTAP. Three independent scorers (JTA, CH, RAM), blinded to the CDKN2A status of the tumors, evaluated the percentage of positive tumor cells for each marker. The scores were then correlated to OncoScan results with an arbitrary IHC cutoff of < 10% indicating potential homozygous loss.

Results: MTAP IHC showed 100.0% specificity and 93.6% negative predictive value for homozygous CDKN2A loss in tumors with < 10% staining. p16 IHC in these tumors showed a lower specificity (78.6%) but a slightly higher negative predictive value (95.3%). The sensitivities and positive predictive values for MTAP and p16 were 61.1%/100.0% and 77.8%/38.9%, respectively. No consistent cutoff was identified in tumors with hemizygous loss.

Conclusions: Our results suggest that MTAP IHC has high specificity and negative predictive value for CDKN2A status in IDH-mutant astrocytomas, meaning the presence of retained MTAP staining strongly suggests that there is no homozygous loss of CDKN2A. Additional testing may be unnecessary in these tumors. In agreement with previous studies, retained p16 is less specific. In cases with heterogenous staining, or when p16 and MTAP show discrepant staining, additional testing should be pursued for accurate tumor grading and prognostication.

22

Histopathological and Molecular Heterogeneity of Novel Adult High-Grade IDH-wildtype Glioma Subgroups (HGG_B, HGG_E, and HGG_F)

Y Wang, J Serrano, C Schroff, M Snuderl; NYU Langone Health

Background: Adult-type diffuse gliomas are a heterogeneous group of CNS tumors. In addition to glioblastoma, IDH-wildtype, epigenetic studies have identified novel molecular subtypes. This study investigates the histopathological and molecular features of three novel IDH-wildtype high-grade glioma (HGG) subgroups: HGG_B, HGG_E, and HGG_F, identified through DNA methylation profiling.

Methods: Clinical, pathological, and molecular data were retrospectively analyzed from 24 tumors (2017-2024) and classified as HGG_B, HGG_E, or HGG_F using the Heidelberg DNA methylation classifier. Mutational, copy number, and gene fusion data were obtained from clinical next-generation sequencing (NGS) reports, including NYU Genome PACT (DNA) (n=10), NYU Oncomine (RNA & DNA) (n=6), NYU FusionSEQer (RNA) (n=10), and copy number analysis (CNV) was obtained from DNA methylation (n=24) using the conumee package.

Results: Of 24 tumors, 17 (HGG_F), 5 (HGG_E), and 2 (HGG_B) had male predominance (63%) and average age of 42 years (range: 11-83 years). HGG_F on radiology (n=14) exhibited gliomatosis cerebri-like growth (8/14) or enhancement (9/14), histologically were diffuse gliomas lacking microvascular proliferation or necrosis (16/17), and were all negative for IDH1 R132H and retained ATRX (n=14). The most common driver in HGG_F was a TERT promoter mutation (8/10), and 5/17 HGG_F had +7/-10 chromosome CNV. HGG_E (3/4) had radiation prior to glioma diagnosis. HGG_E histologically showed microvascular proliferation and necrosis (3/4). HGG_F (8/8) and HGG_E (3/3) exhibited no gene fusions. Two HGG_B had MYC and MYC-N amplification, respectively. HGG_F had an average overall survival (OS) (n=3) of 20 months (range: 19-25) and progression-free survival (PFS) (n=7) of 7 months (range: 1-12). HGG_E OS ranged from 5 to 34 months (n=2), with PFS of 8.5 months (n=1).

Conclusions: This study shows that HGG_B, HGG_E, and HGG_F subtypes are characterized by unique histopathological, molecular, and clinical features and may not display classic histological or imaging features of GBM. DNA methylation is required for accurate classification.

23

Second-line treatment duration associated with remote SOX2 positivity in glioblastoma pateints at autopsy

S Bobholz [1], A Winiarz [2], B Chao [2], A Lowman [2], D Kim [2], M Mizraei [2], B Nath [2], S Duenweg [2], M Barrett [2], F Kyereme [2], J Connelly [2], K Mrachek [2], J Jacobsohn [2], E Cochran [2], M Krucoff [2], P LaViolette [2]; [1] Radiology, [2] Medical College of Wisconsin

Background: Following initial surgery, chemoradiation, and eventual tumor recurrence, glioblastoma patients are often introduced to second-line treatments such as bevacizumab (Bev), an anti-angiogenic agent that prevents the tumor from developing new vasculature, and tumor treating fields (TTFields), a worn treatment that uses low intensity alternating electric fields to disrupt mitotic events. This study tested the hypothesis that increased duration of these treatments is associated with distant tumor presence at autopsy, using sex-determining region Y-box 2 (SOX2) staining as a surrogate marker pluripotent tumor activity.

Methods: This study examined autopsy tissue samples (3-5 per patient) collected in line with last imaging prior to death for 23 patients treated with Bev and 15 patients treated with TTFields. These samples were processed and stained for SOX2 positivity, digitized at 40X resolution, and computationally segmented to count the percent of positive cells. Samples were then downsized and aligned to the last imaging prior to death using a control-point based non-linear warping that accounts for shrinkage due to formalin fixation, implemented via custom in-house software. Masks for T1 contrast enhancement (CE) were then drawn, and the furthest point distance from a 25% SOX2 positive region (SOX2+) and the edge of the CE mask was computed.

Results: A significant positive association was observed between Bev duration and furthest SOX2+ distance ($r = 0.579$, $p=0.006$), with a trending positive association between TTFields duration and furthest SOX2+ distance ($r = 0.503$, $p = 0.067$).

Conclusions: These results support the hypothesis that these treatments may be associated with distant tumor invasion. Contrast enhancement is dependent on angiogenic activity to highlight tumor presence, meaning Bev may reduce the capacity for imaging to highlight non-enhancing tumor invasion, and TTFields has been associated with distant tumor recurrence. Therefore, future research into the mechanisms of how treatment impacts the furthest extent of tumor migration is warranted.

24

Two cases of Glioneuronal Tumor Kinase-Fused (GNT_KinF_A) from a Single-Center Experience

E Pai [1], A Viaene [2], M Li [3], M Nasrallah [1], M Santi [2]; [1] Hospital of the University of Pennsylvania, [2] Children's Hospital of Philadelphia, [3] Children's Hospital of Philadelphia

Background: Glioneuronal tumors (GNTs) in children and adolescents are challenging to diagnose due to unique and overlapping histomorphologies. Most GNTs are driven by alterations in the MAPK pathway, with receptor tyrosine kinase (RTK) alterations playing a smaller role. Gene rearrangements, particularly fusions, dominate this molecular landscape and are linked to a younger age of onset and a more indolent clinical course. DNA methylation profiling has identified GNT with kinase fusions (GNT_KinF_A) as a provisional entity. Limited information is available on the radiologic features and clinical outcomes of these tumors.

Methods: Thirty-five adult and pediatric brain tumors with RTK fusions (MET, ROS1, ALK, NTRK1/2/3) diagnosed between 2018 and 2024 were reviewed. Five cases lacked entity-defining histomorphology were analyzed by DNA methylation profiling. Two were classified as GNT_KinF_A with high confidence.

Results: Case #1 was an 11-year-old status-post a right frontal lobe tumor resection 3 years prior at an outside institution and chemotherapy who underwent surgery for a recurrence of a non-enhancing lesion. The tumor was diagnosed as a low-grade glioneuronal tumor with an SPECC1L::NTRK2 fusion. The disease remained stable for seven years before a third resection was performed. The patient is currently tumor-free 10 months post third craniotomy. Case #2 was a 12-year-old with worsening headache, found to have a right parietal solid-cystic lesion with focal nodular enhancement. Craniotomy demonstrated a glial neoplasm with microcystic changes and increased mitotic activity. A SNRNP70::MET fusion was identified. After craniotomy and chemoradiation, the patient remained recurrence-free at 6 years.

Conclusions: Two GNT_KinF_A cases are presented with clinical, radiologic, histologic, and molecular features, contributing to the understanding of this rare entity.

PLATFORM 4: Neurodegenerative: Alzheimer, Other

25

Harnessing Spatially Distinct Microglial Subpopulations as a Novel Approach to Alzheimer's Disease Treatment

A Ardura-Fabregat, ; Columbia

Background: Microglial spatial heterogeneity remains a crucial yet poorly studied question in light of potential cell-directed therapies for Alzheimer's disease (AD). Little is known about the dynamics of spatially distinct microglia states, which are either adjacent or non-associated with the plaque site, and their selective contributions to neurodegeneration in vivo. So far, research has primarily focused on pathology-associated microglia, leaving a gap in understanding how non-plaque-associated microglia function and transition during disease progression.

Methods: To address this gap, we combined novel multicolour fluorescence fate mapping, single-cell transcriptional analysis, epigenetic profiling, advanced immunohistochemistry, and computational modelling. These approaches allowed us to comprehensively characterize the relationship between plaque-associated and non-plaque-associated microglia during neurodegeneration in mice. The integration of these techniques enabled a detailed assessment of spatially distinct microglial states and their molecular features.

Results: In 5xFAD mice, plaque-associated microglia (PAM) arise from non-plaque-associated microglia (non-PAM) through clonal expansion driven by constant recruitment. Notably, only non-PAM respond to peripheral stimuli such as chronic inflammation, which accelerates pathology, boosts clonal expansion, and worsens cognitive impairment—paralleling the disease state of mice six months older. This differential response is linked to their chromatin accessibility: PAM exhibit a restricted state, while non-PAM remain accessible. Furthermore, CSF1R, preferentially expressed in non-PAM, emerges as a therapeutic target; activation with M-CSF markedly reduces amyloid pathology, diminishes clonality, and improves cognition.

Conclusions: This study provides a comprehensive description of the dynamics of spatially segregated microglial states and their distinct molecular features. By revealing the adaptability and regulatory capacity of non-plaque-associated microglia, our findings may open promising new avenues for state-specific therapeutic interventions targeting microglia during neurodegeneration in AD.

26

Machine Learning Quantification of Amyloid-β Deposits in Frontal, Temporal, and Parietal Cortices in a Diverse Cohort with Alzheimer Disease

D Garcia [1], S Rai Sharma [1], N Saito [2], L Beckett [2], C DeCarli [2], D Gutman [3], J Vizcarra [3], D Coughlin [4], A Teich [5], L Garcia [2], D Mungas [1], C Chuah [2], B Dugger [1]; [1] University of California Davis, Sacramento, California, [2] University of California Davis, Davis, California, [3] Emory University, Atlanta, Georgia, [4] University of California San Diego, La Jolla, California, [5] Columbia University, New York, New York

Background: There has been a dearth of Alzheimer Disease (AD) autopsy-based studies including persons who identify as Hispanic. The advent of machine learning (ML) models has accelerated the accurate and scalable quantification of neuropathology. Evaluating more diverse cohorts with ML tools can aid in generalizability, providing deeper phenotyping of the AD neuropathologic landscape.

Methods: We evaluated densities of amyloid beta (Aβ) deposits in non-Hispanic White decedents NHWD (n = 183) and Hispanic decedents HD (n = 90) compiled across three institutions: University of California Davis, University of California San Diego, and Columbia University. Decedents with a final neuropathologic diagnosis of intermediate/high AD were included. A total of 691 Aβ stained slides of frontal, temporal, and parietal cortices were digitized into whole slide images and subjected to a previously published ML pipeline to evaluate grey matter (GM) and white matter (WM) densities (#/um2) of cored and diffuse Aβ plaques, and total cerebral amyloid angiopathy (CAA). Wilcoxon rank sum tests were used to compare HD and NHWD groups.

Results: Examining the entire cohort, parietal cortex had the greatest densities of cored plaques and CAA, followed by temporal and frontal cortices. Densities of diffuse plaques were similar across the three cortices. Log-transformed linear models of neuroanatomic specific ML quantification of Aβ deposits, adjusted for age at death, sex, and center, revealed 1.62-fold higher CAA density in the temporal lobe (95% CI 1.13, 2.32), and lower cored plaque density in the frontal and parietal lobes WM of HD compared to NHWD (0.72 fold (0.56, 0.93) and 0.69 fold (0.52, 0.91) respectively). There were also differences in densities based on center.

Conclusions: This study validates a published pipeline, revealing similarities and differences in Aβ densities in a diverse cohort, aiding in precision medicine approaches for AD.

27

Factors underlying rapid progression and resilience in patients with high-level Alzheimer disease neuropathologic change

T Richardson [1], F Almeida [2], S Rohde [3], L Canbeldek [1], S Hiya [1], C Maldonado-Diaz [1], J Samanamud [1], K Clare [1], C Slocum [1], L Kulumani Mahadevan [1], L Chiu [1], K Farrell [1], J Crary [1], E Daoud [4], C White, III [4], M Gonzales [5], T Oliveira [2], J Walker [1]; [1] Icahn School of Medicine at Mount Sinai, [2] University of Minho, [3] Amsterdam University Medical Center, [4] UTSW Medical Center, [5] Cedars Sinai Medical Center

Background: Although Alzheimer disease neuropathologic change (ADNC) is the most common process underlying cognitive impairment and dementia, there is significant clinical variation among affected individuals. Moreover, other common neurodegenerative processes (including limbic-predominant age-related TDP-43 encephalopathy [LATE], Lewy body disease [LBD], and cerebrovascular disease [CVD]) are often concurrent and may significantly worsen global cognition and negatively impact select cognitive domains in subjects with ADNC, but do not necessarily affect the rate of cognitive decline.

Methods: We evaluated the additive effects of various combinations of LATE, LBD, and CVD on longitudinal neurocognitive decline in a cohort of 1,074 subjects with intermediate- and high-level ADNC using mixed-effects multiple linear regression modeling. We then evaluated a cohort of 586 subjects with high-level ADNC, divided into those with slow progression ("resilient"; n=75), intermediate progression (n=255), and rapid progression (n=256) based on rate of CDR-SB/MMSE decline and final global cognitive performance. Demographic, cognitive, neuropathologic, genetic, and clinical features were evaluated between these groups using univariate and multivariate logistic regression analysis.

Results: The addition of co-morbid neuropathologic processes further impaired cognition in subjects with ADNC but did not hasten the rate of decline in this study. Subjects with slow progression were significantly older, more likely to have APOE ε2 alleles, and less likely to have APOE ε4 alleles. They had relatively less severe neocortical p-tau and β-amyloid pathology, and lower LBD pathology. Conversely, subjects with rapid progression were younger, were more likely to have APOE ε4 alleles, had more severe p-tau and β-amyloid pathology and white matter rarefaction, and were less likely to be treated with anticoagulants, ACE inhibitors, anti-hypertensives, statins, and NSAIDs.

Conclusions: These data suggest that resilience and rapid progression in ADNC are impacted by genetics, co-pathologies, the progression of late-stage ADNC pathology, and potentially the treatment of underlying systemic disorders.

28

Factors influencing the spread of early tau pathology in the brain

R Rodriguez Reyes, M Morris, H Guo; Johns Hopkins School of Medicine

Background: Alzheimer's disease is characterized by the aggregation of phospho-tau protein which begins initially in the locus coeruleus in the brainstem. As age progresses, amyloid and tau deposition increases until tau pathology reaches the supratentorial cortex and causes clinical manifestations. However, factors associated with the supratentorial spread of tau are not well characterized.

Methods: We identified 126 people who died at Johns Hopkins under age 65 with no known clinical history of neurodegenerative disease. We performed immunohistochemistry (phospho-tau and amyloid) in multiple brain regions including to determine Braak staging and the presence of amyloid in the cortex and mesial temporal lobe, as well as immunofluorescence (phospho-tau and tyrosine hydroxylase) in the locus coeruleus.

Results: Older individuals were found to have more tau pathology in the mesial temporal lobe and higher Braak staging. Immunofluorescence also showed that phospho-tau was more densely distributed in the locus coeruleus of older patients. Amyloid was also more likely to be present in older individual and was associated with higher Braak staging.

Conclusions: We describe pathology in a large cohort of young patients that died without clinical neurodegenerative disease. In particular, phospho-tau accumulation in the locus coeruleus and higher Braak staging were present in older patients without neurodegenerative disease. Our findings support the previously described hypotheses about the spread of tau pathology in developing Alzheimer's disease. Future directions include genetic analysis of known Alzheimer's risk factors including ApoE and investigating microglial activation in these early affected brain regions.

29

Relationship between histologic neuropathology and RT-QuIC seeding in neurodegenerative and normal brain

A Hiniker [1], D Browne [2], I Peng [2], H Zamore [2], D Smirnov [3], C Shin [2], D Coughlin [4], M Avina [1], D Pizzo [4], A Unapanta [4], A Kraus [2]; [1] University of Southern California, [2] Case Western Reserve University School of Medicine, [3] Harvard Medical School, Mass General Brigham, [4] University of California, San Diego

Background: Real-time quaking induced conversion (RT-QuIC) assays provide a quantitative and sensitive measure of abnormally folded propagative amyloidogenic species ("seeds") including tau and a-synuclein. However, the extent to which these measurements mirror or potentially precede regional histologic neuropathology is largely unknown. Whether and how regional co-pathologies influence seeding also remains an open question. This abstract presents data from multiple ongoing studies related to these questions.

Methods: We used a combination of classical and digital neuropathology, RT-QuIC seeding assays, and quantitative immunostaining on >100 cases ranging in age from 24-104 with a variety of well-characterized neuropathologies, including high and low stage Alzheimer's Disease, Primary Age Related Tauopathy (PART), Parkinson's Disease, normal controls, and cases with more than one pathology. Cases were staged for AD Neuropathologic Change, Lewy pathology, and TDP-43 pathology. Digital pathologic quantification for Abeta, tau and Lewy pathology was performed on a subset of cases. We evaluated a range of neuroanatomic regions including cortical, limbic, and brainstem structures for histologic neuropathology, seeding for tau and a-synuclein, and the presence of specific disease-relevant post-translational modifications (PTMs) including p217, p202/205, and c-terminally truncated tau and pS129-a-synuclein.

Results: We observed frequent and often robust tau seeding and less frequent a-synuclein seeding in neuroanatomic regions lacking overt histologic neuropathology, including in individuals in their 30s. Tau seeding appeared to follow but precede Braak staging of tau histopathology. Similarly, a-synuclein seeding appeared to anticipate Braak staging of a-synuclein histopathology. Increasing amounts of co-occurring Abeta histopathology, particularly neuritic plaques, were associated with increasing amounts of tau seeding and tau PTMs in the neocortex.

Conclusions: The combination of histologic neuropathology and RT-QuIC provides insights into neuroanatomic and age distribution of tau and a-synuclein seeds. Analysis of co-occurring pathologies raises the question of synergistic effects of Abeta on tau seeding and PTMs and suggests that not all seeds are equivalently pathogenic.

30

Spatial Transcriptomic Insights into Neurodegeneration: pTDP-43, Synuclein Gamma, and Immune Modulation

A Gonzalez [1], S Kazempour Dehkordi [2], C Corbett [2], K Clarke [2], M Dopler [2], B Danner [2], S Babu [2], J Parker-Garza [2], A Ghaseminejad-Bandpey [2], M Keating [2], M Alhneif [2], K Bieniek [3], S Seshadri [2], S Etemadmoghadam [2], H Zare [2], M Flanagan [3]; [1] Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA, [2] Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA, [3] Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA; Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA.

Background: Phosphorylated trans-active response DNA-binding protein 43 (pTDP-43) is a pathological hallmark of several neurodegenerative diseases, including Limbic-predominant Age-related TDP-43 Encephalopathy and Amyotrophic Lateral Sclerosis (ALS). Other Proteins have been observed to interact with TDP-43, potentially leading to diverse effects, some of which might be protective. This study explores the relationship between pTDP-43, neuronal integrity, and gene expression patterns using spatial transcriptomics.

Methods: We conducted 10X Visium spatial transcriptomic analysis on formalin-fixed paraffin-embedded hippocampal sections from two cases obtained from the Biggs Institute Brain Bank. Both cases exhibited low Alzheimer disease neuropathologic change. Coexisting pathologies, such as alpha-synuclein, were excluded in the hippocampal region. Following data normalization, expression-based clustering revealed eight distinct clusters. The MAST tool identified differentially expressed genes between the cases. Validation was performed using multiplexed immunofluorescence with cell-specific markers, pTDP-43 (pS409/410), and γ-Synuclein, followed by additional validation using publicly available datasets from the National Institute on Aging International Lewy Body Dementia Genetics Consortium Genome Sequencing in Lewy body dementia case-control cohort.

Results: We identified 12 differentially expressed genes, which included 2 neurodegeneration genes, including synuclein gamma (SNCG), and 10 immune system genes, such as complement component 3 (C3). Compared to the control, pTDP-43 correlated with significant, moderate over-expression of neurodegeneration genes and significant under-expression of immune system genes.

Conclusions: Our results suggest that SNCG may be associated with molecular pathways linked to neuronal and synaptic stability in TDP-43 proteinopathies. While the role of SNCG in neurodegeneration is not fully understood, SNCG-positive inclusions have been observed in a variety of neurodegenerative diseases involving pTDP43 pathology, such as Alzheimer’s disease

and ALS. Due to the possible link between pTDP-43 and disrupted axon formations, further investigation into SNCG-associated pathways may offer insights into potential compensatory or adaptive responses in neurodegenerative diseases.

31

Determining the spatiotemporal pattern of T cell infiltrates during the course of Alzheimer's Disease

Y Cheng [1], M Taga [1], V Marshe [2], Y Zhang [2], W Cao [2], S Engel [2], M Fujita [2], T Lama [2], P De Jager [2]; [1] Columbia University Irving Medical Center, [2] CUIMC

Background: Recently, T cells in the central nervous system have attracted significant attention in Alzheimer's disease (AD) research. However, most studies are small and focus primarily on the hippocampus at later stages of AD, and little is known about the roles of T cells throughout AD. To understand the temporal and spatial dynamics of T cell involvement throughout AD progression, we assessed T cell frequencies and phenotypes in aging and AD brains.

Methods: We analyzed T cell frequency in three brain regions affected by AD—prefrontal cortex, posterior cortex, and hippocampus—across all 6 Braak stages. We conducted automated customized segmentation and quantitative analysis of immunofluorescence-stained 389 paraffin-embedded post-mortem brain tissue sections from two brain banks with 115 participants. Furthermore, based on scRNAseq analysis of immune cells from fresh autopsies of various neurological diseases, we characterized the phenotypes and distribution of T cells in their perivascular and parenchymal niches at both proteomics and transcriptomics levels using iterative indirect immunofluorescence imaging and MERscope spatial transcriptomics.

Results: T cell percentage in the grey matter of the hippocampus is higher than that in the other brain regions. Additionally, T cell percentage is increased at Braak stage 5 compared to Braak stages 0/1; while it is reduced in Braak stage 6. This suggests that enhanced T cell infiltration is a relatively late phenomenon limited to the brain region affected early in AD. Many T cells in the parenchyma exhibit tissue-resident traits , while some in the perivascular space are activated CD8+ T cells. The accumulation of granzyme K-secreting T cells and C3 complement activation in AD brains might be associated with microglial inflammation in the brain.

Conclusions: This study contributes to our understanding of the dynamics of T cell prevalence across the course of AD: T cells do not appear to anticipate but rather follow the spread of Tau pathology.

32

Chronic Traumatic Encephalopathy Neuropathologic Change in Military Personnel: Continued Assessment from the DoD/USU Brain Tissue Repository

D Priemer [1], S Abdallah [2], P Smith [2], D Perl [1]; [1] The Uniformed Services University School of Medicine, [2] The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

Background: Military personnel with blast-related traumatic brain injury(TBI) may develop persistent neuropsychiatric sequelae. In 2022, the Department of Defense/Uniformed Services University Brain Tissue Repository (DoD/USU BTR) published an analysis of 225 military brains for chronic traumatic encephalopathy(CTE) and found it was uncommon(4.4%), and infrequently co-observed with examined neuropsychiatric factors. Of TBI factors examined, contact sports history was noted in all CTE cases, and blast had the lowest statistical association with CTE.

Methods: We expand our published data to a current total of 427 military brains(average age, 48.2 years) analyzed for diagnostic CTE pathology, defined by consensus criteria, via blind review of all tau-immunostained cerebral cortical sections containing sulcal depths(average, 13 sections per case).

Results: 27 cases(6.3%) had CTE. The majority were mild, including 9 minimally diagnostic cases with a single CTE pathognomonic lesion. All 26 CTE cases with completed clinical histories involved civilian repetitive impact-TBI exposures, including 25 with contact sports history (relative risk[RR]: 44.6078 [95% CI: 6.1038 to 326.0010, P = 0.0002]) and 15 with civilian impact-TBIs unrelated to sports(RR: 6.28, 95% CI: 3.00 to 13.13, P < 0.0001). 13 CTE cases involved evidence of blast exposure (RR: 1.7872 [95% CI: 0.8630 to 3.7010, P = 0.1180]). CTE was infrequent among the total cases involving psychiatric diagnoses(182), alcohol/substance misuse(196), or suicide(98).

Conclusions: In this update from the DoD/USU BTR, CTE remains uncommon in military brains, and is usually mild. CTE does not appear to be related independently to blast, but rather is overwhelmingly seen in context with civilian impact-TBI exposures, notably contact sports. CTE was also uncommonly coincident with analyzed neuropsychiatric sequelae that were frequent in the series. The opinions or assertions expressed herein are those of the authors and do not reflect the official policy/position of USU, the DoD, or the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc.

PLATFORM 5: Tumors: Nonglial

33

WNT signaling regulates melanoma brain invasion and colonization

K Zhang [1], D Balandin [2], V Wang [2], M Ramos Rocha [2], F Huang [2], C Palm [2], A Carey [2], E Black [2], E Harper [2], R Koya [2], E Kumah [2], J Rincon-Torroella [2], C Eberhart [2], C Lucas [2], A Weeraratna [2]; [1] Johns Hopkins University, [2] Johns Hopkins School of Medicine

Background: Outside the CNS, melanoma cells can dynamically alter between transcriptional states promoting either quiescence or proliferation, thereby modulating invasiveness and therapy resistance. We report that non-canonical WNT signaling through WNT5A promotes melanoma brain invasion and colonization, while reduced WNT5A levels lead to metastatic proliferation in brain tissue.

Methods: We examined modulators of non-canonical WNT signaling in functional studies using human extracranial melanoma cell lines and an organotypic mouse brain xenograft system. Brain cocultures were analyzed via confocal microscopy.

Results: We observed increased proliferation of human melanoma lines in the presence of WNT5A antagonist SFRP1, and reduced proliferation with recombinant WNT5A in culture. Overexpression or pharmacologic induction of WNT5A increased melanoma migration and invasion toward brain explant conditioned media in transwell assays. Xenografting melanoma cells with varying WNT5A expression levels displayed a spectrum of colonization patterns on brain explants, mirroring clinical dormancy or proliferative outgrowth. Melanoma overexpressing WNT5A preferentially formed single-cell dispersions perivascularly, while silencing WNT5A in syngeneic cells produced large proliferative clusters. Exogenous SFRP1 administration shifted WNT5A-high melanoma toward increased tumor size and accelerated tumor appearance. Finally, the intrinsic metastatic potential of invasive melanoma was demonstrated by higher protein expression of cell adhesion molecules (including integrins β1, β5, and α4) that facilitate tumor extravasation when compared to syngeneic WNT5A-silenced melanoma. The invasive cell lines concomitantly yielded a two-fold increase in adhesion to endothelial cell culture and extracellular matrix coating with laminin or collagen IV. The affinity of invasive melanoma to laminin was also recapitulated in ex vivo xenografts, with WNT5A-high melanoma adhering to the endothelial basement membranes.

Conclusions: Our findings indicate that melanoma brain invasion, colonization and proliferation can be regulated by WNT signaling and integrin adhesion. These insights uncover potential therapeutic targets for preventing and limiting melanoma brain metastasis.

34

RNA Sequencing Reveals Novel SYN2::PPARG Fusion in a Subset of Gonadotroph Pituitary Neuroendocrine Tumors (PitNETs)

S Belakhoua [1], G Shen [2], S Subramaniyam [3], D Jones [3], M Snuderl [2]; [1] NYU Langone Health, [2] NYU Grossman School of Medicine, [3] NYU Grossman Long Island School of Medicine

Background: The majority of gonadotroph pituitary neuroendocrine tumors (PitNETs) are clinically silent, manifesting by compression of adjacent structures, and express variably SF1, FSH, and LH on immunohistochemistry (IHC). Gonadotroph PitNETs form a distinct clinical-pathological-molecular entity. However, to date, no known molecular drivers or recurrent genetic alterations have been described for this group.

Methods: We retrospectively analyzed 192 PitNETS diagnosed and treated at NYU Langone Health between 2021-2025. RNA next-generation sequencing by NYU Fusion SEQER using ArcherDx custom panel. Tumors were profiled using clinical DNA methylation analysis and Heidelberg Classifier. Tests were performed as part of the clinical care for PitNETs resected at NYU Langone Health. Confirmatory studies were performed using FISH and Sanger sequencing using custom developed SYN2 and PPARG probes and primers. Clinical and pathological data were retrieved from patients' medical records, including secretion status, outcome data, and IHC for pituitary hormones and transcription factors.

Results: One-hundred-and-four gonadotroph PitNETs, diagnosed by IHC and DNA methylation, underwent Fusion SEQER analysis. Among these cases, 50 (48.1%) showed a fusion between SYN2 and PPARG. No clinical or pathological differences were detected between fusion positive and fusion negative gonadotroph PitNETs in our cohort. By DNA methylation, they were all classified as PITAD_GON with positive scores. Copy number analysis showed a simple profile in these cases. In addition, 88 PitNETs from Pit1 and T-Pit lineages also underwent Fusion SEQER analysis. However, none of them showed the SYN2::PPARG fusion.

Conclusions: SYN2::PPARG fusion is a frequent driver of clinically silent, gonadotroph PitNETs. It is the first recurrent genetic alteration described in gonadotroph PitNETs, affecting approximately half of the cases. SYN2::PPARG fusion has been previously reported in a small subset of small cell neuroendocrine carcinoma. PPARG gene has been previously described to have oncogenic effects in multiple types of cancer. This fusion may represent a potential diagnostic or prognostic factor.

35

Brain Invasion and Other Histological Grade 2 Features in Whorling-Sclerosing Meningiomas

J Houpt [1], A Ahmed [2], I Balki [3], L Ang [4]; [1] Department of Pathology and Laboratory Medicine, London Health Sciences Centre, London, ON, CA, [2] Schulich School of Medicine and Dentistry, [3] Department of Medical Imaging, London Health Sciences Centre, [4] London Health Sciences Centre Department of Pathology and Laboratory Medicine

Background: Whorling-sclerosing meningioma (WSM) is a rare subtype of meningioma characterized by a preponderance of paucicellular collagenous whorls intermixed with fascicles of more conventionally meningothelial cells. These typically lack higher-grade histological features and thus are often assigned a WHO grade of 1. However, the potential for brain invasion, elevated mitotic activity, and other concerning histological findings prompts consideration for higher grade designations, even in this relatively hypocellular variant of meningioma.

Methods: We reviewed all meningiomas diagnosed at London Health Sciences Centre as “sclerosing” or “whorling-sclerosing”, revealing 10 cases total. These cases were split evenly between males and females, with an average age at presentation of 54 years. The more common locations were the frontal convexities (4/10) and the cerebellar tentorium (2/10), with others individual cases located at the cerebral falx, cervical spinal dura, cerebellopontine angle, and within the lateral ventricle.

Results: While most of the cases of WSM (7/10) lacked features of higher grade meningiomas, three demonstrated convincing brain invasion, with one of the cases also featuring elevated mitotic activity (12 figures per 10 high-powered fields), focal hypercellularity and micronecrosis, and prominent nucleoli – findings that would otherwise meet criteria for WHO grade 2. Most notably, one of the brain invading (otherwise benign) WSMs featured invasion by the sclerosed component (as opposed to the meningothelial cell-rich one).

Conclusions: This highlights a potential diagnostic pitfall when encountering this rare meningioma subtype in that, despite its predominant hypocellularity compared to most other meningiomas, higher-grade histological features may still be discerned. Furthermore, brain invasion (which, if unequivocal, is sufficient alone for a diagnosis of WHO grade 2 meningioma) may only be seen in the sclerosed component, necessitating careful examination for accurate determination and grading.

36

Benign Notochordal Cell Tumors with Atypical Features

Z Temerit Kumm [1], M Whisman [2], M Gokden [2]; [1] Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA, [2] University of Arkansas for Medical Sciences

Background: Benign notochordal cell tumors (BNCTs) and chordomas constitute the two main types of notochordal tumors. The most common locations for BNCTs are clivus and sacrococcygeal vertebrae. They are often discovered incidentally on imaging, typically appearing T1 hypointense and T2 hyperintense on MRI. Histologically, they are comprised of sheets of adipocyte-like vacuolated cells. Unlike chordomas, they lack myxoid matrix, cellular atypia, high mitotic activity, bone destruction, intratumoral vascularity, and necrosis; however, some cases can be difficult to classify. Here, we describe two cases of BNCTs with atypical features.

Methods: Cases were identified between 2010-2024 upon searching the department files. Their clinical, radiological, and microscopic findings were reviewed.

Results: Case 1. A 72-year-old woman presenting with abdominal pain was found to have a well-circumscribed, T2-heterogeneous lesion in the sacrum on MRI. Case 2. A 35-year-old woman reporting pelvic discomfort was found to have a T2-hyperintense sacral/presacral bone and soft tissue mass on MRI. Both cases underwent sacrectomy and showed similar microscopic findings with intraosseous and extraosseous components. The intraosseous components consisted of sheets of bland adipocyte-like cells, filling the intertrabecular space, with largely preserved bone trabeculae with some reactive changes. There was extension to extraosseous soft tissues, where the neoplastic cells were embedded in a myxoid matrix. Both tumors were diffusely and strongly positive for pancytokeratin and weakly positive for S-100, EMA, and brachyury. Both cases were diagnosed as BNCTs with atypical features and are free of disease at 19 months and 15 months, respectively.

Conclusions: BNCTs should be considered in the differential diagnosis of metastatic malignancies and chordomas, particularly in small biopsies. Given the histologic overlap, it is crucial to distinguish BNCTs from their more aggressive counterpart, chordomas. The presence of areas with breach of bone and myxoid change suggests possible co-occurrence, continuum and malignant transformation to chordoma, necessitating close follow-up.

37

Improved molecular pathology for assays in meningioma with NICO Myriad system device

G Fernandes [1], O Uchechi [2], K Shade [2], E Kurtz [2], M Franco [3], M Abreu [4], M McDermott [5], K Wu [2], J Otero [5], D Prevedello [6]; [1] Department of Cellular and Molecular Medicine, Florida International University, Herbert Wertheim College of Medicine, [2] The Ohio State University Wexner Medical Center, [3] Florida International University, Herbert Wertheim College of Medicine, [4] Baptist Health South Florida, [5] Florida International University, Herbert Wertheim College of Medicine & Baptist Health South Florida, [6] The Ohio State University Wexner Medical Center & James Cancer Center

Background: Meningiomas are commonly treated through surgery, radiation, or chemotherapy, based on the WHO's classification. Current diagnostic methods based on FFPE samples often fall short of providing precise treatment. However, emerging molecular techniques, such as circular RNA (circRNA) profiling show potential to enhance diagnostic accuracy but are limited by degradation caused by FFPE process. To overcome this challenge, we tested the extent to which the NICO Myriad system enhances tissue preservation. The NICO Myriad system extracts fresh tissue in situ using refrigerator chamber and Ringer's Lactate fluid. This study aims to compare the efficiency of Traditional and NICO protocols for meningioma resection, focusing on circRNA profiles as clinical biomarkers.

Methods: We analyzed 20 tissue samples, collected under identical tumor resection conditions. We performed T-test, linear regression, and hierarchical clustering to compare RNA extraction and sequencing, circRNA detection and profile between protocols. Combat batch effects mitigation, DEseq analysis, and quantile normalization was applied for both protocols to perform circRNAs Differential Expression and Weighted Gene Co-expression Network Analysis (WGCNA) correlated with clinical features followed by GO enrichment.

Results: NICO protocol enhances RNA integrity ($p=0.0023$), yielding a high-quality data (>Q30 median=95%), cleaner reads and bases ($p< 0.01$), with improved GC content, $p< 0.0001$), and reduced variation of circRNA detection and clustering. WGCNA identified two modules correlated with NICO protocol involved with transcriptional and epigenetic regulation and reduced cellular stress, and two modules related with WHO Grade 2 associated with cellular metabolism, and epitranscriptomic regulation.

Conclusions: Notoriously, NICO protocol offers homeostatic environment that significantly improve the precision of circRNA profiling in meningiomas by enhancing RNA preservation, suggesting its potential as a biomarker for personalized prognosis, and treatment. If validated in large cohorts, the integration of circRNA-based profiling into clinical workflows could refine tumor grading, predict patient outcomes, and optimize therapeutic decisions, ultimately improving neuro-oncological care.

38

Survival analysis of brain-invasive otherwise benign meningiomas at a single institution cohort

C Voyles, A Bellizzi, O Lopes Abath Neto; University of Iowa Hospitals and Clinics

Background: Meningioma grading has been evolving over the years. Current 2021 WHO criteria retained brain invasion as a sufficient criterion for a grade 2 classification, but recently published data suggested, not unequivocally, that brain-invasive otherwise benign (BIOB) meningiomas may follow a more benign course than those with additional high-grade features. In this work, we aimed to analyze the survival of BIOB meningiomas in comparison to other meningiomas.

Methods: We established a cohort of meningiomas resected at University of Iowa between 2006 and 2023 and retrospectively analyzed electronic medical records for patient clinical and radiologic data. Microscopic descriptions within pathology reports were used to identify BIOBs, and H&E slides were pulled to confirm brain invasion. Date of first resection and date of radiologic recurrence were used to calculate progression-free survival. Survival curves were estimated using the Kaplan-Meier method, and log-rank test was used to compare survival curves.

Results: We identified 1,043 meningiomas (grade 1 n=692; BIOB n=71; grade 2 n=260, grade 3 n=20). Median progression-free survivals for grade 2 and grade 3 meningiomas were 122 and 40 months, respectively, and undefined for grade 1 and BIOB meningiomas at a maximum follow-up of 16 years. The log-rank hazard ratio for grade 2 vs. BIOB meningiomas was 3.63 (95% CI 2.1 to 5.4, $p = 0.0002$), and was not statistically significant for grade 1 vs. BIOB meningiomas ($p = 0.5766$).

Conclusions: Our data suggests that BIOB meningiomas have improved survival compared to grade 2 meningiomas with additional histological or molecular features, supporting the recent cIMPACT NOW update 8 recommendations to assign grade 1 to these tumors when no high-grade molecular features are present.

39

Concordance of Molecular Testing for Evaluation of High-Risk Molecular Features in Meningiomas

B Crumley, E Russler-Germain, S Dahiya; Washington University in St. Louis

Background: Meningiomas are the most frequent intracranial primary tumor, with three potential grades based on morphology and molecular data. However, the newest cIMPACT-NOW update has further increased the importance of molecular testing for grading meningiomas. Specifically, a meningioma that fails to meet WHO grade 2 criteria morphologically but demonstrates concurrent loss of 1p and 22q on molecular testing is prognostically akin to WHO grade 2.

Methods: This project aimed to investigate the concordance of copy number changes using fluorescence in situ hybridization (FISH) and chromosomal microarray (CMA) testing, given their variable turnaround times, cost, and accessibility across institutions. We reviewed the pathology reports of 51 meningiomas diagnosed at our institution, comparing the results of FISH and CMA testing when evaluating for loss of 1p, homozygous CDKN2A deletion, monosomy 10, loss of 14q, and loss of 22q. Cases where both analyses were not performed for a given target were excluded.

Results: Our analysis showed that CDKN2A loss was the least discordant target, with FISH being discrepant in 3.03% of cases. 22q loss was discrepant in 6.45% of cases, while 1p loss was discrepant in 15.63% of cases and 14q loss was discrepant in 30.30% of cases. Monosomy 10 was the most discordant, being discrepant in 31.25% of cases.

Conclusions: These results suggest that institutional preference for a given molecular platform may directly impact patient care, especially when a result leads to a change in tumor grade. While CMA appears superior to FISH for evaluating meningioma copy number profiles, it may not be feasible in all instances, whether due to lack of insurance coverage, lack of institutional access to CMA, or other factors. Improved FISH probe design, potentially with a larger coverage area, could be a viable alternative that would mitigate this discrepancy.

40

Embryonal Tumor with Multilayered Rosettes: A Single Institution Series of Six Cases

C Takahashi, M Majeed, D Jackson, H Harmsen, W Bell; Department of Pathology and Laboratory Medicine, Indiana University School of Medicine

Background: Embryonal tumor with multilayered rosettes (ETMR) is an exceedingly rare pediatric brain tumor bearing an aggressive clinical course and poor outcome. ETMR comprises the histologically distinct patterns of embryonal tumor with abundant neuropil and true rosettes (ETANTR), ependymoblastoma, and medulloepithelioma as a single entity characterized by shared molecular features, primarily alterations of the chromosome 19q13.42 microRNA cluster (C19MC) and less frequently mutations of DICER1. Herein we report six cases of ETMR to contribute to the understanding of this rare and deadly disease.

Methods: Patients diagnosed with ETMR from July 2021 to November 2024 at our institution were identified. Demographics, clinicopathologic data, radiologic findings, and molecular characterizations were collected and analyzed.

Results: Median age at presentation was 29 months (range: 11-90) with a 4:2 female predominance. Four patients presented with headache and vomiting secondary to increased intracranial pressure. One presented with seizures and one with facial droop and difficulty balancing. Median tumor size was 5.4 cm (range: 2.4-8.3). Location was variable, with four supratentorial, one in the fourth ventricle, and one in the pons. Histologically, most tumors demonstrated embryonal cells forming multilayered rosettes with intervening neuropil. Five cases showed amplification of C19MC by FISH analysis. The sixth case lacked alterations of both C19MC and DICER1 and showed histologic features of ependymoblastoma and medulloepithelioma in addition to mesenchymal features. Ultimately, this case was characterized by DNA methylation profiling and given the diagnosis of ETMR, not elsewhere classified. Posttreatment biopsy was obtained on four patients showing residual disease in three with one additionally showing subsequent neuronal differentiation.

Conclusions: Diagnosis of ETMR is dependent on histologic features and molecular classification. While the vast majority of ETMR cases show the expected alterations of C19MC and to a lesser extent DICER1, a small subset lack these findings. DNA methylation profiling is a valuable tool in such cases.

PLATFORM 6: Neurodegenerative: FTLD/Lewy body/Parkinson, Vascular, Trauma

41

A diagnostic rubric to differentiate LATE-NC Stage 3 from FTLD-TDP

P Nelson [1], R Shahidehpour [1], Y Katsumata [1], D Dickson [2], N Ghayal [2], K Aung [3], X Wu [1], P Phe [1], G Jicha [1], A Neltner [1], J Archer [1], M Corrada [4], C Kawas [4], S Sajjadi [4], D Woodworth [4], S Bukhari [5], T Montine [5], D Fardo [1]; [1] University of Kentucky, [2] Mayo Clinic, [3] Un, [4] University of California Irvine, [5] Stanford University

Background: Limbic-predominant age-related TDP-43 encephalopathy neuropathologic change (LATE-NC) affects >30% of autopsied individuals in advanced old age. Medial temporal lobe structures tend to be particularly vulnerable to TDP-43 proteinopathy in LATE-NC. However, in LATE-NC Stage 3, TDP-43 proteinopathy is present in the middle frontal gyrus (MFG), thus posing a potential diagnostic challenge in distinguishing this entity from frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP). LATE-NC Stage 3 and FTLD-TDP are quite distinct clinically but a diagnostic rubric is required to differentiate between these entities based on pathology.

Methods: We examined LATE-NC Stage 3 cases from the University of Kentucky and Mayo Clinic and from The 90+ Study at the University of California Irvine. Pathologic features of LATE-NC Stage 3 were compared with those of FTLD-TDP and other TDP-43 pathologic entities from additional Mayo Clinic cases. Digital pathology and computational tools were used to quantify pathology burden; these methods were complemented by neuropathologic examinations to evaluate qualitative features such as FTLD-TDP types as well as subtypes of neuronal cytoplasmic inclusions (NCIs).

Results: Focusing on TDP-43 proteinopathy in the MFG and using either digital pathology quantification or a previously-described manual counting method, most cases could readily be classified as either LATE-NC Stage 3 or FTLD-TDP. However, there was a minority of brains with pathologic features that were challenging to assign. These included a subset of FTLD-TDP Type B cases with relatively subtle MFG TDP-43 pathology and another non-LATE-NC, non-FTLD-TDP pathologic entity with extensive MFG pathology. Taking these pitfalls into account, a diagnostic criteria rubric was devised that correctly classified all cases. There was no difference in the Alzheimer's disease pathological load in LATE-NC Stages 2 versus 3.

Conclusions: In a convenience sample from three different brain banks, LATE-NC Stage 3 could be differentiated from FTLD-TDP based on a coherent, data-driven diagnostic rubric.

42

MAPT mutations P301L and R406W are associated with two distinct tau filament folds

B Ghetti [1], M Schweighauser [2], C Qi [2], Y Shi [2], S Lovestam [2], J Murrell [1], A Murzin [2], H Garringer [1], R Vidal [1], S Peak-Chew [2], C Franco [2], S Scheres [2], M Goedert [2]; [1] Indiana University, [2] MRC

Background: Dominantly inherited MAPT mutations cause frontotemporal dementia and parkinsonism linked to chromosome 17 (FTDP-17). Among cases of FTDP-17, tau filament folds have been described in carriers of the MAPT mutations intron 10 +3, intron 10 +16, and □K281. We now report the electron cryo-microscopy (cryo-EM) structures of tau filaments from cases of FTDP-17 with MAPT mutations P301L and R406W.

Methods: For neuropathology, molecular genetics, and cryo-EM studies, we used samples of neocortex from two MAPT P301L mutation carriers belonging to two families and one MAPT R406W mutation carrier. DNA sequencing of exons 1 and 9-13 of MAPT with adjoining intronic sequences was carried out. For histology and immunohistochemistry, 8 □m sections were labelled using antibodies RD3, anti-4R, and AT8 and counterstained with hematoxylin-eosin. For cryo-EM, sarkosyl-insoluble fractions were applied to glow-discharged grids, followed by freezing into liquid ethane at 4° C. Cryo-EM images were acquired on a Titan Krios G2 or G4 microscope operated at 300 kV.

Results: Structural studies carried out using cryo-EM reveal that the R406W mutation gives rise to tau filaments with the Alzheimer fold which consisted of paired helical filaments, with no straight filaments. The P301L mutation gives rise to a novel three-lobed tau fold that resembles the two-layered tau fold of Pick disease. Filaments from the individual with R406W mutation adopt the Alzheimer tau fold and can consist of a mixture of wild-type and mutant proteins. By contrast, filaments of tau from the brains of individuals with the P301L mutation are made only of mutant tau.

Conclusions: The cryo-EM results reported here along with those reported for other MAPT mutations support the view FTDP-17 is not a single disease. It has been shown that the Alzheimer fold occurs in Alzheimer disease and R406W carriers, suggesting that the same fold can result from different pathogenetic mechanisms.

43

Annexin A11 proteinopathy in frontotemporal degeneration and amyotrophic lateral sclerosis

N Ghayal [1], G Sachdeva [2], R Crook [1], S Roemer [1], A Jain [1], W de Coster [3], H Sekiya [1], M DeTure [1], K Josephs [2], R Rademakers [3], M van Blitterswijk [1], D Dickson [1]; [1] Mayo Clinic Florida, [2] Mayo Clinic Rochester, [3] University of Antwerp, Belgium

Background: The molecular basis of FTLD-TDP type C was recently redefined following the discovery that annexin A11 (ANXA11) consistently labeled TDP-43 inclusions, and that both proteins co-assemble into amyloid fibrils. Mixed TDP-43 and ANXA11 proteinopathies were first observed in pathogenic ANXA11 variant carriers with amyotrophic lateral sclerosis (ALS-TDP), characterized by the loss of upper and lower motor neurons (UMN/LMN). Intriguingly, while FTLD-TDP type C is strongly associated with semantic variant frontotemporal dementia (svFTD), variants of clinical or pathologic ALS have been described in FTLD-TDP type C/svFTD patients, including UMN-predominant disease, termed primary lateral sclerosis (PLS), and LMN-predominant disease, termed progressive muscular atrophy (PMA). Notably, ANXA11 proteinopathy has rarely been observed in pure ALS-TDP.

Methods: We investigated the prevalence of ANXA11 proteinopathy in an autopsy cohort of FTLD-TDP (N=171), FTLD-ALS (N=114), and ALS-TDP (N=95) by screening immunohistochemically for ANXA11. Neuronal cytoplasmic and neuritic inclusions were scored semiquantitatively. Further, PLS, ALS, and PMA were defined neuropathologically by semiquantitatively rating UMN and LMN loss.

Results: ANXA11 proteinopathy was rarely observed in pure PLS (1/9), ALS (1/63), and PMA (0/23). Unexpectedly, we observed ANXA11 proteinopathy in most FTLD-PLS cases (34/37) and only a subset of FTLD-ALS (8/49) and FTLD-PMA cases (1/23). Phospho-TDP-43 and ANXA11 inclusions were similarly abundant in all ANXA11-positive FTLD-PLS cases, whereas pTDP-43 inclusions were significantly more abundant than ANXA11 inclusions in remaining ANXA11-positive cases. Two distinct morphologies/distributions of TDP-43/ANXA11 proteinopathy (TAP) were identified in FTLD-PLS cases and were distinguishable from twelve FTLD-TDP type C cases via manhattan distance-based clustering analyses of ANXA11 and pTDP-43 lesions. Clinically, the prevalence of cognitive impairment (relative-risk=2.338;P=0.008) and aphasia (relative-risk=3.306;P=0.046) was significantly different between FTLD-PLS TAP types. No pathogenic ANXA11 variants were identified in this study.

Conclusions: The identification of novel FTLD-PLS-associated subtypes of ANXA11 proteinopathy unrelated to ANXA11 variants broadens the scope of ANXA11 proteinopathy in neurodegenerative disease.

44

Age-Related Prevalences of Parkinson Disease Neuropathological Comorbidities in Comparison to Non-Demented, Non-Parkinsonian Subjects

T Beach [1], C Adler [2], H Shill [3], A Atri [1], I Lorenzini [1], L Sue [1], G Serrano [1]; [1] Banner Sun Health Research Institute, [2] Mayo Clinic Arizona, [3] Barrow Neurological Institute

Background: Coexisting neuropathological comorbidities have been repeatedly reported to be extremely common in subjects dying with dementia due to Alzheimer disease while they have received much less attention when coexisting with Parkinson's disease (PD).

Methods: We have here examined the decadal-wise presence of multiple co-pathologies, and their clinical effects, in a series of autopsies of PD and control subjects from the Arizona Study of Aging and Neurodegenerative Disorders.

Results: Amyloid plaques and Braak neurofibrillary stages greater than IV were present at increasing prevalences with age, reaching 40% for those in their 60s and 85% for those in their 90s. Both plaques and tangles were significant predictors of a lower MMSE score but not of a higher UPDRS motor score. The ApoE4 allele was not an independent predictor of function. Non-AD tauopathies, including progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD), as well as the microscopic changes of argyrophilic grains (ARG) and aging-related tau astrogliopathy (ARTAG), also coexisted with PD, ranging between 20% and 80% across decades; we did not find significant associations of either with final MMSE or UPDRS scores. Limbic TDP-43 histopathology was present together with PD in up to 45% of case but was not predictive of either final MMSE score or final UPDRS motor score. Several cerebrovascular pathologies, including brain infarcts, circle of Willis atherosclerosis, and higher white matter rarefaction score, were common co-pathologies, up to 80%, and were significant predictors of both cognitive and motor impairment. All of the investigated pathology types were common and increased with age in the non-demented, non-parkinsonian control subjects.

Conclusions: The high concurrence rate of the neurodegenerative protein aggregate diseases is suggestive of either a synergistic co-pathogenesis, where one aggregate type may instigate or accelerate another type, or of one or more underlying predisposing physiological or molecular mechanisms.

45

Florbetapir positron emission tomography with autopsy comparison in patients presenting with primary progressive aphasia

P Kakodkar [1], P Jamshidi [2], D Mashoudy [2], D Gutstein [2], T Gefen [2], T Parrish [2], M Mesulam [2], R Castellani [3]; [1] University of Saskatchewan, [2] Northwestern University Feinberg School of Medicine, [3] Northwestern University

Background: Amyloid positron emission tomography (PET) scanning is used as an Alzheimer's disease (AD) biomarker and for treatment monitoring. Florbetapir, a commonly used PET ligand said to bind amyloid-β (Aβ) plaques, is often used in the work-up of patients with cognitive deterioration or consideration for any-Aβ immunotherapy. Primary progressive aphasia (PPA) is an ideal clinical presentation for exploring diagnostic utility of Aβ PET because of distinct pathological phenotypes associated with PPA clinical subtypes.

Methods: We compared Florbetapir PET with autopsy neuropathology in 27 subjects presenting with PPA. Florbetapir PET interpretation was binary – positive or negative. The interval between Florbetapir PET and autopsy examination varied from 1 to 11 years.

Results: 17 subjects had logopenic PPA and advanced Alzheimer's disease pathology at autopsy. Of these, 14 were PET positive. One patient had discrepant results (6 years prior to autopsy). Two subjects were Florebetapir PET negative (6 and 11 years prior to autopsy). Four subjects had frontotemporal lobar degeneration (FTLD)-TDP (3 type C – semantic PPA, 1 type A – agrammatic PPA). Of these, two were Florbetapir PET positive. Six subjects presented with agrammatic PPA and had FTLD-tau at autopsy (including Pick disease, progressive supranuclear palsy, and corticobasal degeneration pathologic subtypes). All of these were PET negative.

Conclusions: . Our findings indicate that Florbetapir is usually but not always PET positive in patients who had pure Alzheimer's disease pathology at autopsy; the negative results might reflect early disease. FTLD-TDP may be associated with false positive results. FTLD-tau pathology was appropriately negative in this series. Discrepant cases are explored in depth.

46

Hypertensive and diabetic pathologic changes in the kidney are associated with specific cerebrovascular changes

E Higginson [1], J Persons [2], R Tashjian [1], N Becker [1], P Jamshidi [3], E Pinarbasi [1], M Gosse [2], P Rastogi [2], K Conway [1]; [1] University of Michigan, [2] University of Iowa Hospitals and Clinics, [3] Northwestern University, Feinberg School of Medicine

Background: Small-vessel brain arteriolosclerosis (B-ASC) is associated with aging, hypertension, diabetes, and cognitive impairment. Hypertension and diabetes have established pathologic correlates in the kidney, which may help clarify the relative contributions of hypertension and diabetes to B-ASC and other cerebrovascular lesions. For example, a hallmark lesion seen in hypertensive nephrosclerosis – arteriosclerosis of medium vessels (MVA) – is less well-described in the brain. We sought to use renal vascular lesions to better understand patterns of cerebrovascular change.

Methods: We performed a retrospective cohort study of full adult autopsies evaluating four standard brain sections and kidney sections independently. Cerebrovascular lesions were scored according to established criteria, and the presence of brain MVA (B-MVA) was documented. Renal MVA (R-MVA) and diabetic nephropathy (DN) were classified in three tiers of severity. Logistic regression was performed using age, R-MVA, and DN as independent variables and B-ASC (moderate/severe vs. none/mild) and B-MVA (present vs. absent) as endpoints.

Results: 118 autopsies were reviewed (mean age = 63 years, range = 23-88). In univariate analysis, B-ASC was associated with increasing age (OR = 1.04, $p = 0.012$), worsening R-MVA (OR: 2.8, $p < 0.01$), and worsening DN (OR: 3.1 $p < 0.01$), although in multivariate analysis with all three parameters, DN showed the strongest association. B-MVA was associated with increasing age (OR = 1.07, $p < 0.01$) and worsening R-MVA (OR = 2.7, $P < 0.01$), but not DN.

Conclusions: These findings help elucidate the comparative systemic associations for cerebrovascular lesions. Diabetes-associated microvascular injury may play a more significant role in the development of B-ASC, while B-MVA is a distinct cerebrovascular lesion more specifically associated with hypertension. It is warranted to further explore the significance of B-MVA as a distinct lesion, including its relative role in cognitive impairment compared to B-ASC.

47

The ENRICH Study: Investigating Neuroinflammatory Signatures of Cognitive and Psychological Health in Traumatic brain Injury

J Opara [1], K Sytsma [1], S Husarik [1], J Jang [1], L Travis [1], T Louangrath [1], B Edlow [2], C MacDonald [1], K Dams-o'connor [3], C Keene [1], A Nolan [1]; [1] University of Washington, [2] Mass General Research Institute, [3] Icahn School of medicine at Mount Sinai

Background: Traumatic brain injury (TBI) is a leading cause of long-term neurological and psychological disability, increasing the risk of cognitive impairment, mood disorders, and neurodegeneration. Despite its clinical impact, the neuropathological mechanisms underlying these deficits remain poorly understood. Emerging evidence suggests chronic neuroinflammation—marked by persistent microglial activation, astrocytosis, blood-brain barrier dysfunction, and synaptic dysregulation—plays a key role. However, the spatial and temporal evolution of these processes across distinct brain networks remains incompletely characterized. This study aims to quantitatively profile neuroinflammatory responses in key networks involved in cognition and emotional regulation.

Methods: Postmortem brain tissue was obtained from brain donors with a history of TBI and cognitive, behavioral, or mixed decline who donated to the University of Washington biorepository. Immunohistochemistry was performed on key nodes sampled across four networks subserving cognitive (Default Mode Network (DMN) and Executive Control) and behavioral (Salience and Limbic networks) function. Whole-slide scanning using Aperio AT2 Scanner and quantitative image analysis using the Halo software assessed microglial (IBA-1) and astrocytic (ALDH1) activation by determining the percent area of staining across the grey matter in these nodes.

Results: Preliminary findings suggest network-specific neuroinflammatory patterns. Individuals with behavioral decline exhibited greater inflammation in the salience and limbic networks, whereas those with cognitive decline showed more pronounced microglial and astrocytic activation in the DMN, particularly in the hippocampus.

Conclusions: Our findings support the hypothesis that chronic neuroinflammation differentially affects brain networks after TBI, potentially contributing to distinct symptom profiles. By integrating immunohistochemistry, transcriptomics, and advanced imaging, we aim to elucidate regional vulnerabilities and mechanisms linking inflammation to neurodegeneration. Future studies should explore longitudinal changes to inform targeted therapeutic strategies.

48

Associations of cardiovascular risk factors with select neuropathologies in a diverse cohort with Alzheimer disease

B Dugger [1], H Wang [1], N Saito [1], L Beckett [1], L Honig [2], C DeCarli [1], R Rissman [3], A Teich [2], D Mungas [1], L Jin [1]; [1] University of California, Davis, [2] Columbia University, [3] University of California, San Diego

Background: Cardiovascular risk factors are implicated in the progression of Alzheimer disease (AD), yet their specific contributions to regional brain pathology in diverse cohorts remain understudied.

Methods: In this study, we examined the relationship between three-level categorizations (absent, active/recent, inactive/remote) of diabetes, hypertension, and hypercholesterolemia, and select neuropathologies in Hispanic and non-Hispanic White decedents with pathologically confirmed Intermediate/High AD from three Alzheimer's Disease Research Centers, having a total of 276 deceased individuals. Semi-quantitative assessments for regional arteriolosclerosis, cerebral amyloid angiopathy (CAA) density, core plaques (CPs), diffuse plaques (DPs), and neuropil threads (NTs) were done adapting scales from established CERAD criteria.

Results: Active diabetes was associated with increased density of frontal NTs ($p< 0.01$), while active hypercholesterolemia correlated with greater density of CAA in temporal cortex ($p=0.04$) and posterior hippocampus ($p=0.03$), as well as temporal CPs ($p=0.03$), as determined by Kruskal-Wallis test. No significant associations were observed between hypertension status and neuropathology. Ordinal logistic regression adjusting for cardiovascular risk factors, ethnicity, sex, age of death, and center confirmed these associations except for CPs in the temporal cortex.

Conclusions: This study underscores the importance of incorporating diverse cohorts in AD research to ensure broader generalizability and shows links between cardiovascular risk factors and AD-related neuropathologies, advancing precision medicine approaches for dementia.

PLATFORM 7: Developmental/pediatric, Methodologies

49

Stillbirth: Associations Between Major Patterns of Placental Pathology and Acquired Neuropathology

A Viaene, J Steele, R Linn; Children's Hospital of Philadelphia

Background: Perinatal brain injury is a major cause of neurodevelopmental disability worldwide. Placental pathology has been implicated as a likely cause of injury to the developing central nervous system (CNS). This study aims to elucidate the associations of multiple placental pathologies and CNS injury, including subtle brain pathologies associated with adverse neurologic outcomes.

Methods: Stillborns that underwent complete post-mortem neuropathologic examination and placental examination were evaluated. Gross images, autopsy reports, and histologic sections from the CNS and placenta underwent blinded reviewed by experts in perinatal neuropathology and placental pathology, respectively. Placental pathology was classified according to the Amsterdam criteria, and all placental and CNS abnormalities were documented. Immunostains useful in highlighting CNS lesions not apparent on routine histology were performed.

Results: Sixty-five subjects (mean gestational age: 30.8±7.4weeks) met inclusion criteria. Different patterns of placental pathology were associated with different types of CNS injury. A previously undescribed association between white matter injury and fetal vascular malperfusion was seen ($p=0.008$), likely due to improved detection of injury on immunohistochemical stains. Amniotic fluid infection was associated with acute neuronal injury in the cortex ($p=0.039$) and cerebellum ($p=0.045$) as well as subarachnoid hemorrhage ($p=0.008$). Hippocampal injury had the strongest association with high-grade chronic inflammation, and maternal vascular malperfusion showed higher relative frequencies of acute neuronal injury in the basal ganglia ($p=0.009$), brainstem ($p=0.107$), and spinal cord ($p=0.064$).

Conclusions: This is the first study to evaluate hemorrhages and CNS injury across multiple regions independently with standardization of placental pathology according to the Amsterdam consensus criteria and immunohistochemistry to improve detection of white matter injury. The pathogeneses of perinatal gray and white matter injury and hemorrhage are distinct and may be influenced by different placental pathologies. Elucidating the placental contributions to these acquired CNS pathologies in stillborns is crucial for understanding long-term adverse neurodevelopmental outcomes associated with perinatal brain injury.

50

Patterns of Non-Acute Fetal Ischemic CNS Injury

Y Fisher [1], P Shannon [2]; [1] Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada, [2] Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Background: Bilateral, symmetrical tegmental ischemic injury (BSTI) is a well-recognized albeit unusual pattern of injury occasionally seen at fetal or neonatal autopsy, but its clinical associations and correlation with other patterns of fetal brain injury, maternal history, autopsy findings and placental pathologies are poorly explored. We have previously noted an apparent association between BSTI and ischemic spinal cord injury (SCI). In this study we explore the associations between BSTI and other late post-encephaloclastic patterns of in utero CNS ischemic injury, and correlate them with systemic autopsy findings, placental pathology and maternal history.

Methods: We identified a series of 48 fetal autopsies with subacute or remote in utero hypoxic ischemic CNS injury. Supratentorial injury was classified in 3 mutually exclusive groups: porencephaly/schizencephaly (P/S), polymicrogyria without P/S (PMG), and other supratentorial (OS). Brainstem injury was recorded as BSTI or non-tegmental injury. Cerebellar and spinal cord injury (SCI) were also recorded.

Results: BSTI was identified in 22 cases. None had P/S. PMG was present in 10, OS in 12, and SCI in 12 cases. In 26 cases where BSTI was absent, 11 demonstrated P/S, 6 demonstrated PMG only, and 9 showed other patterns. None showed SCI. Cerebellar injury was present in 10 cases, 5 with P/S and one with BSTI. The incidence of placental pathology and significant maternal history were similar in the presence or absence of BSTI.

Conclusions: The strong negative correlation between BSTI and P/S and the strong positive association between BSTI and SCI are novel findings. This series suggests two distinct patterns of fetal CNS injury: one with tegmental injury, with or without PMG or SCI, and a second group with porencephalic lesions, with or without cerebellar injury. Clinical history and placental disease in both are similar. We suggest that the severity and temporal course of the ischemic injury possibly determine its late sequela.

51

Generation of a temporal and spatial transcriptomic atlas for motor neuron development

M Rose [1], N Shirooni [1], V Padisetti [1], P Sureshkumar [1], X Yang [1], J Li [1], K Kermani [1], I Whedon [1], A Barroga [1], F Munawar [1], L Nguyen [1], S Thayer [1], A Tenney [2], A Gelber [2], D Creighton [2], F Chen [3], E Engle [2]; [1] University of California Irvine, [2] Boston Children's Hospital, [3] The Broad Institute of MIT and Harvard

Background: Ocular motor neurons (OMNs) in the brainstem mediate eye movement and are differentially affected in some rare congenital neurologic diseases. In cases such as Duane Syndrome, specific OMN subpopulations show disrupted or aberrant innervation while other subpopulations remain unaffected, but mechanisms underlying differential susceptibilities have not yet been identified. Here we generate a transcriptomic atlas to analyze unique gene expression patterns of each developing MN type as a toolbox to help study these disorders.

Methods: We combined multiple mouse genetic reporter lines with intersectional temporal (embryonic days E9.5 to E18.5) and spatial transcriptomics (single cell/nuclei RNA-seq, and Slide-Seq) to isolate and compare eight distinct mouse MN populations: the three oculomotor nuclei (CN3, CN4, CN6) and the other primary MN types (CN5, CN7, CN9/10, CN12 and spinal MNs). Sample integration posed a significant “batch effect” challenge since different types of samples were acquired via multiple methods over many ages. We compared multiple benchmarked high quality integration pipelines to balance batch correction vs. bioconservation. Once cells were identified and labeled we used scDREAMER-SUP, a semi-supervised deep learning algorithm, using cell label annotations as a means to achieve further bioconservation and batch correction.

Results: We built a visualization tool to investigate integration quality. Cell clusters were mapped onto spatial transcriptomic slide-seq samples from E11.5 and E14.5 and compared with developmental mouse atlases to confirm cell identities. Candidate marker genes of each cell population were further validated via database analysis and RNA in situ hybridization. We successfully integrated a developmental time course of mouse MN gene expression from disparate sample types.

Conclusions: The resulting atlas can be transposed to label and identify spatial structures within slide-seq datasets to identify cells in time and space. Overall, this atlas uncovers distinct developmental gene expression patterns and provides new tools to study their differential vulnerability in motor neuron related disorders.

52

White matter injury in the term stillbirth

S Beldick, P Shannon, Y Fisher; Mount Sinai Hospital

Background: Axonal pathology in the form of axonal swelling and amyloid precursor protein (APP) reactivity is common in stillbirths, but its clinical relevance is not always clear.

Methods: To clarify the relationship between white matter injury (WMI) and established neuronal injury (pontosubicular necrosis (PSN)), we characterized the spectrum of axonal injury using APP immunohistochemistry in a series of 30 extensively and systematically sampled term stillbirths, 15 with and 15 without PSN. We categorized WMI by the degree of axonal swelling and its geographic pattern.

Results: In this series, singly scattered reactive, swollen axons were present in all cases and were very widely distributed. Clusters of enlarged reactive axons were present in cases without PSN in the internal capsule and corona radiata in 60% and 25% of cases respectively. When PSN was present, these frequencies increased dramatically to 93% and 42%, respectively. Large patches of enlarged axons were present in 27% (internal capsule) and 17% (corona radiata) of cases without PSN. In PSN, this increased to 64%, and 42%, respectively. In cases without PSN, clusters of enlarged dystrophic axons were absent in the cerebral peduncle (0%), rare in the centrum (9%) and ventrolateral thalamus (7%), and infrequent in the putamen (20%). In cases of PSN, this increased to 27% in the peduncle, 42% in the centrum, and 40% in each of the ventrolateral thalamus and putamen.

Conclusions: Our findings suggest that some degree of axonal injury is ubiquitous in term stillbirths and may not indicate consequential pathology. PSN is associated with WMI that is more extensive and appears more prolonged, suggesting that PSN represents a sub-lethal event that is on average more distant in time and/or more severe than WMI alone. These data form the basis for a targeted approach to the evaluation of perinatal WMI in neuropathologic autopsy.

53

Congenital syphilis with overwhelming leptomeningeal growth of Treponema pallidum

M Del Bigio, E Ferreira, S Kosteniuk, P Rahaman; University of Manitoba

Background: Treponema pallidum (T. pallidum), which causes syphilis, is transmitted by sexual interactions or across the placenta. Congenital syphilis has been recognized for centuries although the role of infection was not known until c1905. Its incidence dropped precipitously with the advent of antibiotics in the 1930s. There are few descriptions of the pathology since the 1950s. In North America, the incidence of syphilis has been climbing since c2013.

Methods: In Manitoba (population ~1.4 million), we undertook a retrospective and prospective analysis of our fetal / pediatric autopsy cases (~150/year) from 1990-2024 inclusive. We reviewed all cases with word variants of ‘syphilis’ or ‘Treponema pallidum’.

Results: Five cases of congenital syphilis were encountered in 2016-19 and 26 in 2020-24. Seventeen were stillbirths 22-39 weeks gestation. Fourteen were infants and children < 18 months age (5 were preterm births < 36 weeks). Among stillbirths, 7/17 had T. pallidum evident on immunostains with overwhelming growth in the leptomeningeal blood vessels and along vascular tracts of the thoracoabdominal fetal viscera (e.g. lungs, liver, spleen, kidneys, adrenals)with very few bacteria in the brain tissue proper or placenta. Notably, there was negligible inflammation; immunostains showed a slight increase in HLA-DR positive meningeal macrophages and very rare to no CD3 positive lymphocytes. There were no obvious brain malformations, with autolytic fragmentation a limiting analytic factor. Most cases had a positive PCR detection on the placental or nares swab. Among the 14 children, all of whom had been treated with antibiotics, none had malformations, detectable T. pallidum, or tissue inflammation. One had coarse perivascular mineralization in the white matter.

Conclusions: We conclude that congenital syphilis is an increasing problem. Vascular infection might contribute to fetal death in spite of insignificant inflammation. If congenital syphilis is suspected, T. pallidum immunostaining of the leptomeninges and/or fetal viscera is a sensitive means of detection.

54

SlideRelabeler: a user-friendly, stand-alone open-source software application for creating deidentified whole-slide images

A Rosado [1], D Gutman [1], T Pearce [2]; [1] Emory University, [2] University of Pittsburgh

Background: Digital pathology adoption is increasing within clinical, educational, and research domains including neuropathology and other subspecialities. Whole-slide images (WSIs) of histologic sections are frequently captured with patient identifiers or other protected health information (PHI) in multiple places: the label image, macro image, and internal WSI file metadata. For educational and research purposes, removing PHI from WSIs protects patients and allows research utilization outside of standard clinical use. Re-digitizing slides with identifiers removed eliminates PHI but requires costly personnel and equipment time. Alternatively, the original files can be manipulated to remove identifiers, but this typically requires proprietary vendor software or software engineering experience.

Methods: To address the need for better WSI deidentification workflows, we created SlideRelabeler, a stand-alone installable application with a user-friendly interface to manage the deidentification process without technical knowledge.

Results: The application combines an Electron-based front-end with a Python back-end that leverages open-source Python packages to support multiple WSI file types: Aperio SVS, Hamamatsu NDPI, Phillips TIFF, and others by lossless TIFF conversion. Configuration options allow output file format customization, including the ability to embed images, text, and QR codes within label images. PHI within the internal slide metadata are redacted with an audit log showing before and metadata views. Finally, the application can be configured to automatically upload deidentified WSIs and associated metadata to a Digital Slide Archive server, streamlining local-to-remote data transfer.

Conclusions: We have created a open-source stand-alone application capable of easily deidentifying WSIs. To streamline workflow, these files and associated non-PHI metadata can be configured to upload to cloud-based file storage solutions or Digital Slide Archive servers.

55

Multicompartment neuroanatomic segmentation of autopsy brain tissue sections using deep learning methodologies

T Pearce [1], L Nadeesha [2], A Neltner [2], M Klusty [2], C Ti [2], M Gokmen [2], J Vizcarra [3], C Cadano [3], N Jaafari [1], S Cheung [2], Q Gu [1], A Tafti [1], C Ozcan [2], C Bumgardner [2], P Nelson [2], D Gutman [3]; [1] University of Pittsburgh, [2] University of Kentucky, [3] Emory University

Background: Neuropathology across many conditions differentially affects subregions of the brain and adjacent tissue compartments. Quantitative analysis of whole-slide images (WSIs) is increasingly used in research and clinical diagnostics, but applying quantitative metrics to an entire WSI is typically less valuable than region-specific analysis, necessitating annotation of regions of interest. Automated tissue segmentation methods reduce the burden of manual annotation work and can help mitigate potential biases introduced by manual processes. I

Methods: In this study, the originality lies in the comprehensive comparison of multiple deep learning-based approaches for automated segmentation of neuroanatomic compartments in whole-slide brain tissue images, offering valuable insights into computational demands, model performance, and practical implementation for large-scale neuropathologic analysis. A training set of 60 neocortical H&E-stained WSIs was hosted on a Digital Slide Archive server to allow remote access. A customized web-based toolkit integrated with a WSI viewer enabled user-friendly annotation of white matter, gray matter, superficial cortex, leptomeninges, background, and artifacts. Semantic segmentation models were trained based on SAM-Path (Segment Anything Model-Pathology), SegFormer, and U-Net architectures. To enable these models to work at a WSI level, a Python-based pipeline was created to assemble annotations of entire tissue sections from inference on individual higher-magnification patches.

Results: Here, we present our comparative experience with these different model architectures, including the computational hardware and time requirements for model training and inference, performance metrics, and examining failure modes. Interestingly, the models could learn to segment tissue more accurately than the coarse annotations provided for certain tissue compartments such as leptomeninges. Despite the imprecision of the training data, models achieved Dice scores of over 0.94 and intersection-over-union scores exceeding 0.88. Inference time varied widely across model architectures, hardware, and level of magnification, ranging from 12 seconds up to 10+ minutes per WSI.

Conclusions: Deep learning can effectively and efficiently segment neuroanatomic structures.

56

3D scanning and printing to improve brain tissue sampling and research

K Bieniek, M Smith, E Ochoa, M Keating, N Honnorat, M Mojtabai, M Flanagan, M Habes, S Seshadri; UT Health San Antonio

Background: Proper brain tissue sectioning is critical for capturing precise neuroanatomical regions as part of routine neuropathology practice. However, freehand brain cutting with an autopsy grossing knife can lead to variability in tissue slab thickness and sectioning plane, particularly for novices. Technologies and protocols that overcome these challenges could improve sectioning standardization within and across brain banks.

Methods: Following tissue fixation, three-dimensional (3D) hybrid-light scanning of postmortem hemibrains was performed using an EinScan H2 scanner for 212 brains in our repository. Postmortem ex vivo magnetic resonance imaging (MRI) was also performed on all hemibrains. For about half of these hemibrains, custom brain cutting tissue matrices were designed and 3D printed with polylactic filament using a Raise3D Pro2 printer. Hemibrains were sectioned and blocked in accordance with standard Alzheimer's disease neuropathological guidelines.

Results: 3D scanning took approximately an hour to complete, generating scan files averaging 1.5 GB (3MF, OBJ). 3D printed matrices averaged 42 hours in print time, consumed an average 340 g of filament, and cost $8-10/print. Superb control and uniform thickness was achieved matrix-cutting infratentorial tissue in a coronal plane. Stereotaxic cutting also improved co-registration with postmortem MRI, facilitating deep learning segmentation and analysis of white matter hyperintensities (Honnorat et al., NeuroImage 2025). Care in cutting speed/consistency as well as ensuring the brain remains stationary within the matrix were identified as issues for further instruction and improvement.

Conclusions: 3D scanning and printing is a cost- and time-effective strategy for improving brain sectioning and sampling efficiency. The enhanced accuracy augmented co-registration with postmortem MRI. 3D object files may also be a useful research and education resource for neuropathology (model segmentation and analysis, virtual reality teaching, etc.). Implementation of 3D scanning and printing by other neuropathology laboratories could improve practice standardization, tissue cataloguing, and occupational safety in brain banks studying different neurological conditions.

PLATFORM 8: Demyelinating/inflammatory, Peripheral Nerve/Muscle

57

Neuropathologic findings in cases of Stiff Person Syndrome and Progressive Encephalomyelitis with Rigidity and Myoclonus

A Denney, A Wohlfert, A Granholm-Bentley, A Piquet, S Guzman; University of Colorado Anschutz Medical Campus

Background: Glutamic acid decarboxylase-65 (GAD65) is a key enzyme that converts glutamate to GABA, particularly crucial for inhibitor signaling in the brain. Stiff Person Syndrome spectrum disease (SPSD) features rare entities with high anti-GAD65 titers and an excitatory motor phenotype, for which neuropathologic characterization has never been carried out. Our hypothesis is that disruptions to GABAergic motor cortex pathways underlie the pathogenesis of SPSD.

Methods: Three pathological evaluations were carried out: one case with classic Stiff Person Syndrome (SPS) and two cases of Progressive Encephalomyelitis with Rigidity and Myoclonus (PERM). Consent for autopsy was obtained through the Rocky Mountain Multiple Sclerosis Center Tissue Bank. Brain tissues were analyzed for neural and glial markers, inflammatory markers, GAD65/67, and parvalbumin by immunohistochemistry and immunofluorescence multiplex staining, and were analyzed by a board-certified neuropathologist.

Results: All patients exhibited histopathologic evidence of disrupted inhibitory neuron function with activated microglial cells within the motor cortex. IBA1 highlighted microglial cells surrounding neurons in layers 4 and 5 of the motor cortex, with only minimal neuron loss. GAD65 highlighted strongly positive microglial cytoplasm with loss of normal GAD65-positive staining of the neurons in the motor cortex. Parvalbumin showed a disrupted pattern of staining, with only scattered positivity compared to normal controls. Immunofluorescence multiplex staining results supported immunohistochemistry results described above. Each case also showed neuron loss within the ventral horn of the spinal cord. Minimal lymphocytes were identified in the brain.

Conclusions: Anti-GAD65 neurologic autoimmunity exhibits an excitatory pathophysiology in the motor cortex of individuals with SPSD. Here we demonstrate for the first time the disrupted inhibitory neuron networks in the motor cortex which provide a novel histological fingerprint for cases of SPSD. Further evaluation may aid in developing biomarkers and therapeutic targets.

58

Uncovering Novel Extracellular Matrix Transcriptome Alterations in Lesions of Multiple Sclerosis

E Stephenson [1], R Jain [2], S Ghorbani [2], R Gorter [2], C D'Mello [2], V Yong [2]; [1] University of Calgary/Alberta Health Services, [2] Hotchkiss Brain Institute and Department of Clinical Neurosciences, University of Calgar

Background: The extracellular matrix (ECM) of the central nervous system (CNS) is an interconnected network of proteins and sugars with critical roles in both homeostasis and disease. In neurological diseases, excessive ECM deposition and remodeling impact both injury and repair. CNS lesions of multiple sclerosis (MS), a chronic inflammatory and degenerative disease, cause prominent alterations of the ECM. The purpose of this research was to investigate the spatial heterogeneity of ECM changes in MS.

Methods: Active and inactive demyelinated lesions from brain tissues from people with multiple sclerosis were investigated with a combination of in-house spatial mRNA-sequencing (2 controls and 3 patients) and publicly available single-nucleus RNA sequencing (5 progressive MS patients and 3 samples of normal white matter from neurologically healthy brains).

Results: The spatial and single-nucleus datasets demonstrated widespread changes in ECM molecules and their interacting proteins, including alterations to proteoglycans and glycoproteins, that varied across different MS lesion types. The greatest differentially expressed ECM members were matricellular proteins, particularly the SPARC family. SPARC had the highest normalized mean expression of any of the ECM members in MS lesion cores. SPARC was elevated in MS lesions compared to control, and SPARC upregulation was greatest in chronic inactive lesions. Immunohistochemistry of MS lesions corroborated the increased expression of SPARC in MS lesions.

Conclusions: Our results highlighted the significant alterations that ECM members undergo during MS, as well as how the ECM differed between the edge and core of chronic active lesions. In particular, one of the greatest altered ECM components was SPARC. Despite being some of the highest altered components, the SPARC family has not previously been described in MS. The profound changes to the ECM in MS lesions deserve more scrutiny as they impact neuroinflammation, injury, and repair.

59

Immune-Mediated Necrotizing Myopathy (IMNM): An Underdiagnosed Entity

M Sharma [1], N Rajput [2], B Jassal [2], A Dhall [2], V Suri [2], V Vishnu [2], R Bhatia [2], S Jain [2]; [1] Department of Neuropathology, NSC, [2] AIIMS, New Delhi

Background: IMNM is a form of idiopathic inflammatory myositis characterized by progressive weakness, notably elevated serum creatine kinase (CK) levels, anti-SRP or anti_HMGCR autoantibodies, and necrosis as a distinctive muscle biopsy feature.

Methods: This is an ambispective study that included 28 IMNM patients diagnosed with muscle biopsy over 6 years. The clinical and histopathological features were reviewed. The antibody profile was done using Euroline immunoblot.

Results: Age of onset varied from 6 to 65 years, with a mean age of 35.5 years and an average duration of illness of 10 months—all patients presented with progressive quadrilateral muscle weakness, which progressed from proximal to distal. Dysphagia was an associated feature in 8 cases, of which 4 showed positivity for anti-SRP antibodies. CPK levels range from 724 U/L to 30000 U/L with a mean of 6436 U/L. Sixteen cases were anti-SRP positive, 5 were HMGCR positive, and six were seronegative. On histopathology, inflammatory infiltrate was either not seen or was sparse except in two cases. MHC 1 was faintly upregulated on myofibres in all cases, and MHC 2 was upregulated upregulation in 15% of cases. C5b-9 showed variable deposition on sarcolemma and endomysial blood vessels.

Conclusions: IMNM is an underdiagnosed entity, given its overlapping features with other inflammatory and non-inflammatory myopathies. Marked myofibres necrosis with sparse or absent inflammation, upregulation of MHC class1, MAC deposits on myofibres, fine granular deposits of p62, and serological markers benefit the diagnosis.

60

Exploring the Connection Between MAST Cells and Symptomatic Pineal Cysts

C Allen [1], T Baker [2], R Norris [2], S Patel [2], C Welsh [2]; [1] Medical University of South Carolina, [2] MUSC

Background: MAST cells (MCs) are one of the most abundant immune cells in the central nervous system (CNS). Their progenitors come from the bone marrow and enter the CNS through the blood-brain barrier (BBB). MCs complete maturation in one of many resident tissues throughout the body, and then proliferation may occur. While maintaining close spatial relationships with vessels, MCs produce inflammatory mediators contributing to endothelial dysfunction and BBB permeability. Those residing close to peripheral nerves modulate neuron excitability, directly causing hypersensitivity and pain. More complex interactions between MCs, meningeal afferent nerves, and dural vasculature are thought to be involved in migraines. CNS MCs reside around the third ventricle—patients with mastocytosis have reported memory changes, dizziness, and headache. Furthermore, patients with pineal cysts have reported similar symptoms. Here, we quantify MCs in symptomatic pineal cysts and normal pineal controls for comparison.

Methods: Our lab performed 1 Hematoxylin and Eosin (H&E) stain and 1 Von Leder (VL) stain on 54 pineal specimens per protocol. They were diagnosed microscopically and then grouped as follows: Group 1: Normal pineal controls (4) Group 2: Symptomatic pineal cysts (50) Pineal parenchymal area (mm2PP) and number of MAST cells (MCs) were determined manually on digital H&E/VL slides (Philips Digital Pathology Solutions). MAST cell density (MCs/mm2PP) was calculated for each specimen. Averages and standard deviations for each group were determined (Group1MEAN/Group1STDEV; Group2MEAN/Group2STDEV).

Results: Group1MEAN: 0.11 MCs/mm2PP Group1STDEV: 0.09 MCs/mm2PP Group2MEAN: 1.35 MCs/mm2PP Group2STDEV: 1.26 MCs/mm2PP

Conclusions: The average parenchymal MAST cell density was higher in symptomatic pineal cysts (1.35 MCs/mm2PP) than in normal pineal controls (0.11 MCs/mm2PP). Increasing sample size, especially the number of controls, may be necessary to determine statistical significance given the unequal variance between both groups (Group1STDEV: 0.09 MCs/mm2PP; Group2STDEV: 1.26 MCs/mm2PP). No conclusions can be made about causality, further RNA and proteomics studies are being conducted.

61

Severe neurotoxic syndrome in six post-solid organ transplant patients on calcineurin inhibitors: Clinical and histopathological features

M Vizcaino [1], D Tajfirouz [1], A Sharma [1], A Madhavan [1], L Eckel [1], S McCarter [1], E Flanagan [1], Y Guo [1], M Toledano [1], A McKeon [1], I Carabenciov [1], D Dubey [1], A Orandi [1], M Bhatti [1], C Schinstock [2], C Kennedy [1], M Leise [1], B Boilson [1], J Chen [1], D Salomao [1], C Giannini [1], R Vaubel [1]; [1] Mayo Clinic, Rochester, MN, [2] Medical Clinic, Rochester, MN

Background: Calcineurin inhibitors (CNIs) are widely used immunosuppressive agents in solid organ transplant. We describe a severe neurotoxic syndrome associated with long-term CNIs (tacrolimus and cyclosporine) use in post-solid organ transplant patients.

Methods: Six patients (three women; median age 62.5 years) developed symptoms mimicking optic neuritis progressing to encephalomyelopathy. Five were on tacrolimus and one on cyclosporine, with a median treatment duration of five years. Despite having normal drug levels and stable graft function, all patients developed bilateral optic neuropathy with vision loss and myelopathy. MRIs at symptom onset showed bilateral optic nerve enhancement and T2 hyperintensity, which later extended to optic chiasm/tracts, brainstem, and spinal cord. Extensive infectious, inflammatory and paraneoplastic evaluation resulted negative.

Results: Optic nerve biopsy from one patient demonstrated severe atrophy with abundant microglia/macrophages admixed with scattered bizarre glial cells, while corona radiata biopsy from one patient showed mild microglial activation. Spinal cord biopsies from three patients showed acute necrosis with variable axonal injury and lymphohistiocytic inflammation. Despite aggressive treatment, three patients who continued CNIs developed disease progression and ultimately died. In contrast, the three who discontinued CNIs showed stabilization of symptoms within 1-3 months. One patient with late drug discontinuation remained clinically stable but died of complications of immobility, while two others showed improved radiologic findings at 12 months. Brain and spinal cord autopsy evaluation performed in 3 patients consistently demonstrated marked optic pathway atrophy with increased microglia/macrophages and bizarre astrocytes, pyramidal tract degeneration, and spinal cord pathology that ranged from severe vacuolar and necrotizing myelopathy, patchy white matter spongiosis, to gliosis without significant axonal injury. No evidence of neoplasm or infection was identified.

Conclusions: This series emphasizes the diagnostic challenge of identifying CNI-associated neurotoxicity and highlights the importance of early recognition and intervention, since prompt drug discontinuation may prevent irreversible progression and improve outcomes.

62

Epineurial perivascular inflammation in peripheral nerve biopsies: a clinicopathologic evaluation

N Becker [1], B Becker [1], J Persons [2], P Jamshidi [3], D Manthei [1], S Stone [1], K Conway [1]; [1] Michigan Medicine, [2] University of Iowa, [3] Northwestern University

Background: Lymphocytic perivascular inflammation (PI) around small epineurial vessels in peripheral nerve biopsies (PNB) – sometimes referred to as "microvasculitis" – has been described in association with various etiologies but has not been evaluated comprehensively. We evaluated the pattern and severity of PI within PNB to determine its clinicopathologic significance.

Methods: We reviewed PNB at Michigan Medicine from 2013-2023 with any reported PI. Slides were evaluated for number of perivascular inflammatory foci (one focus ≥10 lymphocytes), lymphocyte count in the largest focus, and presence of wall invasion. Focus severity and foci density were graded as mild/moderate/severe. Clinical data including biopsy site, diagnosis, serum antibodies, electromyography (EMG) results, and therapy were collected. Binomial logistic regression was performed between pathologic findings and association with axonal loss severity, abnormal sensory response in the affected nerve or multiple mononeuropathies by EMG, unifying clinical diagnosis, and treatment response.

Results: We identified 112 unique PNB (M: 47, F: 65; age at biopsy ranging 24-83 years). The range of perivascular inflammation per biopsy was 0 to 34 foci. Size of the greatest focus ranged from < 10 to 418 lymphocytes, with 18 biopsies (16.1%) having >100 lymphocytes in one focus. The likelihood of vessel wall invasion increased with the number of lymphocytes in a focus (OR=1.2 per 10 lymphocytes; $p< 0.001$). In univariate analysis, density of inflammation was associated with EMG finding of multiple mononeuropathies (OR=2.4, p=0.018), abnormal sensory response in the affected nerve (OR=2.0, p=0.041), and treatment response (OR=2.5, p=0.045). Vessel wall involvement showed no clear associations with any endpoints.

Conclusions: Our findings show no amount of PI, even with wall involvement, clearly associated with a unifying diagnosis of vasculitis. The potential associations of foci density with treatment response and electrodiagnostic abnormalities suggests a greater density of inflammatory foci may indicate an immunologic etiology in a subset of cases.

63

Molecular and Clinical Insights into Calpainopathy (LGMDR1) in India: A single centre experience

A Dhall [1], B Jassal [1], M Faruq [2], U Shamim [3], R Bhatia [1], V Vishnu [1], V Suri [1], M Sharma [1]; [1] All India Institute of Medical Sciences, [2] 2. CSIR-Institute of Genomics and Integrative Biology,New Delhi,India, [3] CSIR-Institute of Genomics and Integrative Biology,New Delhi,India

Background: Limb girdle muscular dystrophy (LGMD) refers to a group of rare, highly heterogeneous, autosomal dominant (AD) and recessive (AR) neuromuscular disorders. The relative occurrence of each subtype of LGMD varies among different ethnic populations, however, among patients diagnosed with AR LGMD, LGMDR1 (Calpainopathy) is the most frequent form caused by CAPN3 gene. Recent developments have led to proposed gene replacement therapies directed against gene mutations in inherited muscular disorder. As a few such therapies are currently in pre-clinical phase there is a demand to explore the variant landscape of these causative genes to guide trials.

Methods: In our study,192 patients(2018-2022) suspected of MD from unrelated families underwent phenotypic characterization,muscle histopathological analysis followed by targeted next generation sequencing(NGS) using a customized panel of 88 genes.Sequencing data was annotated using VariMAT(Variation and Mutation Annotation Toolkit)pipeline for generating variants

Results: A total of 19 patients (10 males and 9 females) were diagnosed with Calpainopathy out of 113 LGMD patients. Mean age of diagnosis was 19.9 years with onset as early as 8.5 years.CPK levels ranged from 212-8460U/L.EMG was myopathic in 47% (9/19)patients. Histomorphological analysis showed muscle fiber size variation in 94% (16/17) cases, loss of fascicular architecture in 47% (8/17), inflammation 17% (3/17), fibrosis 35% (6/17) with few showing myophagocytosis 17% (3/17) and myofibrocytosis 11% (2/17). Sequencing detected 9 novel and 18 reported mutations including frameshift, non-frameshift, nonsense, missense and splice variants. A considerable proportion of hotspot variants (17) were detected including Aggarwal founder mutations. Majority of variants were in the Calpain catalytic (6) domain involved in calcium-dependent autolysis and enzymatic activation while 3 variants were in PEF (penta-EF-hand) domain that mainly participates in calcium ion binding and CAPN3 homodimerization.

Conclusions: In conclusion, the discovery of novel and recurrent mutations, particularly founder variants, highlights potential candidate variants for future gene therapy approaches.

64

Spectrum of Peripheral and Autonomic Neuropathies in Patients with wtATTR Amyloidosis and Response to Patisiran Therapy

H Hashim [1], Y Hussain [2], E Hmedat [3], J Numan [4]; [1] University of Central Florida/ HCA Healthcare, [2] Austin Neuromuscular Center, [3] University of Kufa, [4] Marshall University

Background: Transthyretin-related amyloidosis (ATTR) involves the accumulation of abnormal transthyretin protein. Wild-type transthyretin amyloidosis (wtATTR) is mainly linked to cardiac dysfunction, such as cardiomyopathy. However, wtATTR may also cause neurological and autonomic dysfunction, beyond its known association with carpal tunnel syndrome. This poster presents a single-center, ongoing pilot study on patisiran in patients with wtATTR.

Methods: To evaluate the efficacy and safety of patisiran in patients with wtATTR amyloidosis and symptomatic polyneuropathy by assessing its impact on neurological impairment and quality of life over a 24-month treatment period.

Results: We conducted single-center pilot study, that is still ongoing. The study involves 10 adult patients diagnosed with wtATTR amyloidosis and symptomatic polyneuropathy. Patients receive patisiran intravenous infusions every 21 days for 24 months. Various assessments are conducted to evaluate efficacy and safety. The absence of results at this stage limits conclusions; however, comprehensive assessments are designed to capture nuanced changes in neurological function and quality of life. The data collected may provide critical insights into the efficacy of patisiran in this patient population.

Conclusions: This pilot study aims to explore the potential benefits of patisiran in treating symptomatic polyneuropathy in patients with wtATTR amyloidosis. The outcomes may enhance understanding of the neurological involvement in wtATTR and support the development of targeted therapeutic strategies.

POSTERS

Posters: Tumors: glial

1

Combinatorial targeting of avapritinib-driven MAPK activation in high-grade glioma

K Schwark [1], S Kong [1], M Miclea [1], T Patel [1], A Stanczak [1], B Lau [1], R Cartaxo [1], D Messinger [1], R Doherty [1], S Ji [1], J Wadden [1], M Clausen [1], F Momen [1], T Adam [1], K Wink [1], A Hutchinson [1], M Niculcea [1], H Serhan [1], N Merrill [1], L Mayr [2], S Neyazi [2], D Muñoz [3], N Nuechterlein [1], E Fernandez [4], J Pavisic [4], D Klawinski [5], S Merajver [1], A Beck [6], M Filbin [2], J Coppé [3], C Koschmann [1]; [1] University of Michigan, [2] Dana-Farber Cancer Institute, [3] University of California San Francisco, [4] Columbia University, [5] Nemours Children's Health, [6] Ludwig Maximillian University of Munich

Background: PDGFRA is a frequently altered gene in HGG, driving aggressive behavior and worse prognoses. Avapritinib, a potent CNS-penetrant PDGFRA inhibitor, has shown promise in vitro, in vivo, and in HGG patients. Given the failure of single-agent trials in targeting PDGFRA-altered HGG, combinatorial therapy is likely needed with other targetable pathways for treatment.

Methods: We performed a high-throughput kinase-activity mapping (HT-KAM) screen to detect the catalytic activity of >900 kinase-substrate nodes in avapritinib-treated HGG models. We performed sole and combinatorial treatment of HGG models with avapritinib and several MAPK inhibitors: ONC201, ONC206, selumetinib, trametinib, ulixertinib, both in vitro and in vivo. We also gathered clinical data from patients treated with avapritinib/MEK inhibitor combination therapy.

Results: Supraphysiological doses of >=1uM avapritinib treatment of PDGFRA-altered HGG cells in vitro results in sustained activation of the MAPK pathway. Specifically, short-term avapritinib treatment with >=1uM doses resulted in MEK/ERK (MEK2) and MEK/JNK (MKK4/7) activation, and long-term treatment resulted in sustained MEK/ERK (MEK2) activation across all models. Dose-dependent pERK upregulation in response to avapritinib was confirmed in multiple HGG in vitro and in vivo models. Furthermore, upregulation of the ERK-driven anti-apoptotic protein MCL-1 was found in short-term avapritinib-treated HGG cells in vitro. Trametinib demonstrated the strongest combinatorial survival benefit among preliminary results in PDGFRA-driven HGG models in vivo. We subsequently showed in vitro synergy between avapritinib and trametinib in a tumor-derived organoid from a pediatric patient with PDGFRA D842V-mutant metastatic CNS sarcoma that grew on avapritinib. This patient was later treated with this combination and demonstrated stability for five months. Another patient has 13 months and ongoing survival with avapritinib and selumetinib.

Conclusions: In light of sustained MAPK activation identified in our study, dual avapritinib-MAPK targeted treatment may be an effective approach for PDGFRA-driven HGG.

2

Clinical relevance of EGFR amplification in IDH-mutant astrocytoma

C Slocum, P Nguyen, M Vij, D Hambardzumyan, J Walker, M Umphlett, N Tsankova, T Richardson; Icahn School of Medicine at Mount Sinai

Background: The 5th edition of the WHO CNS Tumors Guidelines incorporated the addition of EGFR amplification, TERT promoter mutation, and +7/-10 co-alteration as criteria for grade 4 designation IDH-wildtype diffusely infiltrating gliomas, as they confer dismal prognosis even in the absence of grade 4 histologic features. These features may also rarely be found in IDH-mutant astrocytomas, but with unclear prognostic significance

Methods: A cohort of 790 IDH-mutant astrocytomas was established using data from publicly available datasets, including the GLASS, MSKCC, TCGA, and GENIE cohorts. Using this combined cohort, we determined the frequency with which EGFR amplification, TERT promoter mutation, +7/-10 co-alteration, and homozygous CDKN2A deletion were present, and how these related to other clinical, histologic, and molecular features. Kaplan-Meier plots and Cox multivariate hazard regression analysis were performed to evaluate the impact of these molecular alterations on progression-free survival (PFS) and overall survival (OS).

Results: TERT promoter mutation and +7/-10 co-alteration were vanishingly rare in IDH-mutant astrocytomas, but EGFR amplification or activating mutation was present within 2.7% of cohort cases (21/790) compared to 12.3% of cases with CDKN2A homozygous deletion (97/790). The presence of EGFR amplification or activating mutation was associated with significantly decreased OS ($p < 0.0001$) and PFS ($p=0.0046$) compared to IDH-mutant astrocytomas without EGFR alteration or CDKN2A homozygous deletion, similar to the effect of CDKN2A deletion. Cox multivariate hazard regression analysis showed that the presence of EGFR alteration independently and significantly impairs PFS (HR=1.92, $p=0.0415$) and OS (HR=2.99, $p=0.0005$) across multiple variables, including cohort of origin, age, sex, histologic grade, and homozygous CDKN2A deletion. Of note, IDH-wildtype glioblastoma still had worse overall survival compared to IDH-mutant astrocytoma with EGFR alteration ($p < 0.0001$).

Conclusions: These results suggest that while EGFR amplification/activating mutations are much less common than CDKN2A homozygous deletion in IDH-mutant astrocytomas, when present they independently confer significantly decreased survival.

3

Improving glioblastoma survival by combining YAP-TEAD inhibitors with surgical resection in preclinical xenograft models

T Silva Hurtado [1], B Pai [1], R Yong [1], T Tang [2], N Tsankova [1]; [1] Mount Sinai Hospital, [2] Vivace Therapeutics

Background: The infiltrative phenotype of glioblastoma (GBM) poses a major challenge to treatment, leading to incomplete tumor resection and inevitable recurrence by residual disease. Standard-of-care therapy does not inhibit GBM infiltration, and most preclinical models do not mimic surgical resection. The Hippo pathway, specifically YAP/TAZ-TEAD signaling, has been implicated in GBM plasticity and tumor migration, making it a promising therapeutic target.

Methods: In this project, we tested the preclinical efficacy of novel YAP-TEAD inhibitors from Vivace Therapeutics (VT), VT103 and VT104. To better replicate clinical GBM treatment, we also developed a surgical resection model in mice with PDX gliomas.

Results: Anti-migration efficacy of VT103 and VT104 in vitro was demonstrated using cell migration assays, in three different patient-derived GBM cell lines ($p < 0.01$, each). Additionally, VT103 and VT104 inhibited TEAD1 transcription activity, with reduced expression of TEAD1-target genes CYR61 ($p < 0.001$) and CTGF ($p < 0.05$) detected by qRT-PCR, confirming the drugs' anti-TEAD pharmacodynamic activity. Notably, pharmacokinetics analysis demonstrated robust brain penetrance of VT103 and VT104 (Brain: Plasma >200%). Finally, orthotopic patient-derived xenograft (PDX) mice with infiltrative GBM-like tumors showed delayed tumor progression after VT104 treatment, compared to vehicle controls ($p=0.03$; $n=8$). We implanted the infiltrative PDX GBM line G16302-Akaluc in the frontal cortex and resected the large, proliferative core via craniotomy six weeks after implantation. Histological analysis confirmed the removal of tumor and the presence of residual disease at the margin post-resection. Mice undergoing resection exhibited significantly prolonged survival, compared to non-resected controls (log-rank p-value = 0.0448; $n=6$), with survival range of 91-100 days in controls versus 97-107 days in resected mice, paralleling the clinical benefit seen in human GBM patients.

Conclusions: By integrating YAP-TEAD inhibition with surgical resection in PDX models, we now aim to evaluate the synergistic effects of standard-of-care, targeted YAP-TEAD inhibitor therapy and tumor debulking in a clinically relevant setting.

4

High-Grade Astrocytoma with Piloid Features is a Histologically and Molecularly Heterogenous Group With Poor Survival

S Belakhoua [1], J Wu [2], E Freitag [2], C Schroff [2], N Dhasmana [2], J Serrano [2], V Vasudevaraja [2], M Snuderl [2]; [1] NYU Langone Health, [2] NYU Grossman School of Medicine

Background: High-grade astrocytoma with piloid features (HGAP) is a rare glial tumor defined by an astrocytic morphology, a distinct DNA methylation profile, and provisional Grade 3. Since the publication of the 5th edition of CNS WHO, new entities with epigenetic proximity to HGAPs such as GTAKA and HPAP were described, which requires the review of diagnostic and prognostic criteria for this entity.

Methods: We analyzed 56 tumors that were pathologically suspicious for HGAP, using DNA methylation and Heidelberg classifier 12.5 at NYU Langone Health, and clinically validated DNA and RNA next-generation sequencing assays. Clinical, pathological, molecular, and survival data were retrieved from medical records.

Results: DNA methylation showed that out of 56 tumors, 49 classified as HGAP, three as pedHGG_RTK1, two as GBM_RTK1, one as GBM_CBM, and one as GTAKA. DNA and RNA NGS were available for 14 patients and showed recurrent alterations of ATRX(9), NF1(6), FGFR1(4), PIK3CA(3), BRAF(2), TSC2(2), H3K27M(1), ERBB2(1). Most HGAPs showed complex CNV patterns with recurrent amplifications of MDM2/4, CDK4, PPM1D, PDGFRA, TERT, and MYC. CDKN2A/B was lost in 49 cases (88%). A history of neurofibromatosis was recorded in eight patients, and Turner syndrome in one. Recurrent specimens were analyzed for three patients: one was a stable HGAP for three years, one HGAP progressed to GBM_CBM, and one presented initially as pilocytic astrocytoma (PA), progressed to HGAP, then to pedHGG_RTK1. Available survival data showed death within three years of diagnosis in 18 cases. A single case had a long recurrence-free survival (9 years) and a simple copy number profile.

Conclusions: HGAPs are complex, high-grade tumors that involve the activation of multiple oncogenic pathways. They may evolve from a preexisting PA, and be a precursor to glioblastoma, especially in neurofibromatosis patients. The poor survival of this entity may warrant a WHO grade 4 designation.

5

High-Throughput Screening Reveals K784-6195 as a Selective Therapeutic Candidate for NF1-Associated High-Grade Gliomas with ATRX Deficiency

F Rodriguez [1], S Dubey [2], S Rai [2], S Aung [2], F Guillen [2], M Yuan [3], C Eberhart [3]; [1] Department of Pathology and Laboratory Medicine UCLA, [2] UCLA, [3] Johns Hopkins University School of Medicine, Baltimore, MD 21218, USA

Background: Neurofibromatosis type 1 (NF1)-associated high-grade gliomas (HGGs) with ATRX mutations exhibit aggressive clinical behavior due to heightened genomic instability and metabolic reprogramming. Current treatment options remain limited by resistance mechanisms and secondary malignancies, necessitating novel therapeutic strategies.

Methods: We conducted a high-throughput screening of 10,000 small molecules to identify compounds selectively targeting vulnerabilities associated with concurrent ATRX and NF1 loss. Hits were refined based on survival assays, biological database curation (PubChem, BindingDB), and machine learning approaches incorporating unsupervised (UMAP) and supervised classification models. Prioritized candidates were evaluated for potency and selectivity in NF1-associated ATRX-deficient HGG cell lines (JHH-NF1-GBM1 and TM31) compared to sporadic HGG (U251 and its ATRX knockout). Mechanistic studies utilized steady-state and isotopically labeled metabolomics to assess metabolic disruptions induced by the lead compound.

Results: Our screen identified 105 initial hits, leading to 17 prioritized candidates, among which K784-6195 emerged as the most potent and displayed specificity for NF1-associated high grade glioma cell lines over sporadic HGGs. K784-6195 exhibited an IC50 value of 4.84 and 5.02 µM in JHH-NF1-GBM1 and TM31 (NF1-associated ATRX mutant lines), respectively. In comparison, wild-type ATRX sporadic glioma cell lines (U251) exhibited significantly reduced sensitivity to K784-6195 (IC50 = 37.03 µM). However, ATRX knockout U251 glioma cells recapitulating concurrent ATRX and NF1 loss exhibited heightened susceptibility to K784-6195 (IC50 = 20-23 µM) compared to their wild-type counterpart. Metabolomics revealed that K784-6195 treatment disrupted key metabolic pathways, including fatty acid beta-oxidation, spermidine/spermine biosynthesis, and homocysteine degradation, suggesting an early cellular response to ferroptotic stress. Global metabolomic profiling further highlighted dysregulation in pyrimidine and nicotinamide metabolism, underscoring potential metabolic vulnerabilities in NF1/ATRX-deficient HGGs.

Conclusions: These findings identify K784-6195 as a promising therapeutic candidate for NF1-associated gliomas with ATRX deficiency and highlight metabolic adaptations that may inform future therapeutic strategies.

6

Assessing Nectin and Nestin Expression in Adult and Pediatric Diffuse Midline Gliomas: A Step Toward HSV-Based Oncolytic Viral Immunotherapy

A Santos [1], F Repetto [2], S Alexandrescu [3], I Solomon [2]; [1] Brigham and Women's Hospital, [2] Brigham and Women's Hospital, [3] Boston Children's Hospital

Background: Diffuse midline gliomas (DMGs), H3 K27-altered, are responsible for the majority of brain tumor-related deaths in children and also constitute a subset of adult high-grade gliomas. Despite extensive research and clinical efforts, this tumor subtype shows poor overall survival and response to therapy in both age groups. Recent studies show increased survival in HSV-seropositive glioblastoma patients treated with CAN-3110 oncolytic HSV-1 immunotherapy (PMID: 37853118). Additionally, the oncolytic adenovirus DNX-2401 has shown promising results in treating diffuse intrinsic pontine gliomas (DIPG) in pediatric patients (NCT03178032). Given these promising findings, we explored the feasibility of utilizing CAN-3110 and other viral oncolytic immunotherapies for DMG treatment.

Methods: We identified 22 patients with DMGs and used immunohistochemistry (IHC) to assess the expression of Nectin, an entry receptor for HSV-1, and Nestin, a neural stem cell marker and transcriptional regulator of the HSV neurovirulence factor ICP34.5 protein in CAN-3110. Our cohort includes DMGs involving multiple anatomical sites (pons, thalamus, cerebellum, and spine), a wide age range (4 to 70 years of age), and a variety of co-occurring somatic mutations that might influence tumor biology (BRAF V600E, TP53, NF1, PIK3CA). All cases were surgical pathology specimens, with one representative tissue block stained per case for IHC analysis.

Results: Nectin was expressed in 83% of pediatric and 85% of adult DMG cases analyzed and showed strong staining in the majority of lesional cells, indicating potential accessibility for HSV-1 entry. Nestin was also highly expressed in tumor cells in 83% of pediatric and 90% of adult cases, suggesting the feasibility of targeted CAN-3110 viral replication.

Conclusions: The co-expression of Nectin and Nestin in DMGs suggests that HSV-based oncolytic viral immunotherapies such as CAN-3110 could be used to effectively treat DMGs. Further studies are needed to explore this approach's therapeutic potential and clinical application in DMGs.

7

Cellular Deconvolution of the Tumor Microenvironment in Pleomorphic Xanthoastrocytoma

G Pinto [1], V Zschernack [1], V Dreschmann [1], T Goschzik [1], E Dörner [1], M Toma [2], T Pietsch [1]; [1] Institute of Neuropathology and DGNN Brain Tumor Reference Centre, University Hospital Bonn, Bonn, Germany, [2] Institute of Pathology, University Hospital Bonn, Bonn, Germany

Background: Pleomorphic xanthoastrocytoma (PXA) is a rare astrocytoma, presenting distinctive morphological features and pronounced immune infiltrates. This study characterizes the tumor microenvironment (TME) of PXAs through reference-based cellular deconvolution from DNA methylation (DNAm) data and immunohistochemistry.

Methods: Twenty-six PXAs (twenty-one grade 2, five grade 3) and a comparison cohort of seventeen supratentorial pilocytic astrocytomas (PAs) underwent DNAm analysis through the Infinium MethylationEPICv1 (Illumina) array. DNAm data was processed in R and MethylCIBERSORT (cibersortx.stanford.edu) was used to deconvolute ten different cell types, including stromal and immune cells. The data was compared with the results of immunohistochemistry.

Results: TME in PXAs and PAs showed high fibroblast content (median 37.0% vs. 31.3%). PXAs exhibited a lower endothelial-cell content (median 19.3% vs. 22.3%; p=0.05), reflecting the histological observation of more frequent endothelial proliferates in PAs. Higher fractions of CD8+ cells were detected in PXAs (median 4.6% vs. 2.5%) by deconvolution, consistent with CD8 immunohistochemistry (median 2.8% vs. 0.7%), highlighting a higher frequency of CD8+ cells. Tregs fractions were similar between the two groups (median 7.8% vs 8.4%) as well as CD14+-monocyte levels (median 15.6% vs 16.6%); the latter however showed a trend towards higher levels in grade 3 and recurrent PXAs (up to 36.6%), probably due to reactive changes post-surgery. CD19+ B-cells were lower in PXAs (median 6.1% vs 7.7%; $p < 0.05$), whereas no statistically-significant difference was found for CD4+ (median 2.1 vs 2.7%), CD56+ (median 2.1 vs. 2.2%), and neutrophils (1.5% vs 0.5%). In contrast, immunohistochemistry revealed a higher presence of CD4+-cells in PXA (median 4.0% vs. 1.2%).

Conclusions: DNAm analysis plays a role not only for methylation-based classification of PXAs, but also for the characterization of their TME. DNAm-based deconvolution represents a powerful complementary tool for TME characterization but it should be carefully interpreted in conjunction with in-situ immunophenotyping of TME cells.

8

Pediatric H3 G34-Mutant Diffuse Hemispheric Glioma: Unique Biology and Clinical Behavior

J Chiang [1], D Tlais [1], Q Zhang [1], J Roach [1], C Tinkle [1], T Lin [1], X Li [1], A Mostafa [1], D Moreira [1], R McNall-Knapp [2], S Rush [3], B Le [4], S Sinno [5], A Agarwal [6], K Ginn [7], R Green [8], S Partap [9], A Onar-Thomas [1], L Furtado [10], A Bag [1]; [1] St. Jude Children's Research Hospital, [2] University of Oklahoma Health Sciences Center, [3] Akron Children's Hospital, [4] University of North Carolina School of Medicine, [5] American University of Beirut Medical Center, [6] UT Health San Antonio, [7] Children's Mercy Kansas City, [8] Kaiser Permanente Los Angeles Medical Center, [9] Stanford University, [10] St. Jude Children's Research Hospital

Background: H3 G34-mutant diffuse hemispheric glioma is a newly recognized tumor type in WHO CNS5. Previous studies have demonstrated inferior outcomes in pediatric patients, but the underlying mechanisms remain unknown. Additionally, the effectiveness of Temozolomide (TMZ) and the role of surgery in pediatric G34 tumors remain uncertain.

Methods: We conducted a multi-institutional analysis of 36 newly diagnosed pediatric (≤ 18 years) H3 G34-mutant diffuse hemispheric gliomas to address these questions, assessing their clinical, imaging, and molecular characteristics.

Results: The median progression-free survival (PFS) and overall survival (OS) were 0.7 years (95% CI: 0.4-1.2 years) and 1.8 years (95% CI: 1.1-3.0 years). Tumor progression with the high-dose radiation field was seen in 78%. Frontline TMZ use (n=21, 58.3%) correlated with improved PFS (p=0.0049). However, paradoxically, MGMT promoter methylation status did not predict PFS (p=0.7581), OS (p=0.2675), or TMZ efficacy (p=0.9073 and 0.7759 for PFS and OS, respectively), distinct from adult tumors, where the lack of MGMT promoter methylation predicts inferior outcomes. Instead, we found that gene body and intronic CpG methylation—but not promoter methylation—regulates MGMT expression in pediatric G34-mutant diffuse hemispheric glioma (r=0.9288, p=3.7x10^-7). Additionally, while patients undergoing gross-total resection (GTR, n=11, 30.6%) had better PFS (p=0.0046) and OS (p=0.0362), the presence of gliomatosis cerebri in 36.1% of pediatric patients limited surgical options. We also identified PDGFRA amplification (n=10) and CDKN2A homozygous deletion (n=14) as predictors of inferior OS (p=0.0403) and PFS (p=0.0352), respectively. While in adult patients, G34V and male sex are linked to worse outcomes, no significant associations were found in pediatric cases.

Conclusions: Our findings reaffirm the dismal outcomes of pediatric H3 G34-mutant diffuse hemispheric glioma, which uniquely exhibits radiation resistance, a tendency of widespread disease, and a novel mechanism of MGMT regulation. Our data supports frontline TMZ use in pediatric patients and underscores the importance of GTR when feasible.

9

Integrative Molecular Analysis for Enhanced Ependymoma Classification

M Sharma [1], R Malik [2], A Sharma [2], V Suri [2]; [1] Department of Neuropathology, NSC, [2] AIIMS, New Delhi

Background: Ependymomas (EPNs) are CNS tumors with molecular subtypes influencing prognosis and treatment. DNA methylation profiling with the DKFZ classifier improves classification but has limitations in detecting fusion-driven subtypes and CNVs. RNA sequencing (RNA-seq) and CNV analysis enhance fusion detection and genomic insights. This study integrates these approaches to refine classification and assess RNA-seq as a cost-effective tool.

Methods: Twelve ependymomas (2012–2023) and four controls were classified per WHO CNS5. DNA methylation profiling used the DKFZ classifier, and RNA sequencing was performed on five cases and five controls. RNA-seq findings were validated via IHC and FISH. CNV analysis identified oncogenic amplifications and tumor suppressor deletions, while DESeq (padj < 0.05, log2 fold change ≤ -1 or ≥ 1) correlated gene expression with CNV alterations and fusion events detected via Arriba.

Results: RNA sequencing confirmed fusion-positive cases consistent with DNA methylation classification. YAP1 and ZFTA fusions were found in ST-EPN, NOS cases, while C11-RELA and RELA fusions were identified in a recurrent ST-EPN and a PFB case. Methylation classification correlated with RNA-seq, resolving ambiguous cases through CNV and RNA-seq integration. Two ST-EPN cases harboured YAP1 and ZFTA fusions, validating methylation results. A PFB case initially unclassified by methylation (score < 0.3) was confirmed as RELA-ZFTA fusion-positive via RNA-seq. A spinal ependymoma remained unclassified due to a low methylation score. CNV analysis revealed SMARCB1 (22q) deletions in ST fusion-positive cases. DESeq analysis showed CNV-driven gene expression changes, with FGFR1, MYB, TACC2, and SMARCA1 upregulated, while NF2, PDGFRA, and MET were downregulated. This approach classified 11 of 12 cases, reinforcing RNA sequencing's role in complementing methylation profiling.

Conclusions: Integrating RNA sequencing with DNA methylation profiling and CNV analysis improves ependymoma classification, enhancing diagnostic precision and personalized treatment. Refining molecular classifiers will further optimize clinical decision-making.

10

Unveiling the Spread: Molecularly Defined Oligodendroglioma with Osseous Metastases

E Pai [1], Y Matsumoto [2], D Dou [2], S Nelluri [1], P Devi [1], S Priori [1], N Amankulor [1], M Alonso-Basanta [1], O Singh [3], Z Abdullaev [3], K Aldape [3], A Desai [1], S Mohan [1], M Nasrallah [1]; [1] Hospital of the University of Pennsylvania, [2] University of Pennsylvania, [3] National Cancer Institute

Background: Histological features such as increased mitotic activity, microvascular proliferation, necrosis, and molecular alterations— including CDKN2A/B homozygous deletion— are linked to aggressive tumor behavior and poor prognosis. Even in the setting of these features, extra-neural metastasis of oligodendroglioma is rare, and the tumor evolution in such cases is poorly understood.

Methods: Here, we molecularly profile sequential resection specimens from a young male with a 16-year history of oligodendroglioma who developed multi-focal osseous metastases with unusual osteolytic imaging features.

Results: Histologically, tumor from the brain demonstrated increasing cytologic atypia and mitotic activity over time; the bone metastasis demonstrated classic oligodendroglioma features. Genetic studies revealed similar molecular profiles across specimens, including IDH1 mutation and 1p/19q co-deletion. Given the genetic consistency, we hypothesize that methylome changes may explain the tumor's malignant behavior. Hierarchical clustering analysis with CpG probes that define IDH-mutant glioma subtypes (G-CIMP high, G-CIMP low, Codel) placed the second and third resections within the ‘oligosarcoma’ group. Dimensionality reduction analysis using 125 cancer-cell-specific probes that distinguish glial/glioneuronal tumor types positioned the second resection within the Codel cluster and the third resection in the G-CIMP high cluster, near the oligosarcoma cluster. Continuous Grading Coefficient (CGC) analysis based on epigenetic signature that reflect tumor malignancy classified the second resection as CGC Medium and the third resection as CGC High. These findings are consistent with increased malignancy over time and demonstrate epigenetic changes despite the lack of difference among specimens over time of gene sequencing findings. Gene Ontology analysis of differentially methylated genes revealed (1) promoter hypomethylation in cell adhesion and metabolic pathways, and (2) gene body hypomethylation in tissue morphogenesis and synaptic/neurotransmission pathways in the third resection.

Conclusions: We present a case of oligodendroglioma with multiple osseous metastases 16 years after initial diagnosis, with methylome data shedding light on the molecular mechanisms underlying its metastatic potential.

11

Methylation Profiling Limitations for High Grade Brain Tumors

M Milani [1], C Chen [2], L Chen [1]; [1] University of Minnesota, [2] University of Minnesota Medical School

Background: DNA methylation profiling has revolutionized the subclassification of central nervous system (CNS) tumors, providing insights into tumor prognosis, recurrence, and personalized treatments. Despite its utility, challenges persist in classifying rare or poorly understood high-grade gliomas (HGGs) that fail to match existing methylation data. This study evaluates the clinical, histopathological, and molecular characteristics of four such cases, emphasizing room for improvement of methylation profiling in refining diagnoses and treatment.

Methods: We retrospectively analyzed data from four adult patients with HGGs unclassified by methylation profiling. Clinical features, imaging, histopathology, and next-generation sequencing results were reviewed. Methylation profiling was performed by the NIH. Cases were evaluated for histopathological features, molecular markers, and survival outcomes.

Results: All patients exhibited diverse clinical presentations, with MRI and histopathological findings confirming high-grade gliomas. Histopathological analysis revealed varied features across the cases including bizarre multinucleated giant cells and deeply infiltrating small round blue cells. Immunohistochemical markers highlighted GFAP positivity and ATRX retention across cases, with TP53 mutations identified in three cases. Methylation profiling failed to yield clear matches for any known class. Instead, profiling suggested a high-grade epithelioid neoplasm for Case 1, while Cases 2-4 were deemed indeterminate IDH-wildtype neoplasms with aggressive clinical courses. Despite treatment, two patients experienced disease progression and died, while the remaining two showed stable disease on follow-up.

Conclusions: This study highlights the diagnostic challenges of unclassifiable CNS tumors in the context of DNA methylation profiling, reflecting the need for expanded reference datasets. While profiling has transformed the field of tumor diagnostics, its limitations still exist. Enhanced collaboration and data sharing to broaden diagnostic categories is essential to improving methylation profiling. Until then, integration of clinical, histological, and molecular findings are imperative to optimize patient management, improve classification accuracy, and increase positive therapeutic outcomes.

12

Pituicytomas with unusually high-grade features: a series of two cases

R Landvater [1], E Pinarbasi [1], N Becker [2], S Stone [2], P Jamshidi [3], K Conway [2]; [1] University of Michigan, [2] Michigan Medicine, [3] Northwestern University

Background: Pituicytomas are tumors arising from specialized glial cells of the neurohypophysis. While they typically show indolent behavior, “atypical pituicytomas” with increased mitotic activity, cellularity, and proliferation have been described, as have a subset of pituicytomas harboring copy number imbalances and showing an increased risk of recurrence. We describe two pituicytomas with high-grade histologic features well beyond those described in “atypical pituicytomas.”

Methods: We reviewed clinical information, histomorphology, immunohistochemistry, results of DNA methylation profiling using version 12.8 of the DKFZ CNS classifier, and copy number variation (CNV) data inferred from the DNA methylation array.

Results: Both cases were sellar masses. Case #1 was a first diagnosis while case #2 was a recurrence after an 11-year interval from initial resection. Both cases showed diffuse TTF-1 expression and were negative for GFAP and S100. Both cases showed substantial mitotic activity (up to 9 and 12 mitotic figures per 10 high power fields, respectively) and high proliferation indices (20% and 25%, respectively). Some unusual immunohistochemical features were identified in each case, including expression of CK7 (case #1), and synaptophysin and neurofilament (case #2). Both cases showed methylation profiles indicative of pituicytoma (confidence scores of 0.99 and 0.84, respectively), and both showed multiple chromosomal imbalances: losses of portions of chromosome 1p and 15 and gains of 1q and 5 in both cases with case #2 additionally showing losses of portions of 2, 6, 9, 10, 12, and 22.

Conclusions: These two cases expand the spectrum of high-grade features described in pituicytomas. The mitotic activity and proliferation indices of these two tumors are well beyond those described in existing studies. The fact that case #2 is a recurrent tumor and showed a particularly complex CNV prolife raises the possibility of high-grade transformation. It is uncertain whether these high-grade features carry specific prognostic significance.

13

S.T.A.G.: Spatial Transcriptomics on Angiocentric Gliomas

M Bui [1], A Dunnon [2], S Guzman [2], A Toland [3]; [1] University of Colorado Anschutz Medical Campus, [2] CU Anschutz Medical Campus, [3] Children's Hospital Colorado

Background: Angiocentric glioma is a rare, low-grade brain tumor of children and young adults characterized by its strong association with drug-resistant epilepsy. Angiocentric gliomas are frequently driven by MYB-QKI fusions, a key oncogenic event. We report the clinical and pathologic findings in four cases, incorporating spatial transcriptomics in two cases to compare to a low-grade glioma.

Methods: The mean age of diagnosis was 8.3 years (range 3-20 years). Three patients were male. All patients had a history of drug-resistant epilepsy. Two tumors were in the frontal lobe and one tumor each was present in the temporal and occipital lobes. Histologically, the tumors were characterized by diffuse growth and prominent perivascular tumor cell arrangements. All cases were negative for OLIG2, positive for GFAP, and showed perinuclear dot-like expression of EMA. Staining for NeuN demonstrated a paucity of neurons at the center of tumors, suggesting neuronal effacement. MYB-QKI fusion was confirmed in a single case via next-generation sequencing.

Results: Compared to the control low-grade glioma, spatial transcriptomics by 10X Genomics Visium revealed homogenous tumors with significantly upregulated MYB, QKI, and AKT1 expression. MYB appears to promote proliferation, potentially via AKT1-mediated cell cycle dysregulation. Interestingly, the spatial component revealed upregulation of glutamate signaling that coexists in MYB upregulated tumor cells as well as the upregulation of GABAnergic signaling at the brain-tumor interface. These findings are supported by immunohistochemistry.

Conclusions: This study underscores the utility of spatial transcriptomics in dissecting the microenvironment of epileptogenic gliomas. By delineating gene expression patterns within the tumor and adjacent parenchyma, this approach offers insights into tumor biology, epileptogenesis mechanisms, and potentially informs future diagnostic and therapeutic strategies.

14

Posterior fossa high grade glioma with MYB::QKI fusion

M Ospina-Romero [1], S Powell [2], M Gubbiotti [3]; [1] Department of Pathology and Genomic Medicine, Houston Methodist Hospital, [2] Houston Methodist Hospital, [3] MD Anderson Cancer Center

Background: MYB::QKI is most commonly associated with angiocentric glioma, CNS WHO grade 1. Malignant transformation of angiocentric glioma is rarely described and high-grade gliomas with MYB::QKI fusion are uncommon with only one reported incidence in a pediatric high-grade glioma.

Methods: A 66-year-old man presented with gait imbalance as well as mild headaches. MRI showed a midline posterior fossa mass (3.7 x 3.4 x 2.9 cm) with heterogeneous enhancement, surrounding vasogenic edema, and enhancement along the folia of the cerebellar vermis concerning for leptomeningeal spread. Radiology favored an ependymal origin within the fourth ventricle.

Results: Histology revealed a hypercellular glioma with scattered angiocentric arrangement of tumor cells and high grade features including elevated mitotic activity, tumor necrosis, and microvascular proliferation. Tumor cells were diffusely positive for GFAP, variably positive for Olig2, and negative for EMA. Ki-67 proliferative index was up to 37.3%. Molecular testing revealed MYB::QKI M9Q5 with accompanying mutations in PIK3CA, ROS1, TRAF7, and TERT promoter. IDH1/IDH2 and H3-3A mutations were not present. DNA methylation profiling resulted in no consensus match, but a possibility of pediatric-type high grade glioma, H3-wildtype and IDH-wildtype was suggested.

Conclusions: We report a case of a high-grade glioma with MYB::QKI in the posterior fossa. Though glioblastoma, IDH-wildtype, CNS WHO grade 4 is a diagnostic possibility, no MYB::QKI fusion has been reported in this entity and there is no epigenetic evidence to support a diagnosis of glioblastoma in this tumor.

15

High-grade astrocytoma with pleomorphic and pseudopapillary features (HPAP) – expanding the clinicopathologic spectrum of an emerging entity

H Smith [1], D Meredith [2], K Conway [3], S Venneti [3], R Castellani [1], P Jamshidi [1], X Lu [1], M Sukhanova [1], B Nezami [1], L Jennings [1], D Duckett [1], L Santana-Santos [1], J Ahrendsen [1]; [1] Northwestern Memorial Hospital, [2] Brigham and Women's Hospital, [3] University of Michigan

Background: High-grade astrocytoma with pleomorphic and pseudopapillary features (HPAP) is an emerging entity defined by distinctive methylation profile and characteristic nuclear pleomorphism, papillary-like architecture, TP53 mutations, and monosomy 13. Herein, we describe the morphologic, molecular, and clinical features of a novel cohort of HPAP, including cases with indolent behavior and/or low-grade histology.

Methods: A series of eleven cases were identified that matched with high confidence to HPAP on the National Cancer Institute's Bethesda v2 classifier. Collected data included clinical outcome, histomorphology, and molecular characteristics.

Results: Eight cases (72%) showed high-grade morphology with increased mitotic activity, necrosis, or microvascular proliferation. 87.5% had at least focal nuclear pleomorphism, and 37.5% had pseudopapillary architecture. Next-generation sequencing showed mutations in TP53 (50%), RB1 (37.5%), BRAF (37.5%), NF1 (25%), and NF2 (25%). One recurrent case had a YAP1::MAML2 fusion that was not detected in the initial specimen. Seven cases with available copy number data showed numerous chromosomal losses with monosomy 13 in 85%. Six cases with long-term follow-up all had prolonged clinical courses (median follow-up 60 months, range 13-336 months) with multiple recurrences. Three cases demonstrated low-grade histology, with variable pseudopapillary architecture and pleomorphic nuclei. One case showed dysmorphic ganglioid cells and eosinophilic granular bodies. Two had BRAF p.(V600E) mutations, one with concurrent CDKN2A deletion. One had a TP53 mutation at a low variant allelic frequency (3%). Copy number profiling showed predominantly chromosomal gains and all lacked monosomy 13. Follow-up data was available for one patient, who was disease-free after 12 months.

Conclusions: A subset of tumors that match to methylation class HPAP show morphologic, molecular, and clinical features of other low-grade glial/glioneuronal tumors. The incidence of such low-grade "HPAPs" is relatively small but suggests a broad spectrum of disease. These findings should be taken into consideration when defining HPAP in future classification schemes.

16

Evaluating SOX2 Immunohistochemistry for Tumor Specificity in Gliomas

D Kim, S Bobholz, M Mirzaei, B Nath, S Duenweg, A Lowman, B Chao, A Winiarz, M Barrett, F Kyereme, J Connelly, E Cochran, J Jacobsohn, E Mrachek, M Krucoff, P LaViolette; Medical College of Wisconsin

Background: Recent studies have shown SRY-box 2 (SOX2) immunohistochemistry (IHC) may be a sensitive marker of pluripotency for gliomas without the need for mutation-specific markers like IDH1. Unlike GFAP, which is also expressed in mature astrocytes, SOX2 may better identify infiltrating tumor cells due to its expression only in immature glia. However, stem cells and CNS stress-related reactivation of astrocytes raises concerns about non-tumor staining. This study assessed potential non-tumor SOX2 expression in patients at autopsy.

Methods: SOX2 IHC was performed on FFPE brain tissue from 49 patients with glioma (38 glioblastoma, 5 astrocytoma, 3 diffuse midline glioma, 3 oligodendroglioma), including 4 IDH1-mutant tumors, as well as 7 non-glioma (1 ALS, 2 Alzheimer's, 4 metastatic cancer). Comparative IDH1 staining was performed on the IDH1-mutant gliomas. Slides were digitized and manually reviewed. Positive cell density maps were calculated computationally.

Results: IDH1-mutant gliomas showed strong colocalization of cells expressing IDH1 and SOX2 within tumor area. In addition to ependymal and subventricular SOX2+ cells, there were significant SOX2+ cells within the neocortex in 36/38 GBM, 3/5 astrocytoma, 3/3 diffuse midline glioma, 3/3 oligodendroglioma, 1/2 AD, 0/1 ALS, and 3/4 metastatic tumors. Neocortical SOX2+ cells did not stain for IDH1 in IDH1-mutant tumors. Observationally, neocortical non-tumor SOX2+ cells showed similar staining pattern across all disease types studied, with moderate nuclear and weaker perinuclear staining in a stellate shape, while tumor cells appeared spindle-shaped with strong staining throughout.

Conclusions: SOX2 expression is high in glioma at the cellular level, however specificity is limited by non-tumor staining in subventricular zones and neocortex. Exploiting staining intensity and morphology may be required for differentiation between tumor and non-tumor cells. Though healthy controls were not included, it has been reported that there are little to no SOX2-expressing cells in adult neocortex, suggesting that reactive, non-neoplastic processes may explain the observed SOX2 expression.

17

Perivascular Invasion in Glioma: Characterization and Treatment Associations Using SOX2 Immunohistochemistry

D Kim, S Bobholz, B Nath, A Lowman, S Duenweg, B Chao, A Winiarz, M Mirzaei, M Barrett, F Kyereme, J Connelly, E Cochran, J Jacobsohn, E Mrachek, M Krucoff, P LaViolette; Medical College of Wisconsin

Background: Perivascular invasion (PVI) of glioma is hypothesized to be one mechanism of recurrence through seeding distal to the main tumor mass. However, a thorough understanding of effects and risk factors of PVI is uncharacterized partly due to large numbers of tissue samples needed and challenges in visualizing PVI. SRY-box 2 (SOX2) immunohistochemistry (IHC) has recently emerged as a marker of pluripotency that may provide improved visualization of infiltrating glioma; thus we sought to use it to characterize the frequency, degree, and treatment association of PVI.

Methods: SOX2 IHC was performed on whole mount FFPE brain tissue from 41 patients with GBM (n=32) and other gliomas (4 astrocytoma, 3 diffuse midline glioma, 2 oligodendroglioma). Manual review of digital histology was performed and PVI was identified and graded semi-quantitatively. This scale was defined as: no clear PVI (0), limited PVI with co-optation of perivascular walls but no clear cells encapsulating the endothelial layer (1), PVI with cells filling PVS and circling the endothelium of small vessels (2), and many areas of high cell density dilating PVS, greatly exceeding proximate perineuronal spread (3). Grading was repeated in randomized order for consistency and consensus score for each case was used for analysis.

Results: 9 GBM cases showed a high degree (3 score) of PVI, including both patients with spinal metastasis. GBM patients that had been treated with bevacizumab, CCNU, or surgical resection had higher PVI scores (Mann-Whitney U: $P < 0.05$). GBM trended towards higher PVI scores over non-GBM gliomas (Mann-Whitney U: $P < 0.1$).

Conclusions: We attempted to initially characterize PVI and found that treatment with bevacizumab, CCNU, or surgical resection may increase the likelihood or acceleration of PVI. Interestingly, bevacizumab and surgery have been previously thought to increase PVI, but this study represents among the first to identify this association in human autopsy tissue.

18

DNA Methylation Profiling of Adult High-Grade Gliomas

A Gilani [1], A Denney [2]; [1] University of Colorado Anschutz Medical Campus, [2] University of Colorado Anschutz Medical Center

Background: Molecular testing, especially target-panel NGS and DNA methylation profiling, has been successful in identifying clinically significant subtypes in many tumor types but the relevance of this information for adult high-grade gliomas, histologically identical to glioblastoma, IDH-wildtype is less clear. Although most high-grade gliomas (HGG) in adults are diagnosed as glioblastoma, IDH-wildtype, this group is likely heterogeneous. To better understand this group, we present a small series of adult HGG in our practice that underwent NGS and DNA methylation profiling.

Methods: Standard immunohistochemistry was performed with 200+ gene fusion and mutation panel and FISH-based copy number testing for EGFR/ PTEN in most cases. DNA methylation profiling was performed at the NIH/ NCI and the DKFZ/ Heidelberg classifier and/ or the NCI classifier was used.

Results: 14 adult HGG are included in the study. Reasons for DNA-methylation profiling requests were: atypical ATRX/ P53 immunohistochemical profile (n=5), suspicion for high-grade astrocytoma with piloid features (HGAP) (n=5), young adult age (n=2), and unclear diagnosis (n=2). DNA methylation returned no match in 6 cases, confirmed a diagnosis of HGAP (3/5 suspected cases), and suggested a diagnosis of diffuse pediatric-type high-grade glioma, RTK1 subtype in 2 cases. Other methylation-based diagnoses were HGG MAPK altered (1 case) and high-grade glioma with pleomorphic and pseudopapillary features (HPAP) in 1 case. Only a single case was diagnosed as GBM, mesenchymal subtype.

Conclusions: A significant number of IDH-wildtype, H3-wildtype adult HGG resolve into distinct subgroups on DNA methylation-profiling, although these tumors were not treated any differently from standard GBM in our hospital. More research is needed to delineate the exact proportion of these tumor types in histologically defined GBM as well as any prognostic or therapeutic importance of DNA methylation profiling in adult HGG.

19

Next generation sequencing and methylation profiling of a composite pleomorphic xanthoastrocytoma-ganglioglioma

M Ospina-Romero [1], A Haws [2], L Prasannan [3], M Lee [4], M Quezado [5], K Aldape [6], D Lopez-Terrada [7], J Gastier-Foster [8], A Roy [9], K Fisher [7], C Mohila [7]; [1] Department of Pathology and Genomic Medicine, Houston Methodist Hospital, [2] Pathology, Pathology Associates of San Antonio, CHRISTUS Children's and Baylor College of Medicine, San Antonio, USA., [3] Pediatric Hematology/Oncology, CHRISTUS Children's and Baylor College of Medicine, San Antonio, USA., [4] Neurosurgery, CHRISTUS Children's and Baylor College of Medicine, San Antonio, USA., [5]): Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA, [6] Laboratory of Pathology, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, USA, [7] Pathology, Texas Children's Hospital and Department of Pathology & Immunology, Baylor College of Medicine, [8] Pathology, Texas Children's Hospital and Department of Pediatrics, Section of Hematology/Oncology, Baylor College of Medicine, [9] Pathology, Texas Children's Hospital; Department of Pathology & Immunology, and Department of Pediatrics, Section of Hematology/Oncology, Baylor College of Medicine

Background: Composite pleomorphic xanthoastrocytoma (PXA)-ganglioglioma (GG) is an exceedingly rare diagnosis, the etiopathogenesis of which is poorly understood. Recent studies have suggested composite PXA-GG may result from divergent evolution of one common precursor lesion with a BRAF V600E mutation.

Methods: We present a 13-year-old girl with seizures and a non-enhancing right temporal lobe mass. Serial MRIs noted an enlargement of the mass with a new adjacent enhancing insular nodule. The temporal and insular lesions were resected separately.

Results: The temporal mass shows histologic features characteristic of a PXA with variable tumor cell morphology, including xanthomatous cells and pleomorphic multinucleated cells. Tumor cells are diffusely positive for OLIG2 and variably positive for GFAP, synaptophysin, NeuN, and MAP2. In contrast, the insular nodule is composed of many neoplastic ganglion cells with intervening glial cells characteristic of a GG. Ganglion cells are positive for synaptophysin, NeuN, and MAP2 and glial cells are positive for GFAP and OLIG2. Next generation sequencing and DNA methylation was performed on each component separately. The PXA component harbors BRAF p.V600E mutation (VAF 41.3%), CDKN2A/B homozygous deletion with loss of p16 by immunohistochemistry, and methylation pattern analysis consistent with PXA. The GG component also demonstrates the BRAF p.V600E mutation (VAF 8.2%) but shows retained CDKN2A/B, and does not match to any methylation tumor class.

Conclusions: This tumor displays distinct histologic, immunophenotypic, and molecular features which support a composite PXA-GG. Consistent with prior reports, both components have a BRAF p.V600E mutation and homozygous deletion of CDKN2A/B limited to the PXA component. To our knowledge, this is the first report of a PXA-GG with DNA methylation

profiling separately performed on each component. The GG component does not match with a known methylation pattern suggesting that the GG component may be epigenetically distinct from PXA and conventional GGs.

20

A Rare Case of Spinal Metastasis in an Oligodendroglioma, IDH-Mutant and 1p/19q-Codeleted

A Aksionau [1], A Felpel [2], M Abedalthagafi [1]; [1] Emory University Hospital, [2] Phoebe Putney Memorial Hospital

Background: Oligodendrogliomas, characterized by IDH mutations and 1p/19q codeletion, are diffusely infiltrating gliomas with a relatively favorable prognosis. While cerebrospinal fluid dissemination is recognized, clinically significant spinal metastases remain exceedingly rare. We present a methylation-defined spinal metastatic oligodendroglioma, contributing to our understanding of its metastatic behavior and emphasizing the critical role of molecular diagnostics in resolving ambiguous cases.

Methods: A 38-year-old woman was initially diagnosed in 2016 with a right frontal “oligoastrocytoma” with focal anaplastic features (CNS WHO Grade 3). Tumor recurrences led to its re-excisions (2020, 2022, and 2023) and reclassification (2022) as oligodendroglioma, IDH2 (R172W)-mutant and 1p/19q-codeleted, CNS WHO Grade 3. The patient underwent multiple surgeries but did not complete radiation or chemotherapy due to financial and social constraints. In October 2024, she developed severe mid-to-lower back pain with progressive ambulatory difficulty. While brain MRI (08/2024) showed no recurrence, spinal MRI revealed multiple metastatic foci in the spine and pelvis, including focal marrow replacement in C5, T2, and T7 vertebrae, with an epidural component extending into the paraspinal soft tissues at T2-3 and T7-8, causing severe spinal canal stenosis.

Results: Histopathology of the paraspinal T7 lesion revealed monomorphic small round blue cells in the background of a myxoid matrix with extensive crush artifact and positive for Olig2 and GFAP. Molecular profiling classified the tumor as Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, with CDKN2A/B homozygous deletion.

Conclusions: This case advances our knowledge as the first spinal oligodendroglioma metastasis confirmed by DNA methylation profiling. It reinforces the necessity of molecular diagnostics in challenging cases and highlights the potential for late-stage spinal metastases in oligodendroglioma, warranting long-term surveillance.

21

Dysembryoplastic neuroepithelial tumor with malignant transformation following radiation

Y Zhu, C Ida, C Zepeda-Mendoza, A Vizcaino Villalobos, R Vaubel, A Raghunathan, J Schwartz, K Miller, C Giannini; Mayo Clinic

Background: Dysembryoplastic neuroepithelial tumor (DNET), a cortical CNS WHO grade 1 tumor, with a specific glioneuronal element and frequent FGFR1 gene alteration, may recur after resection, but malignant transformation is exceedingly rare.

Methods: We report the case of a 17-year-old boy with a 3-year history of intractable complex partial seizures and multiple cystic lesions extensively involving cortex and superficial underlying white matter in the left temporal lobe and insula prompting primary considerations of a low grade glioneural tumor/DNET. Biopsy findings were consistent with DNET, CNS WHO grade 1. Since the patient could not tolerate EEG monitoring to localize seizure activity, the lesion was considered not surgically resectable. Given that long-standing seizure control with chemotherapy is generally poor, proton radiation therapy was chosen as the treatment approach to help with seizure control and to prevent further growth. Four years later, as seizures worsened, imaging showed changes suggestive of tumor progression. While planning for a second biopsy, significant intralesional hemorrhage developed and despite an attempt to surgical evacuation and biopsy, the patient expired.

Results: The initial biopsy revealed a low-grade oligodendroglial-like neoplasm with columnar cell arrangement, myxoid background and isolated ‘floating’ neurons, harboring two FGFR1 mutations (p.K656E; p.N546Y) and an isolated chromosome 6 gain, consistent with DNET. At autopsy, a high-grade glioma with extensive hemorrhage was present. The tumor, which retained the FGFR1 (p.K656E) mutation, showed ATRX (p.D846Ifs*23) mutation and a highly complex copy number profile with numerous intrachromosomal breaks and CDK4, MDM2 and GLI1 amplification suggestive of diffuse pediatric-type high-grade glioma, H3- and IDH-wildtype (pedHGG). By genome-wide methylation array profiling using the NCI/Bethesda classifier v.2.0, the tumor matched to class pedHGG_RTK1C. Multiple small lesions, with DNET features remained in the underlying temporal and occipital lobes.

Conclusions: We report a DNET case with malignant transformation and a genetic and epigenetic signature, consistent with postradiation malignant transformation.

22

Spectrum of Paediatric Diffuse High-Grade Gliomas

G Chacko [1], E Kurien [2], R Jeyachandran [2], R Pai [2], R John [2], K Prabhu [2], R Moorthy [2], V Joseph [2], S B [2]; [1] Neuropathology, Department of Pathology, Christian Medical College, Vellore, India, [2] Christian Medical College

Background: WHO CNS5 2021, emphasizes the role of molecular alterations in addition to the histopathological and immunohistochemical features in the diagnosis and classification of gliomas. Adult-type and Paediatric-type diffuse high-grade gliomas have been recognised as separate entities with distinct molecular alterations.

Methods: This study included 145 cases of paediatric high-grade gliomas reported over a period of 12 years. Patient information, histopathological and immunohistochemical features were reviewed. In addition, 93 cases reported from January 2016 were reclassified according to the WHO CNS5 classification using further immunohistochemistry and molecular analysis. Morphological and clinical details were correlated with outcomes for each tumour type.

Results: Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH-wildtype had the highest prevalence (32%). Adult-type diffuse gliomas constituted 12.9% of cases. The median age at diagnosis was 12 years. In the cohort of 93 patients, Mismatch repair (MMR) deficiency was found in 11.8% of cases. The mean overall survival was 59.9 months, and the mean recurrence-free survival was 52 months. Comparison of overall survival time between Diffuse midline glioma, H3K27 altered and Diffuse paediatric-type high-grade glioma, H3-wildtype and IDH wildtype showed a median survival time of ~24 and 36 months, respectively. Diffuse midline glioma, H3K27-altered, had the worst outcome with a median time to death of 9 months (IQR- 4.3-23.3).

Conclusions: Diffuse high-grade gliomas in the paediatric age group are a diverse group of tumours with distinct clinical, immunohistochemical and molecular features, and prognosis. Adult-type diffuse gliomas constituted 12.9% of cases in this cohort. Worst outcome was seen in Diffuse midline glioma, H3K27-altered. Complete subtyping, according to the WHO CNS5 classification, remains a challenge for resource restrained regions, as reflected by our study, where advanced molecular testing was indicated in ~ 49.5% of cases, consisting of the IDH WT / H3 WT and the Not Otherwise Specified (NOS) category.

23

Still multiforme: transdifferentiation in molecularly characterized glioblastoma

K Pham, C Dampier, S Rajan, M Holdhoff, S Sahebjam, Y Comair, J Weingart, C Bettegowda, J Dudley, M Lin, J Eshleman, C Ho, M Morris, C Eberhart, C Lucas; Johns Hopkins School of Medicine

Background: The term “glioblastoma multiforme” is meant to represent a tumor composed of neoplastic glial cells that can take on many different forms. While contemporary biologic characterization has more narrowly defined glioblastoma as a distinct tumor entity by separating out other histologic mimics, a wide range of morphologies can still be seen in this molecularly-defined tumor type. The WHO recognizes different patterns, including “the formation of small, undifferentiated, spindled, lipidized, granular, epithelioid, and/or giant cells” and transdifferentiation can further be characterized by changes in immunophenotype.

Methods: We highlight the transdifferentiation phenotypes in a series of five glioblastomas. Immunohistochemistry was performed on formalin fixed paraffin embedded sections. Next-generation sequencing analysis was performed in all cases.

Results: Transdifferentiated components were identified at the initial presentation in 3 cases and at recurrence in 2 cases. Histologic sections revealed lesions composed of both conventional glioblastoma (astrocytic/gemistocytic tumor cells) in combination with a separate transdifferentiated component with either a leiomyosarcomatous, liposarcomatous, osteo/chondrosarcomatous, primitive neuronal, or mature ganglion cell appearance. Immunohistochemical evaluation demonstrated transdifferentiated components lost expression of glial differentiation markers (OLIG2 and GFAP) while demonstrating immunoreactivity for other tissue lineage markers that were otherwise negative in the glial component (including SMA, SATB2, synaptophysin, chromogranin). In three cases, p53 immunohistochemistry was diffusely positive in both the glial and transdifferentiated component. Next-generation sequencing was performed in all cases and detected TERT promoter (5/5), TP53 (3/5), and RB1 (2/5) mutations, as well as MYCN amplification (3/5), consistent with the current definition of IDH-wildtype glioblastoma.

Conclusions: This series of glioblastoma with transdifferentiation of neoplastic glial cells to other tissue lineages highlights the heterogeneous, “multiforme” histologic spectrum of this tumor entity. Glioblastoma with transdifferentiation should be considered in the differential of other primary or radiation-related cranial sarcomas in the proper demographic and clinical settings.

24

Low-grade Oligodendroglioma With Sarcomatous Transformation While On A Novel IDH Inhibitor.

L Evans, V Venur, S Emerson, K Galbraith; University of Washington

Background: A 22-year-old male with no significant past medical history presented with new onset seizure activity in 2020. Brain magnetic resonance imaging demonstrated an intrinsic, non-enhancing mass throughout the left temporal lobe. He underwent a subtotal resection, which histologically showed an infiltrating glial neoplasm with minimal mitotic activity and no microvascular proliferation or necrosis. Pathology was finalized as an oligodendroglioma, IDH-mutant and 1p/19q-codeleted, CNS WHO grade 2. The patient enrolled in the INDIGO clinical trial utilizing a novel IDH-inhibitor, vorasidenib, initially in the placebo group, but with subsequent crossover to the treatment arm after disease progression was noted. Surveillance imaging a year after crossover demonstrated a small enhancing extra-axial mass at the posterior margin of the resection cavity. Subsequent imaging demonstrated progressive growth, with primary differential considerations including malignant transformation versus a meningioma.

Methods: He underwent surgical re-resection to clarify the diagnosis. Histomorphologic and immunohistochemical evaluation was completed in addition to next-generation sequencing and DNA methylation analysis.

Results: The specimen contained a hypercellular, pleomorphic glial neoplasm with prominent spindle cell morphology and markedly increased mitotic activity. Neoplastic cells were immunoreactive for GFAP and IDH1 R132H, while demonstrating retained nuclear reactivity with ATRX and increased TP53 staining. 1p/19q co-deletion was detected by fluorescence in situ hybridization. Additionally, the neoplasm showed loss of Olig2 immunoreactivity, with increased reticulin and smooth muscle actin expression, consistent with a sarcomatous transformation. Next-generation sequencing detected mutations in IDH1 R132H, TERT promoter, and TP53, with no CDKN2A/B co-deletion. Additionally, DNA methylation analysis revealed that the tumor classified as an oligosarcoma, IDH-mutant (confidence score of 0.9986).

Conclusions: This is a rare and aggressive malignant transformation of the patient’s prior low-grade oligodendroglioma, a finding that has yet to be documented while on the novel IDH-inhibitor vorasidenib.

25

Sporadic Subependymal Giant Cell Astrocytomas: An Institutional Review of 5 Cases

R Revia [1], S Guzman [1], A Toland [2]; [1] University of Colorado, [2] Children's Hospital of Colorado

Background: Subependymal giant cell astrocytoma (SEGA) is a rare tumor which characteristically occurs within the lateral ventricle near the foramen of Monro in patients with tuberous sclerosis (TS). Rare cases of sporadic SEGA are described in the literature, though no large case series have been published to date. We expand on these tumors with a review of five cases.

Methods: Search terms in the electronic medical record included “subependymal giant cell astrocytoma” and “SEGA” diagnosed between 2000 and 2025. Clinical and imaging information was derived from the patient charts. Histology slides were retrieved, and the diagnoses were reviewed in conjunction with molecular data, if available.

Results: Five cases meeting inclusion criteria were identified. Four cases were confirmed with germline genetic testing and demonstrated a TSC1 or TSC2 mutation in the tumor. Median age at diagnosis was 9 years (range 6-29). Three patients were female. Four patients presented acutely, three with headache and one with vision changes. One patient also had acute intraventricular hemorrhage. The remaining tumor was identified incidentally following trauma. All tumors were located in a lateral ventricle near the foramen of Monro. Detailed radiologic information was available for four cases: Three demonstrated calcifications and all showed peripheral enhancement with focal restricted diffusion. All tumors were ≥2.0 cm. All tumors showed epithelioid cells well-demarcated from background parenchyma. Mitotic activity ranged from 0-4/10 HPF. IHC for TTF-1 was performed on four cases and was diffusely positive. GFAP, S100, and synaptophysin showed variable expression. OLIG2 and SOX10 were negative. MIB-1 showed proliferative indices of < 1-7%.

Conclusions: Given their rarity, sporadic SEGAs may be a cause for diagnostic confusion. However, all cases in this series demonstrated histologic and immunophenotypic features identical to their syndromic counterparts. Additionally, 100% of tested tumors similarly showed TSC1/2 mutations which were not present in the germline.

26

Glial neoplasm with myogenic differentiation and BRAF V600E mutation: a novel entity?

M Elnagdy [1], C Cai [2], E Daoud [2], K Hatanpaa [2]; [1] University of Texas Southwestern Medical Center, [2] UT Southwestern Medical Center

Background: Neoplasms demonstrating biphenotypic differentiation are rare. Dual glial and myogenic differentiation with both GFAP and desmin immunopositivity has not been previously described.

Methods: We report a diagnostically challenging suprasellar neoplasm with distinct histopathological and molecular features, suggesting a novel entity.

Results: A 22-year-old female presented with headaches and right-sided vision loss. MRI revealed a homogeneously enhancing, lobulated suprasellar mass measuring 3.4 cm. A transsphenoidal endoscopic biopsy was performed. Intraoperatively, a grayish tumor which appeared to arise from the optic pathway was encountered. The tumor was composed of spindle cells arranged in fascicles in a collagen-containing stroma. There were no eosinophilic granular bodies, Rosenthal fibers, or pleomorphic astrocytes. There was no necrosis, microvascular proliferation, or infiltration. The immunohistochemical profile was GFAP+(strong, diffuse)/desmin+(strong, diffuse)/SSTR2-/EMA-/TTF-1-/STAT6-/SOX10+/S100+. The mitotic index and MlB-1 proliferation index were up to 5/5 HPF and approximately 10%, respectively. An NGS panel revealed a BRAF V600E mutation and homozygous CDKN2A/B deletion. Methylation profiling (NCI/NIH) was inconclusive, with low-confidence scores split between PXA and HGAP. She underwent radiosurgery. Further treatment with a BRAF inhibitor and bevacizumab is planned.

Conclusions: This is a unique neoplasm with a BRAF V600E mutation and dual GFAP/desmin expression, indicating biphenotypic glial/myogenic differentiation. The differential diagnosis included biphenotypic sinonasal sarcoma (BSNS), which is characterized by dual neural (S-100+) and myogenic (desmin+) differentiation as well as PAX3 fusion; however, BSNS can be excluded in this case based on the molecular findings and GFAP-positivity. The absence of a high-confidence match on methylation profiling supports the possibility of a novel entity.

27

Rare Intronic BRAF Gene Fusion in a Recurrent Parietal Pleomorphic Xanthoastrocytoma: A Case Report

D Mansour, L Chen, P Singh; University of Minnesota Medical School

Background: Pleomorphic xanthoastrocytoma (PXA) is a rare primary astrocytic tumor predominantly affecting children and young adults, with a preference for the temporal lobe. Classified as WHO grade II, PXAs can progress to grade III with anaplastic features, characterized by increased mitotic activity and/or necrosis. BRAF alterations, particularly the V600E mutation, are common in PXAs, driving tumorigenesis via the MAPK pathway. However, BRAF fusions are rarely reported, and intronic rearrangements within the BRAF gene itself are unprecedented. This case discusses a recurrent grade III PXA in a 39-year-old female, harboring a novel BRAF rearrangement, presenting an unusual pattern of disease progression and recurrence.

Methods: The patient's clinical course was evaluated retrospectively. Detailed clinical history, imaging studies, pathology, and genetic analyses were reviewed. Tumor samples underwent next-generation sequencing (NGS) to identify genetic alterations. Treatments, including surgery, radiation therapy, and targeted therapies, were documented to assess clinical outcomes.

Results: The patient presented with neurological symptoms, including headache, vomiting, and left-sided weakness, leading to the diagnosis of a borderline grade III PXA with a BRAF V600E mutation. Despite multiple resections, radiation therapies, and targeted treatments with BRAF and MEK inhibitors (vemurafenib, dabrafenib, and trametinib), the tumor demonstrated persistent recurrence and progression over five years. NGS identified a novel intronic BRAF fusion joining exon 18 (5' partner) with exon 10 (3' partner). Tumor extension into the parietal scalp along the biopsy tract was observed, raising hypotheses of surgical contamination or tract invasion.

Conclusions: This is the first report of an intronic BRAF fusion in PXA. The rearrangement may contribute to the tumor's aggressive and recurrent nature. This case emphasizes the role of comprehensive genomic profiling in uncovering novel genetic drivers and highlights the need for further research to elucidate the clinical implications of BRAF fusions in PXA.

28

Ganglioglioma with KCTD8-NTRK2 Chromosomal Rearrangement

A Krbanjevic [1], B Mobley [2], P Paueksakon [2]; [1] Vanderbilt University, [2] Vanderbilt Unviersity

Background: Gangliogliomas are low-grade, slow-growing CNS tumors composed of glial and neuronal components. These lesions do not show predilection to a specific nervous system anatomic region and can occur both supra- or infratentorially. The mitogen-activated protein kinase (MAPK) pathway, per current WHO classification of CNS tumors, is the signature alteration that underlies molecular pathogenesis of gangliogliomas. Of those, BRAF V600E variant is the most commonly seen in gangliogliomas, while BRAF fusions, KRAS mutations, FGFR1 mutations and NF1 mutations or deletions have also been described. The KCTD8-NTRK2 chromosomal rearrangement represents a rare fusion of the potassium channel tetramerization domain 8 gene (KCTD8) and the neurotrophic tropomyosin receptor kinase (NTRK2) gene and is described in up to 3% of high-grade gliomas.

Methods: Here we report a case of a 12-year-old female who initially presented with focal seizures with aura, right sided numbness, arm and face twitching and normal brain MRI. Six months later, her frequency of seizures increased, and brain MRI demonstrated a cortically based left precentral gyrus ill-enhancing lesion. The radiological differential diagnosis suggested a low-grade neoplasm.

Results: Histologic examination showed neoplastic proliferation of cells with stipulated, round nuclei and scant cytoplasm, scattered neoplastic neurons with distinct nucleoli and occasional binucleation. On immunohistochemistry, tumor cells were diffusely positive for OLIG2 and S100 while partially positive with GFAP or Neu-N stains. NGS data showed presence of three copies of BRAF gene and an unusual KCTD8-NTRK2 fusion. DNA methylation profiling assay did not manage to classify this tumor into any up-to-date known methylation cluster.

Conclusions: Overall, the clinical, radiographic, and histologic findings of this molecularly unusual low-grade lesion are most consistent with ganglioglioma. A postoperative clinical course confirms a low-grade tumor behavior despite the “aggressive” molecular fusion detected.

29

Ultra-hypermutant Astrocytoma with IDH1 Mutation and Epigenetic Features of High-grade Astrocytoma with Piloid Features (HGAP) – A Case Report

H Smith [1], M Mejia-Bautista [1], E Adams [1], J Ahrendsen [1], D Duckett [1], B Nezami [1], L Santana-Santos [1], M Sukhanova [1], L Jennings [1], C Horbinski [1], D Brat [1], R Castellani [1], K Conway [2], P Jamshidi [1]; [1] Northwestern Memorial Hospital, [2] University of Michigan

Background: Methylation profiling has joined next-generation sequencing (NGS) and copy number analysis among the tools used to diagnose and define central nervous system (CNS) tumors. We describe an astrocytoma harboring a mutation in IDH1 with ultra-hypermutant phenotype, and a DNA methylation profile matching high-grade astrocytoma with piloid features (HGAP), meeting criteria for two distinct pathologic entities.

Methods: A 75-year-old male with no relevant medical history presented with headaches and was found to have a large, heterogeneously enhancing right parietal lobe mass on brain MRI. He underwent craniotomy for gross total resection.

Results: Histopathologic examination revealed a hypercellular, infiltrating glioma with pleomorphic nuclei, myxoid matrix, and robust microvascular proliferation. NGS revealed a non-canonical IDH1 (R132C) mutation, microsatellite instability due to somatic mutations in MSH6 and polymerase epsilon (POLE), and a tumor mutation burden of 1368.6 Muts/Mbs. Mutational signature analysis confirmed high contributions from defective DNA mismatch repair (score 0.331) and concurrent POLE mutation (0.146). DNA methylation microarray using the National Cancer Institute's Bethesda v2 classifier matched HGAP with high confidence (score 0.996).

Conclusions: The tumor meets diagnostic criteria for two disparate tumor types within the 2021 WHO CNS Classification – astrocytoma IDH-mutant by NGS and HGAP, by methylation profiling. While never reported in HGAPs, IDH mutations are not listed as exclusion criteria; the sole requirements for diagnosis are astrocytic lineage and a methylation profile matching HGAP. Targeted therapy options depend on objective and reproducible diagnosis. This case raises diagnostic and bioethical challenges in cases with conflicting molecular data.

30

Novel ZFTA fusion partner in supratentorial ependymoma arising in the midbrain and basal ganglia

s ahuja [1], M Edelman [2], M Atlas [3], S Rodgers [3], A Johnson [3]; [1] Long Island jewish Medical Center New York, [2] Long Island Jewish Medican center New York, [3] Long island Jewish Medical center

Background: Supratentorial ependymomas are molecularly divided into ZFTA and YAP fusion positive. We here describe a novel case of supratentorial ependymoma with ZFTA::MRFTA fusion positive. This fusion partner with ZFTA has only been described in chondroid lipomas

Methods: A 17-year-old male presented with worsening headaches, vomiting and slurred speech for approximately 2 months. MRI showed bilobed 5 cm mixed solid and cystic mass involving the left thalamus and midbrain. ROSA biopsy was performed

Results: Histological examination shows an infiltrating glial neoplasm without mitosis or necrosis with unequivocal perivascular pseudorosette formation. By IHC, the tumor is H3K27 wild type, IDH wildtype, ATRX wildtype, negative SOX-10 with limited olig-2 expression and rare EMA dot like labeling. Molecular analysis showed ZFTA::MRFTA fusion. Copy number alterations included whole-arm 1 q gain and terminal 6 q loss which have been described in ependymomas. On Methylation studies, lesion was closest to the ependymal tumor superfamily and supratentorial ependymoma. The ZFTA fusion family /class/subclass show a low classifier score (0.3527 and 0.2864 respectively). Subsequent resection showed moderate to densely cellular glial neoplasm arranged in vaguely formed tubules and prominent perivascular arrangement, typical of ependymomas. The tumor cells were immune negative for EMA and showed positivity for D240. The diagnosis of supratentorial ependymoma, CNS WHO Grade 2 ZFTA::MRFTA fusion positive was made

Conclusions: ZFTA (also known as C11orf95) encodes a zinc finger protein, known to be involved in transcriptional regulation. MRFTA (also known as MKL1 or MAL) belongs to MRTF family, which functions as co-activator in regulation of cytoskeletal genes that are essential for gastrulation, cell survival and apoptosis. This midbrain/basal ganglia tumor represents an infrequent location with novel ZFTA fusion partner

31

Ependymoma-like Tumor with Mesenchymal Differentiation (ELTMD) with ZFTA fusion: a Case Report and Literature Review

D Lombardo [1], A Tannenbaum [1], M Gurney [2], J Helgager [1], K Han [1]; [1] University of Wisconsin Hospitals and Clinics, [2] SSM Health St. Mary's Hospital - Madison

Background: Ependymomas account for 1.6 -1.8% of primary CNS tumors. Modern classification of ependymomas considers histology, location within the neuroaxis, and molecular genetic aberrancies. While different histomorphologic appearances have been described, supratentorial ependymomas characteristically harbor ZFTA or YAP1 fusions, the former with a worse prognosis.

Methods: We present a case of a 42-year-old woman with persistent headaches, who is otherwise healthy. Imaging reveals a multinodular cystic mass, which was resected. Histology, immunohistochemistry, and next generation sequencing is conducted. The patient’s medical record is reviewed, and a literature search with relevant key words is conducted.

Results: Histology reveals nests of embryonal-like epithelioid cells with a myxoid background, with foci of mesenchymal differentiation and necrosis. Immunohistochemistry shows strong Cam 5.2 positivity, while Olig 2, GFAP, and EMA are negative. Next generation sequencing reveals a ZFTA:NCOA1 fusion, which under the current WHO is diagnostic for supratentorial ependymoma with ZFTA fusion. Literature review of similar tumors reveals seven additional cases of the working entity of Ependymoma-like Tumor with Mesenchymal Differentiation (ELTMD). Demographic analysis reveals an average age of 16.75 years, with 75% (6/8 cases) occurring in children under 5 years old and a female predominance (male-to-female ratio of 1:3). The majority of cases (7/8 cases) have both solid and cystic components on imaging, and all 8 cases are located in the cerebrum. All cases demonstrate areas of mesenchymal morphology, many with embryonal-like areas. Immunohistochemistry for CAM 5.2 shows diffuse positivity in 6/8 cases, faint positivity in one, and no staining in the other.

Conclusions: While ELTMD with a ZFTA fusion satisfies the current supratentorial ependymoma WHO diagnostic criteria, it presents a diagnostic challenge in morphology and immunohistochemical studies. With additional data, this tumor may prove to be similar to but distinct from ependymoma, with unique demographic and prognostic characteristics.

32

Rare posterior fossa high-grade astrocytoma with unique dot-like H3k27me3 attenuation and varied histopathologic features

M Milani [1], C Chen [2], R Lall [3], E Neil [2], G Fitzpatrick [2]; [1] University of Minnesota, [2] University of Minnesota Medical School, [3] M Health Fairview

Background: Cerebellar high-grade gliomas (cHGG) comprise 1% of all CNS high grade gliomas. High-grade astrocytomas of the posterior fossa represent a rare subclass and are diagnostically complex, requiring molecular profiling for accurate classification, due to similarities with other entities such as diffuse midline gliomas, H3 K27-altered, or pediatric-type high-grade gliomas.

Methods: We present a case of a 62-year-old female with a high-grade infiltrating astrocytoma located in the right cerebellum, initially presenting with dizziness and right-sided dysmetria. MRI revealed a 5.7 cm heterogeneously enhancing lesion in the right cerebellar hemisphere involving the cerebellar peduncle with mass effect on the fourth ventricle. The patient underwent resection.

Results: Histopathological examination demonstrated a highly cellular infiltrative tumor with morphology resembling small cell glioblastoma, with dense cellularity, palisading necrosis, and focal microvascular proliferation. Additional features include perivascular pseudorosettes, numerous psammomatous microcalcifications, and focal primitive morphology with nuclear molding. Ki-67 labeling index was up to 90%. There was both widespread Olig2 and synaptophysin expression, variable GFAP, and severe attenuation of H3K27me3 with a unique intranuclear dot-like pattern, raising concern for diffuse midline glioma. Next-generation sequencing identified a PDGFRA amplification, deletions of 9p (including CDKN2A/B), 1p, 6q, and 13q, while excluding IDH1/IDH2 and H3-3A mutations. By whole genome methylation profiling, the tumor matched to methylation class "High-grade wildtype astrocytoma, posterior fossa", an uncommon methylation class corresponding best with glioblastoma, IDH-wildtype.

Conclusions: This case highlights diagnostic challenges that posterior fossa high-grade gliomas present, including recognition of rare and evolving entities with heterogeneous morphology lacking traditional molecular features of glioblastoma. Additionally, this case highlights the need for continued attention to H3K27me3 staining patterns in gliomas clinically compatible with diffuse midline glioma.

33

Novel case of ependymoma with clear cell features and IDH2 mutation in a patient with Maffucci syndrome

D BeDell, C Ozutemiz, A Venteicher, G Fitzpatrick; University of Minnesota Medical Center

Background: Maffucci syndrome (MS) and closely related Ollier disease (OD) are characterized by multiple enchondromas and hemangiomas with somatic mosaicism of the IDH1/2 mutation having been detected in 77%–87.5% of MS cases. Several gliomas classified as oligodendroglioma, astrocytoma, and oligoastrocytoma with confirmed IDH mutation in Maffucci syndrome and Ollier disease patients are reviewed in recent reports, as well as one case of ependymoma without an IDH mutation in the tumor. To date, no ependymomas with an IDH mutation have been reported.

Methods: We present a case of a 54-year-old man with a history of Maffucci syndrome with multiple prior excisions of benign soft tissue vascular lesions of the extremities and an intraventricular mass resected 24 years prior which was diagnosed as central neurocytoma. He presented with memory issues, gait unsteadiness, and urinary incontinence and MRI demonstrated a large heterogeneous mixed solid and cystic mass with heterogeneous enhancement involving the septum pellucidum at the site of previous resection. Biopsy and resection were performed.

Results: Histologically, the tumor showed clear cell features reminiscent of either oligodendroglioma or central neurocytoma with rare mitoses and occasional perivascular pseudorosettes. The tumor showed an ependymoma-like immunophenotype, with perinuclear dot-like EMA positivity, patchy GFAP positivity, rare cells positive for Olig2, and no synaptophysin positivity. Molecular testing revealed an IDH2 R172S and TERT promoter mutation, and no copy number alterations were identified by chromosomal microarray. The tumor did not match to any specific methylation class by whole genome methylation profiling.

Conclusions: To our knowledge, this is the first report of an IDH-mutant ependymoma secondary to somatic mosaicism in a patient with Maffucci syndrome, with oligodendroglioma-like cytologic features further complicating the diagnosis.

34

Diagnostic challenges and longitudinal genomic analysis of a highly recurrent MN1:BEND2 fusion tumor lacking classical astroblastoma features

A Huttner [1], M Aboian [2], T Klug [1]; [1] Yale University, [2] Children's Hospital of Philadelphia

Background: CNS high-grade neuroepithelial tumors with MN1 alteration (HGNET-MN1) form a rare subset of CNS embryonal tumors with distinct methylation profile. Most tumors occur in pediatric patients and are viewed as clinically favorable due to reported histological similarities with ‘astroblastoma’. Over the past years, however, the tumor’s striking morphologic diversity was recognized, including the occasional lack of astroblastoma-like features. Further, frequent tumor recurrences and genomic alterations pose additional diagnostic/clinical challenges

Methods: Here, we present the case of a 15-year-old girl who presented 6 years earlier with a large heterogeneous frontal lobe mass with irregular enhancement, focal cystic/necrotic changes and midline shift. Microscopic analyses displayed extensive morphologic heterogeneity with mixed, yet distinct histologic components.

Results: While much of the lesion showed poorly differentiated tumor cells admixed with necrosis and high proliferative rate (Ki6715-20%), only a minute focus suggested the presence of perivascular pseudorosettes, aside from areas of desmoplasia and sclerosis. Despite optimal clinical treatment, the tumor recurred twice over the following 5 years to display only aggressive morphology paired with extremely high proliferative activity (Ki67~60%). Interestingly, astroblastoma-like features were not identified in any of the re-resections. Molecular analyses of tumor recurrence samples demonstrated stability of the MN1:BEND2 fusion, which was originally identified via FISH and categorized by methylation analysis. However, while the molecular profile overall appeared to remain stable, the most recent resection sample demonstrated additional somatic variants involving BRCA2 and CDK12.

Conclusions: Although studies have proposed HGNET-MN1 tumors to be ‘astroblastoma’ due to certain histo-morphological similarities and more favorable outcomes, the degree of diversity within this unusual tumor entity poses significant challenges not only for the diagnostic process but also for treatment. It will be crucial to carefully analyze and dissect the spectrum of this tumor as its recognition will be of critical importance for subsequent efficient neuropathological workups, molecular characterization and treatment.

35

Identification of MYO5A::NTRK3 Gene Fusion in a Recurrent IDH1 R132G-Mutant Astrocytoma: Implications for Targeted Therapy

A Aksionau, S Neill, M Abedalthagafi; Emory University Hospital

Background: We report a unique case of recurrent IDH1-mutatnt astrocytoma with a MYO5A::NTRK3 gene fusion, a rare finding with significant therapeutic implications. The patient, a 44-year-old male, was initially diagnosed in 2015 with grade 3 IDH1 R132G-mutant astrocytoma and presented with concerns of recurrence.

Methods: Histopathologic examination of the recurrent tumor revealed a high-grade astrocytoma with regions of nuclear pleomorphism, brisk mitotic activity, endothelial proliferation, and necrosis. Immunohistochemistry demonstrated p53 overexpression (>50%, focally), variable ATRX loss, and absence of IDH1(R132H) staining, consistent with a non-canonical IDH-mutant astrocytoma. Molecular analysis identified complex chromosomal abnormalities, including focal homozygous loss of CDKN2A/B and a MYO5A::NTRK3 gene fusion detected through RNA-based fusion panel testing. Retrospective testing of the primary tumor for the fusion was inconclusive due to poor-quality genetic material, leaving uncertain whether the fusion was present at initial diagnosis.

Results: To our knowledge, this is the first reported case of MYO5A::NTRK3 gene fusion in an adult high-grade IDH-mutant astrocytoma. The presence of this fusion in the recurrent tumor highlights its potential role as an oncogenic driver and a promising therapeutic target.

Conclusions: This case underscores the importance of molecular testing in recurrent astrocytomas to identify actionable targets, such as MYO5A::NTRK3 fusion, which may guide the use of NTRK-targeted therapies (e.g., larotrectinib, entrectinib). Identifying such alterations provides opportunities for personalized treatment and improved outcomes, particularly in aggressive gliomas. Further studies are warranted to explore the therapeutic potential of NTRK inhibitors in this context.

36

Histological and Immunohistochemical Assessment of Cellular Heterogeneity in Pediatric Ependymomas

M Alturkustani, ; King Abdulaziz University

Background: Molecular studies indicate that pediatric ependymomas exhibit cellular heterogeneity, characterized by distinct cellular populations. However, a major limitation in studying this heterogeneity is the histological identification of these diverse regions. This study compares histological features and the immunostaining patterns of GFAP and EMA across different regions of ependymoma subtypes to determine whether cellular heterogeneity can be identified morphologically.

Methods: Data were obtained from The Children's Brain Tumor Network online database, including 97 cases diagnosed as ependymoma. Methylation profiling was performed using the Heidelberg Brain Tumor Classifier. Inclusion criteria were restricted to cases classified as ependymoma by methylation profiling with available GFAP and EMA immunostaining.

Results: A total of 20 ependymoma cases met the inclusion criteria, comprising 10 posterior fossa type A (PFA), 9 supratentorial ZFTA-fusion-positive (ST-ZFTA), and one posterior fossa type B (PFB). Ependymomas demonstrated regions with variable cellularity and differing GFAP and EMA staining patterns, with slight variations among molecular subtypes. Low-cellularity regions exhibited an extensive fibrillary background with diffuse GFAP staining, whereas EMA staining predominantly displayed a dot-like pattern. High-cellularity regions had a less prominent fibrillary background, reduced GFAP staining, and a different EMA immunopositivity pattern, characterized by dot-like and granular cytoplasmic staining. Perinecrotic zones exhibited increased EMA and GFAP immunostaining in neoplastic cells.

Conclusions: Ependymomas display distinct regions with variable cellularity and differential GFAP and EMA immunostaining patterns, with some features being more common in certain subtypes. However, the ability to distinguish molecular subtypes based solely on these histological and immunohistochemical characteristics is limited, as their distribution is region-dependent rather than subtype-specific.

37

The need of integrated diagnosis in spinal ependymomas. A report of 2 cases

P Loreto Palacio, A Blitz, M Cohen, M Couce, T Hodges; University Hospitals Cleveland Medical Center

Background: Ependymomas comprise a heterogeneous group of central nervous system (CNS) tumors with varying histopathological and molecular characteristics. The 2021 World Health Organization (WHO) classification integrates histologic and molecular features for improved diagnostic accuracy. While classic spinal ependymomas are well characterized, unusual subtypes, particularly those with atypical locations or histology, present unique diagnostic and therapeutic challenges.

Methods: We present two unusual adult spinal ependymomas emphasizing histologic evaluation, immunophenotyping, and molecular characterization using next-generation sequencing and methylation profiling.

Results: Case 1 presented an intra-axial mass at the involving the cranio-cervical junction and inferior medulla. Case 2 demonstrated an intradural/extramedullary enhancing mass extending from T9 through T11. Both cases demonstrated low-grade glial histology without mitoses, necrosis, rosettes or pseudorosettes. Both were positive for GFAP, exhibited perinuclear dot-pattern EMA immunoreactivity, and did not react with OLIG2 or SOX10 antibodies. Case 1 contained NF2 and SUFU mutations, while Case 2 showed an NF1 mutation and MYCN amplification. Methylation profiling confirmed spinal ependymoma in both cases, and Case 2 classified as the MYCN-amplified subclass, both with high confidence scores (0.99).

Conclusions: These cases highlight the value of integrating histopathology with molecular diagnostics in suspected spinal ependymomas, especially when encountered in uncommon location and without typical histopathological features. Immunohistochemistry remains essential for narrowing the differential diagnosis, while molecular profiling may provide critical diagnostic and prognostic information. MYCN-amplified spinal ependymomas represent a distinct high-risk subgroup, reinforcing the value of molecular classification to guide management. Our findings contribute to the growing understanding of spinal ependymoma heterogeneity and the importance of comprehensive diagnostic evaluation.

38

Histologic and molecular characterization of a MAZ::NCOA2 fusion-positive intracranial glial neoplasm

E Stalter, O Lopes Abath Neto, C Voyles; University of Iowa

Background: Gene fusions involving the DNA-binding domain of one partner and transactivation domain of the other often drive tumor progression through defective transcriptional programming. While NCOA2 fusions have been functionally characterized within a variety of tumors, a MAZ::NCOA2 fusion has been previously described only in a single case of intraorbital myoepithelioma. An intracranial glial MAZ:NCOA2 fusion-positive tumor has never been previously identified.

Methods: Clinical history and radiologic imaging were reviewed via the electronic medical record. Histologic characterization was performed through analysis of slides stained with hematoxylin and eosin and a targeted panel of immunohistochemical stains. Molecular characterization was subsequently performed utilizing a next-generation sequencing mutation panel, RNA fusion panel, and DNA methylation profiling.

Results: A previously healthy 12-month-old female presented to the emergency department with a 3-week history of progressive developmental regression, intermittent convulsions, and truncal ataxia. Brain MRI revealed a large, heterogeneous, contrast-enhancing left parieto-occipital mass which underwent subsequent total resection. Histologic analysis revealed a well-circumscribed, variably cellular tumor composed predominantly of spindled cells within a myxoid stroma with hypercellular, mitotically active regions located at areas of interface with reactive brain parenchyma. The immunophenotype was most consistent with a glial neoplasm; GFAP showed predominantly strong positivity but was negative within the hypercellular areas, while OLIG2 showed selective positivity within these regions. SOX10 was positive throughout. Other stains did not support a myoepithelial or polyphenotypic differentiation. Molecular testing revealed a MAZ::NCOA2 fusion. There was no match on multiple classifiers based on DNA methylation profiling.

Conclusions: Because a MAZ:NCOA2 fusion-positive glial neoplasm has yet to be described, this case adds to the body of knowledge of infantile CNS tumors. Lack of DNA methylation classification matching suggests this represents a novel tumor type. Follow-up history and reports of additional cases are needed to define its behavior.

39

Insulinoma-Associated Protein 1 as a Marker for Glioblastoma with Primitive Neuronal Component

G Wakeman [1], J DeWitt [2]; [1] University of Vermont, [2] University of Vermont Medical Center

Background: Glioblastoma accounts for the greatest number of malignant neoplasms of the central nervous system (CNS) in adults, averaging an expected survival of fifteen months post diagnosis. Glioblastoma with primitive neuronal component (GB-PNC) is a subcategory of glioblastoma with features of both malignant gliomas and neuroectodermal tumors. Current methods of diagnosing GB-PNC – evaluation of clinical history and histologic examination with immunohistochemical markers – are imperfect, using nonspecific markers that vary in expression among GB-PNC, other CNS neoplasms, and healthy CNS tissue. The aim of this study was to evaluate the expression of a new immunohistochemical marker, insulinoma-associated protein 1 (INSM1), in GB-PNC, with the hypothesis that INSM1 would show selective expression in tissue containing features suspicious for GB-PNC. INSM1 is a nuclear marker found in many neuroendocrine tumors but had yet to be studied in GB-PNC.

Methods: Tissue samples from eight tumors with histologic features suspicious for GB-PNC were cut and stained with hematoxylin and eosin, synaptophysin, and glial fibrillary acidic protein (GFAP) – standard methods for GB-PNC – as well as the experimental INSM1 marker.

Results: Six samples showed negative staining for GFAP in the PNC component, with weakly positive synaptophysin staining suggestive of a true primitive neuronal component. In these cases, INSM1 showed either variable (n = 1) or block-like (n = 5) staining for INSM1 in regions of the tumor with histologic features of PNC, while background non-PNC tumor showed weak scattered INSM1 staining. Two samples demonstrated patchy or positive GFAP, negative synaptophysin, and negative or scattered positive INSM1 staining, making them unlikely to be GB-PNC.

Conclusions: In specimens that appeared consistent with a GB-PNC diagnosis, strong block-like INSM1 staining correlated with this histologic pattern. When a GB-PNC diagnosis was not supported by GFAP and synaptophysin, INSM1 was not well preserved. This suggests INSM1 may have utility in identifying GB-PNC.

40

SLC44A1::PRKCA fusion in tumor lacking papillary glioneuronal tumor morphology

V Huynh [1], A Raghunathan [1], J Hardcastle [1], S Smoley [1], M Isaacson [1], M Gandham [1], S Dasari [1], Z Abdullaev [2], K Aldape [2], M Quezado [2], D Pratt [2], P Cimino [2], C Ida [1]; [1] Mayo Clinic, [2] National Cancer Institute

Background: The essential diagnostic criteria for papillary glioneuronal tumors (PGNT) per the 2021 WHO Classification of CNS Tumors includes PRKCA fusion (especially SLC44A1::PRKCA) AND a biphasic histology and immunophenotype composed of pseudopapillary glial lining and interpapillary neuronal components. Here, we present the case of a 38-year-old man with a history of migraines, who underwent evaluation for increasingly frequent headaches.

Methods: MRIs demonstrated a 2.2 cm well-circumscribed, heterogeneous, partially cystic, calcified, and focally enhancing mass within the right frontal white matter. Histologically, the lesion showed abundant coarse calcifications associated with a predominantly GFAP-positive/OLIG2-positive atypical glial component, characterized by abundant, fibrillary cytoplasm and relatively monomorphic nuclei, and a neuronal component that demonstrated weak chromogranin positivity in a small population. No papillary/pseudopapillary arrangements, biphasic tissue pattern, binucleated neurons, Rosenthal fibers, eosinophilic granular bodies, or mitotic activity were identified. By immunohistochemistry, BRAF-V600E was negative, and the Ki67 labeling index was < 1%. A neuro-oncology targeted next-generation sequencing panel identified an SLC44A1::PRKCA (exon 15::exon 9) fusion. By genome-wide methylation array profiling using the NCI/Bethesda classifier v.2, the tumor methylation profile matched to low-grade glioneuronal tumor family (score 0.990), with suggested methylation class pilocytic astrocytoma, hemispheric (score 0.839), and clustering within this class.

Results: In light of the absence of PGNT morphology, a descriptive diagnosis of an unusual low-grade glioneuronal tumor harboring SLC44A1::PRKCA fusion was rendered.

Conclusions: Postoperatively, the patient experienced improvement in headache frequency and no new neurologic symptoms at 1-year follow up. The discordance between the histomorphology and molecular/methylation profile in this case suggests that SLC44A1::PRKCA fusion is characteristic of, but may not be specific for, PGNT and may be encountered in a wider spectrum of CNS tumors.

41

Glioblastoma Whole Mount Tissue Immunohistochemical Staining of SOX2 and Ki67, Alignment, and Analysis

B Chao, S Duenweg, S Bobholz, M Barrett, A Winiarz, B Nath, A Lowman, F Kyreme, J Connelly, M Krucoff, P LaViolette; Medical College of Wisconsin

Background: Glioblastoma (GBM) is the most common primary brain tumor with a five-year survival rate of 5%. Despite treatment involving resection, chemotherapy, and radiation, tumors inevitably recur. On histology, clear tumor margins are hard to define, impeding treating clinicians to comprehensively identify burdened regions. Currently a combination of hypercellularity, pseudo-palisading necrosis, endothelial proliferation, and increased cell proliferation (high MIB index) are used to identify GBM. These are identified using H&E and Antigen Kiel-67 (Ki-67) stained histology.

Methods: For this study, we collected whole mount tissue samples that were stained with H&E and immunohistochemically (IHC) stains to better identify tumor burden. The IHC stains we used were Ki-67 to calculate MIB index, and SRY-Box 2 (SOX2), a marker for neural stem cell pluripotency. We registered the IHC stained slides to the H&E slides using Valis, a Python-based histology registration pipeline. We used color deconvolution to identify positively and negatively staining nuclei. We created various heatmaps from this data, and compared IHC stains against each other and against H&E.

Results: Preliminary analyses reveal that SOX2+ overlays with H&E hypercellularity and Ki67+. However, SOX2+ was also identified outside of H&E hypercellular regions. Additionally, high MIB colocalized with hypercellular regions on H&E, as well as SOX2+ dense regions outside of hypercellularity. These findings suggest that regions outside of tumor margins have pluripotent and mitotic characteristics, while not necessarily being hypercellular. This could be due to early tumor invasion, reactive gliosis, or a different process entirely. Future work should be done to better characterize this process.

Conclusions: We found that SOX2 staining in addition to H&E and Ki-67 staining may be a useful tool for clinicians when delineating true tumor extent. Our future work will continue to analyze IHCs use in identifying tumor, and we plan on including additional IHC stains to characterize and identify other features of GBM.

42

An Institutional Experience with the DNA Methylation Class High Grade Glioma with Pleomorphic and Pseudopapillary Features

R Alfattal [1], S Weathers [2], P Dasgupta [2], L Ballester [2], M Gubbiotti [1]; [1] University of Texas MD Anderson Cancer Center, Houston, TX, USA, [2] The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background: High grade glioma with pleomorphic and pseudopapillary features (HPAP) comprises a DNA methylation-defined cluster of circumscribed gliomas characterized by recurrent monosomy of chromosome 13 and frequent TP53 mutations. Though not currently recognized by the World Health Organization (WHO), the distinction between HPAP from other high grade gliomas is important as the prognosis is better than glioblastoma, IDH-wildtype.

Methods: The pathology archives at our institution were searched from 2021-2025 for cases of HPAP. Patient demographics, tumor characteristics, and treatment and patient outcomes were analyzed.

Results: Three cases of HPAP were identified (2 female, 1 male). The average age was 49.7 years (range: 25-62). Tumors were located in the frontal (1 right, 1 left) and parietal (right) lobes. Imaging revealed well-circumscribed lesions with two having hemorrhagic components and two with cystic change. All underwent gross total resection. Histology showed circumscribed gliomas with definitive high grade features in 2 cases. Two cases showed overt pleomorphism, one showed ependymal features, and one had foci of papillary architecture. Ki-67 ranged from 5-15%. All cases showed monosomy of chromosomes 13 and 17. Two cases had TP53 mutations. One case had PBRM1 mutation, one case had a TERT promoter and FGFR1 mutation, and two cases showed gain of chromosome 7 with one case also showing concurrent loss of chromosome 10 with EGFR and MET amplification. All patients have been treated with radiation only (1 proton, 2 photon) and no systemic treatment. One patient's tumor was originally diagnosed in 2016 (diagnosis: ependymoma) which recurred in 2023 (re-classified as HPAP). One patient has had no recurrence 17 months from original diagnosis. The last patient has had no recurrence 2 months since diagnosis.

Conclusions: Our institutional experience supports HPAP as a lower risk circumscribed high grade glioma with favorable response to surgery and radiation.

43

Glioblastomas with composite primitive neuronal and sarcomatous components

M Chung [1], K Aldape [2], Y Comair [1], C Dampier [1], C Eberhart [1], M Holdhoff [1], S Lin [1], C Lucas [1], B Ozer [2], M Quezado [2]; [1] Johns Hopkins University, [2] NIH

Background: Glioblastoma is a histologically and molecularly heterogenous tumor. The WHO recognizes “primitive neuronal cells” and “mesenchymal metaplasia” as two of many different histologic patterns seen in glioblastoma. We present a series of glioblastoma cases in which glial, primitive neuronal, and sarcomatous components are simultaneously present in a single resection specimen.

Methods: Immunohistochemistry was performed on whole mount formalin fixed paraffin embedded sections. Next-generation sequencing and MGMT promoter methylation analysis was performed in a subset of cases.

Results: We identified cases from four patients; 1 male and 3 females, age range 50-65 years. All four cases exhibited distinct glial, sarcomatous, and primitive neuronal components. Two cases harbored all three components at initial presentation, while two cases harbored all three components only at time of recurrence. Glial markers (GFAP and OLIG2) demonstrated extensive immunoreactivity within glial components but were otherwise negative or only focally positive in sarcomatous and primitive neuronal components. Primitive neuronal components demonstrated increased immunoreactivity for neuronal markers (Synaptophysin and INSM1) while sarcomatous components demonstrated increased connective tissue deposition (Reticulin and Collagen IV). By next-generation sequencing, one case harbored TERT promoter, PTEN, RB1, and TP53 mutations while another case harbored TERT promoter and PTEN mutations along with MET amplification. MGMT promoter methylation analysis was performed in 3 cases; 1 unmethylated and 2 methylated.

Conclusions: Glioblastoma harboring multiple transdifferentiated components is a rare occurrence. Molecular characterization of individual components to assess for clonal evolution remains a future direction.

44

High-Grade Glioma with Pleomorphic and Pseudopapillary Features (HPAP): A Case Report on a Rare Entity

A Nobee, J Dailey, J Donahue; Brown University Health

Background: High-Grade Glioma with Pleomorphic and Pseudopapillary Features (HPAP), a recently identified subtype of glioma, is a rare entity with limited number of reported cases. HPAP is distinguished by a unique histomorphologic profile, with similarities to pleomorphic xanthoastrocytoma (PXA), astroblastoma, ependymoma, polymorphous neuroepithelial tumor of the young (PLNTY), and glioblastoma (GBM). Its unique methylation profile is characterized by mutations in TP53, RB1, NF1, NF2, BRAF V600E and CDKN2A/B. Chromosomal alterations include frequent aneuploidy, loss of chromosome 13, losses of chromosomes 3, 6, 10-15, 17, 18, 22, and gains of chromosomes 4q, 5, 7, 19. Here, we report a case of a high-grade glioma in a young female confirmed as HPAP on methylation profiling.

Methods: N/A

Results: A 31-year-old female presented with intermittent headaches and was found to have a large left frontal intra-axial glial neoplasm on imaging. Histology revealed a biphasic tumor with foci resembling pleomorphic xanthoastrocytoma (PXA), admixed with oligodendroglial-like areas, calcifications, necrosis, elevated mitotic count, and increased Ki-67 proliferative index. The lack of reticulin staining and no BRAF alterations made PXA unlikely, while the IDH-wildtype status with retained chromosomes 1p and 19q ruled out an oligodendroglioma. TP53 c.644G>A and CYSLTR2 c.395T>G mutations were also identified. Subsequent testing showed losses in chromosome 13 and 17 and methylation classifier diagnosis of "high-grade glioma with pleomorphic and pseudopapillary features" (HPAP).

Conclusions: Diagnosing HPAP is challenging due to its similarities with other high-grade gliomas. Accurate diagnosis requires a combination of clinical, radiologic, histologic, and molecular data. HPAP generally has a better survival rate than glioblastomas and may have targeted therapies due to its molecular profile, underscoring the need for precise identification. This case report aims to enhance understanding of HPAP, aiding its recognition and differentiation from other high-grade gliomas for accurate diagnosis and management.

45

Pediatric Diffuse Midline Glioma with ACVR1 mutation and subsequent EZHIP overexpression

E Smith [1], D Ellison [2], K Jones [3]; [1] Duke Department of Pathology, [2] St. Jude Children's Research Hospital, [3] Duke University Hospital

Background: Diffuse midline gliomas (DMG) are an aggressive subset of pediatric brain tumors which often harbor the canonical H3 p.K27M mutation resulting in loss of H3K27 trimethylation (H3K27me3). This entity was incorporated into the WHO CNS 5th edition as: “Diffuse Midline Glioma, H3 K27-altered” with recent literature describing a small subset of DMG that exhibit loss of trimethylation in absence of the H3 p.K27M mutation. These less common DMGs harbor EGFR mutations or EZHIP overexpression. EZHIP overexpression can be driven by various molecular alterations; one that has been rarely reported is mutations in ACVR1.

Methods: Here, we report a case of a 10-year-old female with unremarkable past medical history who was admitted to our institution with dizziness, headache, and gait changes. Subsequent imaging demonstrated a large, peripherally enhancing lesion within the mid pons. Biopsy was performed and was diagnosed as glioma, but tissue was too limited for NGS. A limited panel by Sanger sequencing was performed and showed no mutations in IDH1/2, TERT, or H3-3A. Repeat biopsy was negative for H3 p.K27M via mutation-specific immunohistochemistry but demonstrated a significant loss of H3K27me3. An in-house NGS panel identified point mutations in both ACVR1 and PIK3CA. Considering the loss of trimethylation for H3K27 and the ACVR1 mutation, the case was sent to an outside institution for EZHIP immunostaining, which displayed overexpression, confirming the diagnosis of Diffuse Midline Glioma, H3 K27-altered.

Results: N/A

Conclusions: This case highlights the broad and sometimes challenging differential when examining pediatric gliomas. Additionally, it serves as an example of the utility of H3 p.K27M immunostaining in conjunction with H3K27 trimethylation immunostaining, especially when these two tests may demonstrate contradictory staining patterns. Finally, it adds to the growing cohort of pediatric DMG that have non-canonical molecular features, like EZHIP overexpression in the setting of ACVR1 mutation.

46

Metastatic Melanoma Involving a Glioblastoma: a Potentially Tricky Diagnosis Confirmed with Individual Genotypic Profiles

S Cain, J Crow, M Haeri, S Hyter, W Zhang, N Lakis; University of Kansas Medical Center

Background: A 74-year-old male with a remote history of melanoma, status-post resection 35 years prior, was found to have a multiple ring-enhancing supratentorial intracranial lesions. A craniectomy with resection of three separate/distinct masses revealed an epithelioid tumor, a high-grade glioma, and a high-grade glioma focally involved by epithelioid tumor. The epithelioid foci were morphologically compatible with metastatic melanoma. The glioma demonstrated all classic histologic features of glioblastoma.

Methods: N/A

Results: Immunohistochemical stains S100, SOX10, and panMel were positive in the epithelioid components. The high-grade glioma was positive for GFAP and negative for IDH1-R132H (wild-type). Comprehensive next generation sequencing (NGS) was performed on each mass, including a microdissected slide of the combined epithelial and glial focus. The epithelioid tumor showed BRAF V600E and PTEN mutations. The glioblastoma exhibited TERT, NF1, and PTEN mutations and was notably negative for IDH1/2, H3-3A, and BRAF V600E mutations. The final diagnosis included metastatic melanoma, glioblastoma, IDH wild-type, CNS WHO grade 4, and glioblastoma focally involved by metastatic melanoma.

Conclusions: Due to the presence of BRAF V600E mutation in an epithelioid tumor within the central nervous system, epithelioid glioblastoma had to be considered. Although these tumors have BRAF V600E mutations, they do not express specific melanocytic immunohistochemical markers such as MART-1/Melan-A and HMB45 (constituents of panMel). Additionally, the presence of two distinct genotypes in the different tumors is a strong argument against a glioblastoma presenting with multiple phenotypes.

47

Circumscribed astrocytoma with VGLL-fused: A Case Report

Z Piao [1], A Mhoyan [2], S Kirschbaum [2], P Kim [2], R Guzman-Marin [2], R Green [2], F Torres [2], P Gabikian [2], V Chhabra [2], D Wang [2], Y Mao [2], M Ghassemi [2]; [1] Southern California Permanente Medical Group, [2] SCPMG

Background: Background: A 21-year-old female had a history of ocular migraines in the context of harboring a known since childhood. A 1.3 cm enhancing intra-axial mass was in the deep white matter tract of the left temporoparietal lobe with surrounding vasogenic edema based on serial MR imaging. It has been reported that VGLL3 gene fusion has been found in peripheral schwannoma, CNS schwannoma, spindle cell rhabdomyosarcoma, and VGLL3 amplification occurs in myxoinflammatory fibroblastic sarcoma and others; but not been found in astrocytoma.

Methods: Methods: Histological sections reviewed a dense cellular tumor composed of spindle cells with focal cytologic atypia, hyalinized blood vessel, and old hemorrhage. Immunohistochemical studies showed that the tumor cells are diffusely positive for GFAP, SOX10, S100 and focally for Olig2; negative for BRAF, IDH1, synaptophysin, INSM1, and neurofilament. Stain with Ki-67 shows a low labeling index. Second-generation of sequencing (NGS) was performed at Caris life science. Genomic DNA methylation analysis was performed at NIH.

Results: Results: Caris-NGS molecular studies showed that there is a CHD7::VGLL3 fusion. Genomic DNA methylation analysis (NIH) showed that the tumor matches a provisional diagnostic methylation class of CNS schwannoma, VGLL-fused.

Conclusions: Conclusions: We report a well-circumscribed glioma with CHD7::VGLL3 fusion. It has been reported that intracerebral schwannomas are usually diffusely positive for S100, but infrequently express GFAP. The histologic appearance of this tumor in isolation would be most consistent with circumscribed astrocytoma. This tumor is diffusely positive for GFAP and focally positive for Olig2, along with diffusely positive for S100 and SOX10; therefore, it is best to classify this tumor as a circumscribed astrocytoma with VGLL-fused rather than an intra-axial parenchymal schwannoma.

Posters: Neurodegenerative: Alzheimer

48

Neuropathology of NCI, MCI, clinical Alzheimer's dementia, and cognitive decline in community-dwelling elders who die as centenarians

P Mojdeganlou [1], S Agrawal [2], D Bennett [2], J Schneider [2], L Yu [2]; [1] Rush Alzheimer's Disease Center, Rush University Medical Center, [2] Rush Alzheimer's Disease Center

Background: Brain pathologies are common in the elderly; however, their contribution to cognitive decline in those who die as centenarians remains unclear. This study examines the frequency of neuropathologic substrates and their association with cognitive decline in these people.

Methods: Data came from two community-dwelling older cohorts. All the participants (N=106, mean age-at-death=102±1.84 years, 84% women) underwent annual clinical evaluations and autopsy. Neuropathologic evaluation included AD neuropathological changes (ADNC), limbic-predominant age-related TDP-43 encephalopathy (LATE-NC), neocortical Lewy bodies (LBs), hippocampal sclerosis of aging (HS-A), and cerebrovascular disease (CVD) pathologies (atherosclerosis, arteriolosclerosis, cerebral amyloid angiopathy, and cerebral infarcts).

Results: Sixty-one participants (57%) had Alzheimer's dementia, 22 (21%) had mild cognitive impairment (MCI), and 23 (22%) showed no cognitive impairment (NCI) at their last evaluation (mean last clinical evaluation to death = 1.75 ± 2 years). Nearly all three diagnostic groups exhibited pathologies, including any type of CVD (94%), ADNC (74%), LATE-NC (56%, 32% of them exhibiting HS-A, all with HS-A had LATE-NC), and neocortical LBs (11%), except for one participant with NCI and one with MCI, suggesting resilience factors in both groups. Mixed pathologies, particularly LATE-NC+ADNC+any CVD type, were common in the Alzheimer's dementia group (51%) compared to NCI (35%) and MCI (23%) ($P < 0.05$). In mixed-effect models, after adjusting for demographics and other pathologies, only LATE-NC was associated with a faster decline in global cognition, episodic, and semantic memory ($P < 0.05$). Furthermore, only LATE-NC, but not ADNC and other brain pathologies, was associated with increased odds of Alzheimer's dementia (OR=4.66, 95% CI=1.74-12.50). Finally, these associations remained robust even after excluding those with HS-A.

Conclusions: Brain pathology, but not dementia, is nearly inevitable in those who die as centenarians. LATE-NC with and without HS-A is a key driver of cognitive decline. Investigating resilience factors may inform preventive strategies.

49

Common Neuropathological changes from Hispanics and Non-Hispanics enrolled in multiple Alzheimer's Disease Research Centers

G Serrano, S Aslam, J Walker, C Borja, I Lorenzini, M Mariner, T Beach; Banner Sun Health Research Institute

Background: Hispanics seem to be at higher risk of developing Alzheimer's disease dementia (ADD) but there are few neuropathologically validated studies.

Methods: The National Alzheimer's Coordinating Center (NACC) functions as the centralized data repository for the National Institute of Aging's (NIA's) Alzheimer's Disease Research Centers (ADRC) Program and currently hosts data from over 2,100 Hispanic participants who have donated their brains to the study, and close to 60% of those have had full neuropathological evaluations done at 28 different ADRCs. The main goal of this study is to compare the neuropathological changes observed in these subjects to those reported as non-Hispanics.

Results: Hispanics in this study self-identified as Caucasians (72%), African American (4%), Native American (less than 2.5%), or "Other Races or unknown" (20%), as compared to the non-Hispanics, (82% Caucasian, 14% African American, 0.1% Other). Sex distribution was similar in both groups with close to 49% of the participants identifying their biological sex as males. Hispanic participants died at younger ages (83 vs 84 years), had lower brain weights (1093 +/- 152g vs 1116 +/- 157g) and had a higher percentage of Intermediate to High levels of AD Neuropathological Changes (75% vs 67%). Vascular pathology was also more severe in Hispanics, both for moderate/severe cerebral amyloid angiopathy (45% to 29%) and moderate/severe cerebral white matter rarefaction (33% to 31%). Hispanics in this data set also had higher rates of heart attack, congestive heart failure, hypertension, and diabetes.

Conclusions: This also agrees with previous clinical studies suggesting that ethnic Hispanic people have greater white matter hyperintensity volumes and higher vascular risk factors, but additional studies are needed to also understand how race intersects ethnicity.

50

Spatially Mapping Insulin/PI3K/AKT/mTOR Dysregulations in Down Syndrome with Alzheimer's Disease Human Hippocampi

A Wohlfert [1], K Jones [2], S Guzman [1], A Granholm [1]; [1] University of Colorado Anschutz Medical Campus, [2] Bioinformatic solutions

Background: Down syndrome is a chromosomal condition characterized by widespread systemic dysregulations, which increase the risk of various age-related diseases, including Alzheimer's disease (AD). This heightened susceptibility to AD pathology may stem from the triplication of the Amyloid precursor protein (APP) gene or disruptions in key mechanistic pathways, such as the mTOR signaling pathway. mTOR signaling influences many metabolic processes, including proteostasis, cytoskeletal organization, autophagy, and cell survival. Dysregulation of upstream mTOR regulators, including insulin and PI3K/AKT, has been associated with increased accumulation of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFT), hallmark pathologies of AD. Despite these associations, mTOR dysregulations that potentially drive disease progression in DS-associated AD (DS-AD) remain poorly understood.

Methods: In the current study, we used a novel spatial transcriptomic analysis method coupled with immunohistochemical validation methods to investigate possible aberrant expression of genes involved in insulin, PI3K/AKT, and mTOR signaling in postmortem human hippocampi of individuals with DS-AD and healthy controls (HC).

Results: The expression of IGF1, PI3K, AKT, and mTOR was up-regulated in DS-AD cases compared to HC, especially in the dentate gyrus, CA 3 neurons, CA 4 neurons, and subiculum. In contrast, insulin and tuberous sclerosis complex 1/2 (TSC1/2) expression was downregulated, particularly in these same hippocampal regions. The density of phospho-mTOR immunostaining was elevated in the hippocampus of DS-AD cases, compared to age-matched controls and AD cases, especially in the dentate gyrus, CA 4 neurons, and subiculum.

Conclusions: Spatial transcriptomics reveals widespread mTOR pathway activation in DS-AD human hippocampi, with region-specific variations in key regulators. Activators like mTOR, AKT1, and INSR show increased phosphorylation, while inhibitors such as TSC1 and TSC2 are suppressed. RNA expression changes do not always align with phosphorylation activity, suggesting post-translational regulation. These findings highlight complex regulatory mechanisms underlying mTOR dysregulations in DS-AD, emphasizing the need for further investigation into region-specific signaling dynamics.

51

Understanding the role of TDP-43 in Alzheimer's disease via cellular characterization

G Uruk [1], R Gatto [1], K Josephs [2], R Reichard [3], J Whitwell [4]; [1] Department of Neurology, Mayo Clinic, Rochester, MN, USA., [2] josephs.keith@mayo.edu, [3] Department of Laboratory Medicine and Pathology (Neuropathology), [4] Department of Radiology, Mayo Clinic, Rochester, MN, USA.

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and leading cause of dementia in our population. AD is characterized pathologically by beta-amyloid and hyperphosphorylated tau inclusions often associated with TDP-43 inclusions. TDP-43 in AD is associated with cognitive impairment, and while staging is known the localization, cellular and inclusion characteristics of TDP-43 are yet to be elucidated. We investigate relationships between pathological characteristics of TDP-43 inclusions, tangles and harboring cell-types in AD by multiplex immunostaining.

Methods: We analyzed neuropathological samples from 6 high likelihood AD and 3 control cases. Two of the 6 AD cases also had diffuse Lewy body disease. Neuropathological specimens were sampled from seven regions: amygdala and hippocampus (CA1, CA2-3, CA4, dentate gyrus (DG), subiculum, entorhinal cortex). Immunofluorescence stainings were performed with antibodies for phosphorylated TDP-43 (pTDP-43), phosphorylated tau (AT8), vesicular glutamate transporter-1 (Vglut1), choline acetyltransferase (ChAT), tyrosine hydroxylase (TH), dopamine-beta hydroxylase (DβH), vesicular GABA transporter (VGAT), and somatostatin to identify different neuronal subtypes.

Results: We found neuronal pTDP-43 inclusions mostly colocalizing with TH and DβH in amygdala and various regions of hippocampus identifying noradrenergic neurons. CA1, subiculum and DG regions also showed high amount of colocalization between pTDP-43 and VGAT /somatostatin labeling GABAergic interneurons. ChAT+ cholinergic neurons were much less numerous and detectable ones mostly colocalize with TH. Interestingly, viable Vglut1 labeled glutamatergic neurons did not show any pTDP-43. Additionally, AT8 immunoreactivity inversely correlated with number of pTDP-43 inclusions. Tangle associated TDP-43 (TATs), which were identified by pTDP-43 and AT8 double positivity, colocalized with TH/DβH and very low levels of ChAT. However, neurons harboring TATs did not exceed ten percent of the population.

Conclusions: pTDP-43 accumulate in noradrenergic and GABAergic interneurons in the limbic system of AD. Identifying TDP-43 inclusions via cellular characterization provide future insights into understanding the pathophysiology of AD.

52

The interaction of depression and Alzheimer's disease

S Hiya [1], L Canbeldek [1], S Qin [2], J Walker [1], T Richardson [1]; [1] Mount Sinai Hospital, [2] Columbia University

Background: Many questions regarding the relationship between depression and Alzheimer disease (AD) remain unanswered, including whether late-life depression is a risk factor for AD or a prodromal symptom, and whether a common mechanism links the pathophysiologies underlying both conditions. Studies suggest that depression is associated with increased Alzheimer disease neuropathologic change (ADNC) severity, but further research is needed to explore depression as a possible modifiable factor of disease. This study examines the relationship between depression and ADNC severity, with a focus on cognitive outcomes in individuals with and without depression.

Methods: We analyzed the cognitive, neuropathologic, genetic , and demographic variables in subjects with ADNC and depression (n=140), ADNC without depression (n=533), subjects with depression but without ADNC (n=138), and subjects without ADNC or depression (n=325) from the National Alzheimer's Coordinating Center dataset. Individuals with GDS scores >4 at the last visit were considered to have depression and subjects with "intermediate" or "high"-level ADNC were considered positive for ADNC.

Results: The presence of depression was significantly correlated with increased ADNC severity ($p=0.006$). In addition to ADNC, the presence of depression was significantly associated with Lewy Body disease (LBD) stage and Pick disease. Multivariate logistic regression analysis determined an independent risk of cognitive impairment for ADNC (OR=5.92, $p< 0.0001$) and depression (OR=2.37, $p=0.018$). Logical memory ($p=0.006$) and some measures of executive function are significantly affected in individuals with Alzheimer's disease and depression compared to individuals with Alzheimer's disease without depression.

Conclusions: These data contribute to the existing knowledge that depression is significantly associated with increased ADNC severity and may contribute to cognitive impairment independently of AD pathology. Notably, individuals with both Alzheimer's disease and depression exhibit greater deficits in logical memory and executive function compared to those with Alzheimer's disease alone.

53

Investigation of human amyloid pathology with perimortem stable isotope labeling

K Roberts [1], S Koutarapu [1], J Ge [2], M Dulewicz [2], C Guillermier [3], G Strout [1], J Hou [1], S Mukherjee [1], A Upadhyay [4], J Savas [4], R Bateman [1], J Hanrieder [2], K Schwetye [1]; [1] Washington University, [2] University of Gothenburg, [3] Brigham and Women's Hospital, Harvard Medical School, [4] Northwestern University

Background: Amyloid pathology is central to Alzheimer's disease, yet the in vivo aggregation dynamics of amyloid plaques in humans remain poorly understood. Autopsy studies can offer only cross-sectional information and amyloid imaging by PET lacks the resolution to explore aggregation dynamics at the individual plaque scale.

Methods: To address these limitations, we recruited a cohort of hospice patients (n=29) to undergo perimortem oral bolus labeling with 15N spirulina, followed by subsequent autopsy and brain donation with one hemibrain fixed in formalin and one hemibrain frozen. Bulk untargeted proteomics was used to identify proteins that showed 15N incorporation in five patients with short intervals from labeling to death. Amyloid plaques were imaged for isotopic enrichment by two complementary imaging mass spectrometry modalities: MALDI-IMS and Nano-SIMS.

Results: Patients were grouped based on A score/Thal phase. Time intervals from labeling to brain donation varied widely from 0.4 to 534 days. A total of 417 proteins showed 15N enrichment (fractional abundance > 5%), with 104 proteins common among all 5 patients tested. MALDI-IMS was used to visualize Aβ42 in cortical parenchymal plaques and Aβ40 in CAA at 10 μm resolution and 15N incorporation above background was not detected. NanoSIMS was used to image fibrillar cortical plaques identified by SEM at 50 nm resolution and did not show 15N isotope enrichment in plaques.

Conclusions: Cortical fibrillar amyloid plaques do not incorporate perimortem-dosed heavy isotope at a rate above the detection threshold for imaging mass spectrometry techniques, suggesting largely quiescent aggregation dynamics of fibrillar plaques.

54

Association of CNS Corpora Amylacea with Aging and Alzheimer's disease pathology

A Tuzzolo [1], J Vaillareal [2], E Medina-Parrilla [1], T Bathe [2], A de la Rosa [2], R Sharma [2], J Phillips [2], S Prokop [2]; [1] University of Florida Department of Pathology, [2] UF Center for Translation Research in Neurodegenerative Disease

Background: Corpora Amylacea (CA) are considered benign aggregates of sugars, proteins, and waste products, predominantly found in periventricular and subpial regions. CA are thought to increase with age and recently, a correlation of CA accumulation with Alzheimer's disease (AD) neurofibrillary tangle pathology has been reported, potentially linking CA to AD pathogenesis.

Methods: We set out to test these associations in a large cohort of postmortem brain samples from the UF Neuromedicine Human Brain and Tissue bank (UF HBTB). First, we developed an algorithm to detect and quantify CA in Periodic acid-Schiff stained and manually annotated whole slide images using the open-source software QuPath. We applied this algorithm to a total of 219 patient brains from the UF HBTB and analyzed CA density in periventricular areas around the temporal horn of the lateral ventricle at the level of the hippocampus and the amygdala, as well as the hippocampus proper, including the hippocampal pyramidal cell layer.

Results: Our analysis revealed that CA density increased with age in the hippocampus proper, while CA density in periventricular areas was not significantly associated with the age of the patients. Separating the cases by underlying neuropathological diagnosis, we noted that CA in the hippocampal parenchyma were increased in cases with AD neuropathological changes, while other neurodegenerative disorders, such as Lewy body disease or Frontotemporal dementia were not associated with increased numbers of CA. A sub analysis of AD cases demonstrated that CA numbers are correlated with neurofibrillary tangle (NFT) pathology and increase during early stages of NFT pathology (up to Braak stage III). We did not note a correlation with Amyloid beta pathology (Thal phase).

Conclusions: Our findings confirm a correlation of CA deposition with age in the hippocampal parenchyma and further support an association between CA and early stages of NFT pathology in AD.

55

Alzheimer's Disease Pathology in patients with Down Syndrome: Insights from 19 Adult Cases

M Mejia-Bautista, H Smith, P Jamshidi, J Ahrendsen, R Castellani; Northwestern Memorial Hospital

Background: Down syndrome is associated with early-onset Alzheimer's disease, (AD) which is regarded as evidence in support of the so-called amyloid cascade hypothesis.

Methods: We examined brain tissue from 19 adult Down syndrome patients (ages 25-65) sourced from the NIH Neurobiobank.

Results: Advanced AD pathology was noted in 15 subjects, with one case (age 41) exhibiting Braak V, Thal 4 pathology that included perforant pathway tauopathy. Three subjects, all young, had Thal phase 1 amyloid pathology with sparse cortical tau, while one younger subject (age 28) showed no significant amyloid plaque or tau pathology. One subject had AD with neocortical Lewy bodies. Overall, the amyloid burden in this cohort appeared high relative to sporadic AD, especially in the cerebellum, aligning with existing literature. There was no TDP-43 proteinopathy in the series. In the 4 subjects without advanced AD, aging-related tauopathy was sparse. There was no selective CA2 subfield tauopathy. In the medical records available (11 cases), 2 of 8 subjects with advanced AD had no record of cognitive deterioration. 3 subjects with limited proteinopathy (ages 25, 39, and 40) also had no evidence of cognitive deterioration. Three subjects had seizure disorders. The findings in this case series highlight a precipitous progression of proteinopathy beginning roughly in the 5th decade with lagging clinical deterioration, consistent with the literature. Diffuse amyloid plaques as well as sparse cortical tau aggregates appear decades in advance of deterioration. Lewy body pathology is uncommon, but not absent. TDP-43 proteinopathy appears to be uncommon. Aging-related neuronal and glial tau were not prominent.

Conclusions: While it is tempting to consider the pathological findings and clinical progression in concordance with amyloid accumulation, the precipitous progression, the considerable cognitive resilience, and the apparent selective vulnerability in some cases suggest the involvement of additional pathogenic factors beyond proteinopathy alone.

56

Leveraging machine learning and digital pathology to understand microglial activation in atypical Alzheimer's disease

S Dunlop [1], M Rutledge [2], B Boon [2], A Wood [2], D Rothberg [2], I Velez Uribe [3], J Gondrez [4], R Duara [4], N Graff-Radford [2], D Dickson [2], G Day [2], M Murray [2]; [1] Department of Neuroscience, Mayo Clinic Florida, [2] Mayo Clinic Florida, [3] Mount Sinai Medical Center,, [4] Mount Sinai Medical Center

Background: Alzheimer's disease (AD) is typically associated with an amnestic-predominant clinical syndrome. However, ~20% of cases present with atypical, non-amnestic syndromes involving visual, language, and/or behavioral impairments. Activated microglia spatially associate with these neuropathologic lesions and contribute to neuroinflammation. Previous work has revealed greater neuroinflammation in non-amnestic AD cases providing evidence of microglial signaling differences across clinical syndromes. This study aimed to characterize microglial activation and morphology in young-onset AD cases (i.e., cognitive symptoms < 65 years) to examine differences in microglial activation and morphology between amnestic and non-amnestic cases.

Methods: The FLorida Autopsied Multi-Ethnic (FLAME) cohort was queried for neuropathologically-diagnosed AD cases with a clinical diagnosis of AD dementia or an atypical clinical syndrome (e.g., corticobasal syndrome, posterior cortical atrophy) – resulting in n=40 cases studied, 22 amnestic and 18 atypical. Databased clinical diagnosis was assessed to classify amnestic or non-amnestic. 5µm-thick FFPE tissue sections of inferior parietal cortex and hippocampus were stained for HLA-DR (clone: TAL1B5) to assess morphology and burden of activated microglia. Slides were digitized using Leica's Aperio AT2 and annotated using Aperio ImageScope.

Results: Qualitative assessment of HLA-DR positive microglia in parietal cortex revealed greater proportion of HLA-DR positive activated microglia in superficial cortical gray matter of atypical cases compared to amnestic AD cases. Analysis of the hippocampus, assessing all subfields and fimbria, revealed greater burden of activated microglia in the CA2 subfield of atypical AD cases. CA1 HLA-DR immunoreactivity was comparable across clinical syndromes. Ongoing work is being completed to quantify relative burden of HLA-DR immunoreactivity and characterize microglial morphology in both brain regions across all cases.

Conclusions: Qualitative assessment revealed spatial distribution differences in HLA-DR immunoreactivity between amnestic and atypical cases. Future work will use an object detection algorithm to characterize microglial morphology (i.e., ramified, hypertrophic, ameboid, dystrophic) in both gray matter and white matter.

57

Biochemical characterization of Aβ extracted from vascular and parenchymal plaques using mass spectrometry

S Koutarapu, K Roberts, R Coyle, J Mehla, C Sato, G Zipfel, R Bateman, K Schwetye, S Mukherjee; Washington University School of Medicine

Background: Alzheimer's disease (AD) is characterized by amyloid-beta (Aβ) plaques and neurofibrillary tangles, with cerebral amyloid angiopathy (CAA) present in over 90% of cases. Aβ, the main component of both AD plaques and CAA vascular deposits, exhibits distinct proteoforms and post-translational modifications (PTMs) in CAA compared to Aβ plaques.

Methods: In this study, we utilized a well-characterized clinical cohort to investigate Aβ proteoform distribution across neuropathologically determined CAA severity. Tissue was scored by an expert neuropathologist (none, mild, moderate, severe) for both leptomeningeal and parenchymal vessels, taking into account multiple factors including density, circumferential accumulation, and dyshoric features. We isolated cortical vessels using density gradient centrifugation and used immunoprecipitation mass spectrometry (IP/MS) to analyze Aβ isoform distribution in soluble and insoluble cerebral vessel fractions. We determined the N- and C-terminal isoform heterogeneity across severities of CAA and compared them to Aβ from parenchymal plaques. We also characterized post-translational modifications (PTMs) including aspartate isomerization (Asp1 and Asp7) and N-terminal pyroglutamate.

Results: Parenchymal Aβ fibrils exhibit disordered N-termini, allowing truncations and Asp1/Asp7 isomerization. Conversely, moderate and severe CAA vascular Aβ showed intact N-termini and C-terminal truncations. We noted a progressive decrease in the relative abundance of hydrophobic C-terminal species (Aβ41, 42, 43) with increase in relative abundance of hydrophilic C-terminal species (Aβ37, 38, 39, 40) with increasing CAA severity. Notably, Ile41 at the C-terminus is a distinct feature of vascular amyloid, comprising ~20% of insoluble Aβ extracted from brain vasculature.

Conclusions: The heterogeneity of Aβ proteoform between CAA and parenchymal plaques of AD suggests unique pathologic mechanisms of aggregation and deposition. Our results when compared cryo-EM highlight structural differences of the Aβ protofibrils in CAA vs AD will lead to PTMs on either N-terminus or C-terminus. Understanding the diversity of the Aβ proteoforms is critical for the development of better anti-amyloid drugs.

58

Evaluating Pre-Trained Deep Learning Models for Detection of Alzheimer's Disease in Histopathological Images: A Retrospective Study

F Vaibhav [1], A Duhan [2], S Shahi [3], V Kaliraman [4]; [1] Pt. B.D. Sharma PGIMS, Rothak, [2] SUNY Upstate Medical University, Syracuse, NY, [3] University of Louisville, Kentucky, [4] Maulana Azad Medical College, New Delhi, India

Background: Alzheimer's Disease (AD) is a prevalent neurodegenerative disorder for which prompt and accurate diagnosis is critical to effective management. Although traditional histopathological evaluation is the diagnostic gold standard, it is labor-intensive and subject to inter-observer variability. Advances in deep learning offer promising opportunities to automate the detection of neuropathological markers, potentially improving diagnostic efficiency and consistency.

Methods: A retrospective analysis was conducted using histopathological images from 128 patients, equally divided into 64 AD-positive cases and 64 AD-negative cases as determined by the consensus of two independent pathologists. Pre-trained deep learning models were applied to classify the images into AD-positive or AD-negative categories. Model performance was quantified using accuracy, sensitivity, specificity, precision, F1 score, and the area under the receiver operating characteristic curve (AUC-ROC), with the consensus diagnosis serving as the reference standard.

Results: For the balanced cohort (n = 64 AD-positive, n = 64 AD-negative), the models correctly classified 108 cases, resulting in an overall accuracy of 84.38%. Sensitivity was 78.13% (50/64 AD-positive cases correctly identified), and specificity was 90.63% (58/64 AD-negative cases accurately classified). Precision was 89.29%, and the F1 score was 83.20%. Additionally, the AUC-ROC was estimated at 0.85, indicating substantial discriminatory capability.

Conclusions: Pre-trained deep learning models exhibit considerable potential for the detection of Alzheimer's Disease in histopathological images. Although the performance metrics observed in this study are modest relative to larger-scale analyses, these findings support the potential utility of such automated tools as adjuncts to conventional histopathological evaluation. Further prospective studies with larger cohorts are warranted to validate these results and optimize model performance for clinical implementation.

59

Insights into the Anatomical Vulnerability Associated with the PSEN1 L381F Mutation

M Majeed [1], H Garringer [2], K Newell [2], R Vidal [2], M Jacobsen [2], J Bonnin [2], J Mokry [3], P Moretti [4], B Ghetti [2]; [1] Indiana University / School of Medicine, [2] Indiana University School of Medicine, [3] Baylor College of Medicine, [4] University of Utah Health

Background: Two siblings, who presented motor symptoms prior to dementia, were previously reported. Alzheimer disease (AD) pathology was found postmortem prior to the discovery of the causal link between PSEN1 mutations and AD. The L381F mutation in PSEN1 was found in both siblings. The siblings and members of two prior generations suffered of a similar rapidly progressive disease. The age of the individuals at the onset of their symptoms varied from 28 to 32 years. Death occurred following a two- to six- year course.

Methods: Clinical studies were carried out according to protocols used for AD. For neuropathology, neurohistological methods were used; for immunohistochemistry antibodies to tau, amyloid beta, alpha synuclein, and TDP-43 were used.

Results: We report clinical and neuropathologic findings in a male from the fourth generation. At age 26, he showed posturing of arms and legs. At age 29, neurological exams revealed a dystonic posture, spasticity, brisk reflexes, dysarthria, and a Babinski sign. At age 30, gait impairment, hypo/bradykinesia, rigidity, hyperreflexia and ankle clonus, dysconjugate gaze and saccadic visual pursuits, dysarthria, and dysphagia were present. He had a score of 14/30 by MoCA; however, accurate assessment of cognitive status was not possible. At age 31, he was mute and wheelchair bound. Death occurred at age 33. Neuropathologically, amyloid beta deposits, in the form of cotton wool plaques (CWPs), were present in neocortex, striatum, amygdala, and hippocampus; cored plaques were prominent in the cerebellum. In the motor cortex, severe neuronal loss, numerous CWPs and neurofibrillary tangles were evident; In the spinal cord, the lateral and anterior pyramidal tracts had degenerated. The L381F PSEN1 mutation was found.

Conclusions: The evidence of spasticity early in the course of illness and degeneration of the motor cortex and cortico-spinal tracts support the concept that specific PSEN1 mutations may cause selective vulnerability of motor systems.

60

Hippocampal CA1: Early Site of Tau Tangles Associated with Amyloid Aggregates in a Young Population

R Rodriguez Reyes, M Morris, L Gomez-Isaza, M Luongo; Johns Hopkins School of Medicine

Background: CA1 in the hippocampus is a relevant structure in cognitive processes and long-term memory consolidation. It is known in primary age-related tauopathy, phospho-tau tends to aggregate more in CA2 than in CA1 relative to Alzheimer's disease, but it is still unknown if this distribution is the same in young, healthy populations without clinical neurodegenerative disease and whether this is associated with Alzheimer pathology or risk factors.

Methods: Of more than 100 individuals under the age of 65 from the Johns Hopkins Brain Bank, 87 cases had phospho-tau positive pathology in the hippocampus. We developed a semiquantitative method to quantify phospho-tau density in CA1 and CA2, which we correlated with age, sex, race, Amyloid and ApoE genotype.

Results: Overall, in our cohort older patients were found to have higher tau aggregates, with more found in CA1 than in CA2. Amyloid positivity had a stronger association with tau aggregate density. The preliminary ApoE results were that ApoE4 carriers have more deposits in CA1 than in CA2. Overall, no significance was observed at the race distribution even though we have a small tendency to have more tau aggregates in white population. There were no differences by biologic sex.

Conclusions: In our young cohort encompassing a wide age range without diagnosed neurodegenerative disease, we observed that tau pathology is more abundant in CA1 than in CA2. Both amyloid and ApoE4 genotype were associated with greater tau pathology in CA1 compared to CA2. This study supports that the initial tau deposition in CA1 and CA2 during aging is influenced by the presence of amyloid and ApoE4 genotype, recapitulating the patterns of tau pathology observed in older individuals with Alzheimer's disease and primary age-related tauopathy.

61

Multiple neuropathologies underly hippocampal atrophy and hypometabolism in a case with a slowly progressive amnestic syndrome

H Youssef [1], R Gatto [2], N Pham [2], D Jones [2], R Petersen [3], M Machulda [2], J Whitwell [2], K Josephs [2]; [1] Neurology Department, Mayo Clinic, Rochester, MN, [2] Mayo Clinic Rochester, [3] Mayo Clinic, Rochester

Background: TAR DNA binding protein 43 (TDP-43) neuropathology in individuals 75+ is classified as limbic predominant age-related TDP-43 neuropathologic changes (LATE-NC). It often co-occurs with Alzheimer's disease neuropathologic changes (ADNC) and has been linked to a slowly progressive amnesia. In such patients imaging shows medial temporal lobe abnormalities.

Methods: An 83-year-old female with slowly progressive amnesia with MRI head scan showing hippocampal atrophy and [18F]fluorodeoxyglucose (FDG-PET) showing medial temporal hypometabolism died at age 86 and underwent brain autopsy. Beta-amyloid and tau PET biomarkers for AD were negative. Neuropathological assessment adhered to NIA-AA guidelines, assessing ADNC severity via the ABC score. Hippocampal samples were stained for PHF-tau, 4R-tau, TDP-43, and P62, and digital histopathology was utilized to quantify burden of each pathological process in hippocampal subfields. Hippocampal subfield volume loss and rate of hippocampal subfield atrophy for the patient and nine healthy controls were determined using FreeSurfer software.

Results: Microscopic evaluations revealed hippocampal sclerosis (HpScl) and TDP-43 inclusions in the hippocampal dentate and entorhinal cortex. 4R tau immunoreactive argyrophilic grain disease (AGD) were also present. In addition, there was mild ADNC (A1B1C1) consistent with possible primary age-related tauopathy (pPART). Digital histopathological analysis found the highest burden of P62 and TDP-43 in the CA1 subfield, while PHF-tau and 4R-tau burden was highest in CA2/3. The amygdala exhibited the highest AGD burden. Hippocampal subfield volumes were similar to that of controls, except for CA1, which showed greater volume loss and atrophy in the patient.

Conclusions: Multiple pathologies, including pPART, TDP-43, AGD and P62 were identified in the hippocampus in a patient with a slowly progressive amnestic syndrome with focal medial temporal lobe imaging abnormalities. This raises questions about the construct of pure LATE-NC and the notion that a slowly progressive amnestic syndrome in the absence of biomarker proven AD is due to LATE-NC.

62

Postmortem Evaluation of Mineralized Blood Vessels in Hispanic and Non-Hispanic White Decedents with Alzheimer Disease

S Tamizharasu [1], D Garcia [1], N Saito [2], M Luu [1], L Beckett [2], L Honig [3], C DeCarli [2], R Rissman [4], A Teich [3], D Mungas [1], L Jin [1], B Dugger [1]; [1] University of California Davis, Sacramento, California, [2] University of California Davis, Davis, California, [3] Columbia University, New York, New York, [4] University of California San Diego, La Jolla, California

Background: Mineralized blood vessels (MBV) may lead to the stiffening of vasculature and are commonly observed in neurodegenerative disorders, including Alzheimer Disease (AD). There is limited research on MBV in cohorts that include persons of Hispanic descent.

Methods: We examined a cohort of Hispanic decedents HD (n = 92) and non-Hispanic White decedents NHWD (n = 184) with pathologically confirmed AD compiled from three institutions: Columbia University, University of California San Diego, and University of California, Davis. Hematoxylin and eosin slides of the posterior hippocampus, putamen, and globus pallidus were examined to denote the presence/absence of MBV. Chi-square tests for pairwise associations were used to denote clinical and pathological associations based on the MBV presence/absence. Additionally, stratified analysis using the Mantel-Haenszel test and the Breslow-Day test were performed.

Results: The highest frequency of MBV was in the globus pallidus (59.0%), followed by posterior hippocampus (28.6%), and then putamen (14.8%). Examining overall MBV presence, HD had a slightly higher frequency (77.9%) compared to NHWD (74.0%) and was not statistically significant (p=0.63). MBV burden differed among brain regions, with a higher presence of MBV in the: globus pallidus compared to putamen (p= < 0.001), posterior hippocampus compared to putamen (p= < 0.001), and globus pallidus compared to posterior hippocampus (p= < 0.001). There were no significant differences in MBV presence in different brain regions between HD and NHWD. Overall MBV presence and presence within each brain region had no statistically significant association with hypertension, diabetes, or hypercholesterolemia (ps >0.05).

Conclusions: This study highlights the region-specific manifestation of MBV in the setting of AD in a more diverse cohort.

63

Alzheimer's disease Brain Banking at Mayo Clinic in Florida

D Dickson [1], M Murray [2]; [1] Mayo Cliinic, [2] Mayo Clinc

Background: The brain bank for Alzheimer's disease (AD) at Mayo Clinic had its origin in donors from the State of Florida Alzheimer Disease Initiative (ADI) (N=1,184). In addition to ADI, other patients were from Mayo Clinic (N=204) or Einstein Aging Study (N=35). A major sources are the Brain Support Network (N=135) and Cure PSP (N=39), as well as individual donors (N=100). Brains were from 41 States, with 88% from Florida, California and New York.

Methods: This report describes 1,729 pathologically-confirmed AD. Patients were mostly White (N=1592), with fewer Hispanics (N=111) and Blacks (N=20). There were 978 women and 751 men. The average age at death was 80±9 years and the average disease duration was 10±4 years.

Results: The average brain weight for AD patients was 1025±147 grams. The average Braak NFT stage was 5.5±0.7 and the average Thal amyloid phase was 4.7±0.7. AD subtyping using the algorithm developed by Murray, et al. included 74% typical, 14% limbic and 12% hippocampal sparing. Cerebrovascular pathology was common (N=832 (48%)) with pathology ranging from microinfarcts to encephalomalacia, as well as ischemic leukoencephalopathy. Lewy body pathology was also common (N=764 (44%)). Lewy body pathology included amygdala only (N=329), diffuse LBD (N=210), and transitional LBD (N=179), while brainstem predominant (N=31) was less common. Only a few cases (N=15) had incidental Lewy bodies. TDP-43 pathology was detected in 41% of 1,638 cases screened for it. While most patients were thought to have AD, other clinical presentations were Lewy body dementia (8%), vascular dementia (7%), and progressive aphasia (2%). Genotyping in many cases showed 11% were APOE4 and 60% were MAPT H1H1.

Conclusions: The AD brain bank at Mayo Clinic has contributed to over 550 publications related to AD and provided support to over 30 NIH grants. None would be possible without help from families of the deceased.

Posters: Neurodegenerative: Other

64

Mapping Cell Type and Transcriptomic changes associated with TDP-43 Pathology in LATE-NC and FTLD-TDP

E Pinarbasi, R Sudharshan, A Rao, S Barmada; University of Michigan

Background: LATE-NC (limbic predominant age-related TDP-43 encephalopathy neuropathologic change) and FTLD-TDP (frontotemporal lobar degeneration with TDP-43 deposition) are two neurodegenerative pathologies which are united by the mislocalization and aggregation of TDP-43, a highly expressed RNA-binding protein. However, the distribution of TDP-43 pathology and the clinical presentations are very distinct; FTLD-TDP is characterized by widespread TDP-43 aggregates and severe language, personality and behavioral disturbances, while in LATE-NC, TDP-43 pathology is limited to mesial temporal structures and is associated with an indolent amnestic cognitive decline. The cellular and molecular features underlying these differences are not understood.

Methods: Using the Xenium ISS platform, we profiled hippocampus tissue from patients with either FTLD-TDP (C9ORF72) or LATE-NC (n=2/group). The pre-designed human brain panel was used, which includes 266 targets that identify major cell types within the nervous system. This panel was augmented with an additional 100 custom transcripts, designed to assess differential expression of TDP-43 targets as well as identify specific cell types within the hippocampus. Post-Xenium, TDP-43 immunohistochemistry was performed and cells with TDP-43 pathology were manually annotated.

Results: Based on the 366 profiled transcripts, cells were clustered and spatial distribution was delineated. Expression data was mapped for STMN2 and UNC13A, two transcripts that decrease when TDP-43 is lost from the nucleus. The signal for these transcripts is lower in areas with dense pathology. Expression data was also mapped for a set of 14 transcripts previously shown to be upregulated in neurons with TDP-43 pathology in FTLD-TDP. A heatmap demonstrates higher signal in areas with dense pathology.

Conclusions: These findings demonstrate that the Xenium platform can accurately identify cell types affected by TDP-43 pathology and detect expected associated transcriptomic changes.

65

Evaluation of LATE-NC based on pTDP-43 immunoreacitive structure density

A Arakawa [1], A Uchino [2], M Hara [2], T Matsubara [2], S Murayama [2], Y Saito [2]; [1] Department of Neuropathology (the Brain Bank for Aging Research), Tokyo Metropolitan Institute for Geriatrics and Gerontology, [2] Tokyo Metropolitan Institute for Geriatrics and Gerontology

Background: The staging of LATE-NC are defined by the extention of pTDP-43 accumulation, not by the density of immunoreactive structures. We have been evaluating LATE-NC using our original BBAR (Brain bank for Aging research) pTDP-43 stage, which depends on the density of immunoreactive structures. Herein, we discuss its prevalence and its impact on cognitive decline.

Methods: BBAR pTDP-43 stage was evaluated on sections including amygdala and hippocampus in three stages: Stage 1: neurites but no intracytoplasmic inclusions (NCIs), Stage 2: 1 to 4 NCIs per 10x visual field, Stage 3: 5 or more NCIs per 10x visual field. Cognitive function was assessed using the clinical dementia rating (CDR), and CDR ≥ 1 was defined as dementia. Of 452 consecutive brain autopsies from October 2012 to September 2022, 6 patients with destruction of limbic structures, 9 cases with FTLD-TDP, 16 ALS-TDP cases were excluded, and the remaining 421 cases were included.

Results: 234 patients (55.6 %) had LATE-NC, 150 patients were BBAR TDP stage 1, 34 patients were stage 2 and 50 patients were stage 3. The proportion of patients with dementia (CDR ≥ 1) were significantly higher in stage 3 (81.3 %) than in stage 1 (37.5 %), stage 2 (56.7 %) and no LATE-NC cases (29.4 %). There were 74 patients with pure LATE-NC without other comorbid pathology (Braak NFT stage ≤ 2, BBAR Lewy stage ≤ 1, Saito AGD stage ≤ 1), but none of the 58 patients with evaluable CDR had dementia (CDR ≥ 1) and only 3 patients had mild cognitive impairment (CDR = 0.5).

Conclusions: Our results indicate that not only extention of LATE-NC but also density of pTDP-43 immunoreactive structures may affect cognitive function. There were no cases of dementia in patients with LATE-NC alone without other concomitant pathology. Future work is needed to match the other stages.

66

GFAP+ astrogliosis in the striatum of Huntington's disease mice is spatially related to secondary motor cortex axonal bundles

T Brown, E Reid, J VanTreeck, M Thayer, R Gomez-Pastor; University of Minnesota

Background: Huntington’s disease (HD) is a neurodegenerative disease that primarily affects the striatum, a brain region that controls movement and some forms of cognition. Neuronal dysfunction and loss in HD is accompanied by increased astrocyte density and astrocyte pathology. Astrocytes are a heterogeneous population classified into multiple subtypes depending on the expression of different gene markers. Studying whether mutant Huntingtin (HTT) alters specific subtypes of astrocytes is necessary to understand their relative contribution to HD.

Methods: We studied astrocytes expressing glial fibrillary acidic protein (GFAP) in the striatum and cortex of the zQ175 mouse model of HD using immunofluorescence and confocal imaging. We also combined this with viral tracing strategies to map axons from different brain regions.

Results: As HD progressed, the number of GFAP+ astrocytes in the striatum increased as the number of HTT aggregates increased. GFAP+ astrocytes were found spatially clustered in groups, unlike other tiled astrocyte subtypes, predominantly in the dorsomedial striatum. We found that GFAP+ astrocytes preferentially accumulated around white matter fascicles passing through this region. We show that GFAP+ astrocytes are specifically surrounding white matter fascicles that originate in the secondary motor area (MOs) of the cortex and we demonstrate the close proximity of GFAP+ astrocyte processes with MOs axons. We observed the MOs for HD-related pathology and found an increase in GFAP+ astrocytes in the deep cortical layers.

Conclusions: The unique spatial arrangement of GFAP+ astrocytes revealed the involvement of the MOs in HD pathology. The MOs is an understudied brain region involved in goal directed behavior with emerging roles in HD pathophysiology. Our findings suggest an interaction between GFAP+ astrocytes and MOs axons that may offer new insights into the function of a specific astrocyte subtype and its potential implications in HD pathology.

67

Neurodegenerative Disorders Among Older Community-Dwelling Subjects Who Die by Suicide: A Comparative Study Against Natural Deaths

M Elnagdy [1], E DAOUD [1], C WHITE [1], J RAISANEN [1], D BURNS [1], B EVERS [1], J BERNARD [2], T DANIELSEN [3], C HAUCH [2]; [1] University of Texas Southwestern Medical Center, [2] N/A, [3] Dallas County Medical Examiner

Background: Suicide in subjects with neurodegenerative disorders has been reported to have a low incidence. While depression is also not typically associated with neurodegenerative diseases, Lewy body disease (LBD) presents an exception, with a notably higher prevalence of depression among affected individuals. Given the complex interplay between neurodegeneration and psychiatric symptoms, a deeper understanding of the neuropathological differences between suicide subjects and those who died of natural causes is warranted. This study aims to compare the prevalence and types of neurodegenerative disorders in a local community population to explore potential associations with suicide risk.

Methods: We conducted a comparative neuropathological analysis of 21 subjects who died by suicide and 56 subjects who died from natural or accidental causes (mean age = 66.2 ± 9.2 years; all >53 years old). Contemporary diagnostic methods and staging criteria for neurodegenerative disorders were applied, and a systematic comparison between the two groups was performed.

Results: The suicide group predominantly consisted of white subjects (90.5%) with a male-to-female ratio of 6:1. The most common mechanism of suicide was gunshot wound (76.2%). The prevalence of LBD was significantly higher in the suicide group compared to the natural death group (24% vs. 7%, $p < 0.05$). Additionally, primary age-related tauopathy (PART) was observed in 71% of suicide subjects and 59% of natural death subjects.

Conclusions: Our findings suggest a link between neurodegenerative pathology and suicide risk. The significantly higher prevalence of LBD in suicide subjects highlights the need for further investigation into the role and potential contribution of neurodegeneration, and specifically alpha-synucleinopathy, to suicidality in aged subjects. Understanding these associations may provide insights into the underlying mechanisms and inform future prevention strategies.

68

Comorbid Chronic Traumatic Encephalopathy and Progressive Supranuclear Palsy

D Kirsch [1], B Abdolmohammadi [1], M Alosco [1], V Alvarez [1], J Cherry [1], J Crary [2], A McKee [1], J Mez [1], R Nicks [1], T Stein [1]; [1] Boston University School of Medicine, [2] Icahn School of Medicine at Mount Sinai

Background: Chronic traumatic encephalopathy (CTE) and progressive supranuclear palsy (PSP) are neurodegenerative tauopathies. CTE is caused by repetitive head impacts (RHI) exposure, while PSP has no known environmental cause. The UNITE Brain Bank is enriched in RHI exposure; of 900 cases that have undergone complete clinical and pathological analyses, we found 366 cases of pure CTE (mean age=57.21), 9 cases of pure PSP (mean age=77.22), and 14 cases of comorbid CTE-PSP (mean age=76.43), with an overall PSP prevalence of 2.56%.

Methods: To compare clinical and pathological measures, the CTE-PSP (4 college and 10 professional football players) and PSP(5 college and 1 semi-professional football players, 3 had no football experience) groups were compared with an age-matched CTE group (n=14, 2 college and 12 professional football players). Clinical scales and semi-quantitative pathology scores were compared between groups.

Results: We found a similar mean RHI exposure duration for CTE and CTE-PSP but shorter duration for PSP(CTE=17.29 years, CTE-PSP=16.57 years, PSP=5.88 years). Compared to CTE, CTE-PSP had significantly greater NFT density in the pons ($p< 0.001$), locus coeruleus ($p=0.01$), cerebellar dentate nucleus ($p< 0.001$), globus pallidus ($p=0.003$), thalamus ($p=0.027$), and higher Braak Stage ($p=0.026$). Compared to PSP, CTE-PSP had more p-tau glial inclusions ($p< 0.001$), subpial p-tau ($p=0.003$), NFTs in Rolandic cortex ($p=0.029$) and temporal pole ($p=0.005$), hippocampal CA3 ($p=0.036$) and CA4 ($p=0.026$), amygdala ($p=0.009$), thalamus ($p=0.024$), locus coeruleus ($p< 0.001$), and cerebellar dentate nucleus ($p=0.035$). CTE-PSP and PSP groups had more parkinsonism than CTE (CTE=29.0%, CTE-PSP= 85.7%, PSP=87.5%, $p< 0.001$), and CTE-PSP had significantly more functional impairment (Functional Activities Questionnaire, $p=0.033$), and less impulsivity (Barratt Impulsiveness Scale, $p=0.037$) than CTE.

Conclusions: These findings highlight that PSP pathology can be found in some individuals with CTE, and that comorbid CTE-PSP has more p-tau NFTs, parkinsonism, and functional impairment than CTE alone.

69

Neuropathology in the LifeAfter90 Study: 2025 update on an Ethnically Diverse Cohort Study of Oldest-Old

B Dugger [1], V Patel [1], L Jin [1], M Luu [1], M Martinez Pamatz [1], C DeCarli [1], P Gilsanz [2], D Mungas [1], C Kawas [3], M Corrada [3], R Whitmer [1]; [1] University of California, Davis, [2] 2- Kaiser Permanente Northern California Division of Research, [3] University of California, Irvine

Background: Examining the neuropathology of the oldest-old has advanced our understanding of the multiple etiologies in very late life. Most studies include predominately White decedents with limited ethnoracial diversity.

Methods: The LifeAfter90 study is an ongoing cohort study of Kaiser Permanente Northern California members, aged 90+ with targeted recruitment of individuals across different racial/ethnic groups with no prior diagnosis of dementia in their medical record. Interviews and cognitive assessments occur approximately every 6 months. Brain donation was available to all interested consenting participants. Neuropathology was assessed using National Alzheimer's Coordinating Center Neuropathology forms and NIA-AA guidelines for diagnoses.

Results: As of January 2025, 390 participants (34%) had enrolled in autopsy (22% Asian, 20% African American, 18% Latino, 9% Multiracial/Other, and 33% White). Of the 390 participants, 124 had died with neuropathological evaluations completed. The mean age of death was 95 years (range 90-105), 75 (60%) were female, 21 Asian, 15 Black, 23 Latino, 61 White, and 1 Native American. At final clinical exam, 43 participants had dementia (35%), 29 had cognitive impairment without dementia (23%), and 52 had normal cognition (41%). Alzheimer disease (AD) and vascular neuropathologies were the most frequent pathologic findings; 79% of participants had at least low likelihood of AD and all but one had neurofibrillary tangles (NFT). Braak NFT stage VI and Thal phase 5 were infrequent. For vascular pathologies, 73% had moderate/severe arteriolosclerosis, 42% moderate/severe atherosclerosis, and 23% had a least 1 microinfarct. Furthermore, 32% had Lewy bodies (6 cases with diffuse type) and 4 with hippocampal sclerosis. Cognitive status was associated with the presence of AD neuropathologies, but not other neuropathological changes.

Conclusions: This study reveal numerous neuropathologies are present with advanced age, with AD and select vascular pathologies being the most common. This shows as in younger cohorts, AD neuropathologies are an important driver of cognitive impairment.

70

Comprehensive Mapping of Hypoxia/Ischemia-Associated β-Amyloid Deposition Patterns in the Human Central Nervous System

E Karlovich [1], C Rhodes [2], D Premier [2], D Perl [2], K Tanji [1], J Goldman [1]; [1] Columbia University Irving Medical Center, New York, New York, USA, [2] The Uniformed Services University School of Medicine, Bethesda, Maryland, USA

Background: A recently-published study from our group identified β-amyloid deposits in the frontal cortex of individuals who died with hypoxia/ischemia-associated conditions, including COVID-19, non-COVID acute respiratory distress, and severe cardiac malformations. Unlike classic Alzheimer's disease (AD) plaques, these deposits lack Thioflavin-S positivity, phosphorylated tau (p-tau) protein, or amyloid cores.

Methods: We now have examined multiple brain regions from three cohorts: 9 individuals who died from COVID-19 or non-COVID respiratory or cardiac conditions (age: 6 weeks-70 years), 8 military cases with hypoxia risk factors (age: 39-62 years), and 8 individuals with mitochondrial encephalomyopathies, including Kearns-Sayre Syndrome, mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, Leigh's, and Alpers Syndrome (polymerase-gamma mutation). Specimens were analyzed using immunohistochemistry for β-amyloid, p-tau, B- and T-lymphocytes, and microglia, complemented by Thioflavin-S staining.

Results: β-amyloid deposits were predominantly found in isocortical regions, including frontal, temporal, insular, and occipital cortices, without predilection for specific laminae. Lower deposit densities appeared in subcortical structures, including basal ganglia, thalamus, cerebellum, and brainstem. Deposits varied in size (20-100 μm) and often surrounded neurons. No deposits were Thioflavin-S positive and there were no associated inflammatory responses by lymphocytes or macrophages. β-amyloid also accumulated in blood vessel walls, where some was Thioflavin-S-positivity, and in subpial regions. Little to no p-tau pathology was present in the isocortex, hippocampus, or entorhinal cortex in any of the autopsies. The isocortical distribution of β-amyloid deposits paralleled that of early AD amyloid accumulation but these occurred independently of p-tau pathology.

Conclusions: Our findings reveal a distinct pattern of hypoxia/ischemia-associated β-amyloid deposition, suggesting a mechanistic link between hypoxic/ischemic conditions and β-amyloid accumulation in the human brain. This work has implications for understanding both acute brain injury and neurodegenerative disease. Further studies with larger cohorts and appropriate controls are required for better understanding of the mechanisms.

71

A Rare Case of Neurodegeneration with Brain Iron Accumulation and Genetic Characterization

L GOMEZ-ISAZA [1], J Redding-Ochoa [2], S Scholz [1], A Ray [3], J Troncoso [1]; [1] Johns Hopkins University School of Medicine, [2] University of Minnesota, [3] National Institute of Neurological Disorders and Stroke, Bethesda

Background: Neurodegeneration with Brain Iron Accumulation (NBIA) is a rare group of disorders characterized by extrapyramidal symptoms and iron deposition in the basal ganglia. A notable subtype, Mitochondrial Membrane Protein-Associated Neurodegeneration (MPAN), is caused by mutations in the C19orf12 gene. This report details the case of a 21-year-old woman with neuropathologically confirmed NBIA due to a C19orf12 mutation.

Methods: A retrospective clinical review was conducted, autopsy and, neuropathological findings, and whole exome sequencing data.

Results: The patient's clinical presentation began at age 15 with spasticity, gait instability, and dysphagia. Despite initial negative results for PANK2 mutations and metabolic disorders, her symptoms progressively worsened, leading to complete dependency for daily activities. Genetic testing later identified a homozygous missense variant in C19orf12 (c.163G>C, p.G55R), classified as 'likely pathogenic.' Autopsy revealed significant iron deposition in the globus pallidus and substantia nigra, alongside neuronal loss and gliosis. α-synuclein immunostaining revealed prominent Lewy body pathology in the substantia nigra and accumulation in neurons and glia primarily localized in the deep layers of the neocortex. Additionally, neurofilament immunostaining (SMI-31) highlighted axonal balloons, consistent with neuroaxonal dystrophy which was observed in the amygdala, entorhinal cortex, brain stem and neocortex.

Conclusions: This case highlights the complexities in diagnosing NBIA, particularly when multiple genetic variants are involved. A pathogenic variant in the C19orf12 gene was identified, but other benign variants suggest undiscovered mutations contributing to the clinical presentation. These findings emphasize the need for more genetic studies to understand the diversity of NBIA disorders. As there are no curative treatments for MPAN, this condition remains a significant challenge. Ongoing research into the molecular mechanisms underlying the disorder is crucial for advancing diagnostic accuracy and developing therapeutic approaches. This report underscores the importance of integrating clinical and genetic data for more precise diagnoses, improving the management of patients affected by this disease.

72

AI-based prediction of neuropathologic diagnoses from macroscopic findings

S Koga [1], D Ono [2], D Dickson [2]; [1] Hospital of the University of Pennsylvania, [2] Mayo Clinic

Background: Neuropathologic assessment is the gold standard for diagnosing neurodegenerative diseases, with macroscopic findings offering early diagnostic clues. The aim of this study was to objectively assess the diagnostic utility of gross findings and compare two artificial intelligence (AI) approaches for classifying seven major neurodegenerative pathologies.

Methods: We analyzed 5,613 autopsy cases from the Mayo Clinic Brain Bank (1998–2023), including seven diagnoses: Alzheimer disease (AD), progressive supranuclear palsy (PSP), Lewy body disease (LBD), AD-LBD, multiple system atrophy (MSA), corticobasal degeneration (CBD), and frontotemporal lobar degeneration (FTLD). We extracted the age at death, sex, brain weight, and 39 gross findings, such as cortical atrophy, putamen atrophy, subthalamic nucleus atrophy, and substantia nigra pigmentation, from each autopsy report. These gross findings, initially recorded in descriptive terms, were semi-quantitatively converted into numerical values using a trained large language model (LLM) with scales ranging from 0–1 to 0–3, depending on the feature, and compiled into a tabular dataset for further analysis.

Results: We compared two AI-based approaches: a machine learning model (CatBoost) using table-structured inputs and a fine-tuned LLM (ChatGPT) employing textual summaries of the same features. CatBoost achieved an accuracy of 0.704 and a weighted ROC-AUC of 0.909 on a hold-out test dataset. ChatGPT, trained with “dummy” negative statements for unmentioned findings, attained an accuracy of 0.75, though it struggled to predict AD-LBD. While ChatGPT showed slightly higher accuracy, CatBoost offered more transparent feature importance via SHAP analysis.

Conclusions: These findings highlight the educational and diagnostic value of systematically evaluating gross findings, particularly in PSP and MSA with distinctive macroscopic features. Combining table-based classification with an LLM-based text approach can enhance objectivity and improve diagnostic confidence before microscopic or immunohistochemical evaluation. Additionally, AI-driven analysis of disease-specific macroscopic changes may aid clinical imaging research by improving correlations between imaging biomarkers and pathology.

73

Development of a Human Brain Matrix through Advanced Digital Fabrication and 3D Scanning

M Dastmalchi [1], A Goli [2], M Haeri [3]; [1] School of Architecture & Design, University of Kansas, Lawrence, Kansas, [2] School of Architecture & Design, University of Kansas, [3] The University of Kansas Alzheimer's Disease Reasearch Center and the Department of Pathology and Laboratory Medicine, Kansas City, Kansas.

Background: Alzheimer’s disease and related dementias (ADRD) pose a major challenge to neuropathological research, partly due to the lack of a reproducible method for postmortem brain tissue sectioning among different cores. Current approaches suffer from variability in sampling techniques, dependence on pathologist expertise, and limitations in accurately sectioning human brains of varying morphologies. We developed a human brain matrix using advanced digital fabrication and 3D scanning technology, enabling precise, reproducible, and customizable sectioning.

Methods: We conducted systematic observations of neuropathologists to understand the procedural requirements for accurate slicing. Using high-resolution 3D scanning, we digitized multiple human brains, allowing for computational modeling and optimization of the matrix design. Artificial intelligence models were employed to optimize brain morphology while preserving overall mass to facilitate matrix shaping. Finite element analysis was applied to assess material strength and ensure durability under pressure.

Results: The brains were sliced using a matrix, which proved effective in creating precise slices with consistent thickness, angle, and area. The matrix can be utilized without direct supervision of a pathologist, saving the expert's time. It provides precise slices faster than manual sectioning. Thickness variation within each slice is negligible, and superior to that achieved through manual sectioning. Knife marks are negligible and can be completely avoided, if desired. This precise brain slicing method is practical and can be performed in any autopsy setting without complicated or time-consuming preparation. Additional trimming for tissue blocking is unnecessary, as the slice thickness is pre-set to an acceptable range for histology labs.

Conclusions: Our results demonstrate that this matrix enhances consistency, minimizes sectioning errors, and offers a scalable solution for diverse brain sizes. This innovation holds significant promise for ADRD research by improving the reliability and reproducibility of postmortem neuropathological studies. Additionally, this matrix can be easily utilized for any type of brain slicing in general brain autopsies.

74

The Interplay Between Cerebrovascular Disease, TMEM106B, and TDP-43 Pathology

M Dopler, C Corbett, A Gonzalez, A Ghaseminejad-Bandpey, S Etemadmoghadam, M Keating, M Smith, B Danner, J Parker-Garza, M Alhneif, O Ogunbona, K Bieniek, S Seshadri, M Flanagan; University of Texas Health Science Center San Antonio

Background: TMEM106B, a lysosomal protein involved in trafficking and acidification, has genetic variants linked to neurodegenerative diseases like FTLD, LATE, and AD. TMEM106B forms age-dependent amyloid fibrils which are elevated in dementia patients and correlate with increased phosphorylated TDP-43 and its loss-of-function. Cerebrovascular disease (CVD), a major dementia copathology, increases with age and contributes to neuroinflammation. Recent evidence indicates CVD may contribute to TDP-43 dysregulation. Astrocytes and microglia, two main players in neuroinflammation, has shown to express cytoplasmic TMEM106B inclusions and filamentous processes, consistent with an association between TMEM106B and brain inflammation which requires further exploration. Understanding the links among vascular pathology, TMEM106B, and TDP-43 proteinopathies is crucial for developing targeted therapies.

Methods: We compared autopsy brains across TDP-43 proteinopathies and CVD to investigate potential differences in TMEM106B levels. Autopsy brain samples (N=17) were selected from the Bigg's Brain Bank to include FTLD-TDP, LATE, TDP-43 negative AD and non-neurodegenerative controls. Multiplex immunofluorescence staining was performed on formalin-fixed hippocampal sections to assess whether CVD burden had an impact on TMEM staining patterns. Antibodies included: anti-TMEM106B (150-274aa); anti-TMEM106B (239-250aa); anti-TDP43, anti-Iba1 (EPR16588), and anti-GFAP (G-A-5). Quantitative digital pathology analyses were conducted on whole slide images to assess the distribution and levels of TMEM aggregates alone and within microglia and astrocytes.

Results: We observed increased TMEM106B(150-274aa) in LATE cases with severe CVD in comparison to non-neurodegenerative disease with severe CVD ($p =< 0.0001$). In contrast, TMEM106B (150-274aa) levels showed no statistically significant difference when comparing LATE cases with low CVD to non-neurodegenerative low CVD controls ($p=0.1415$).

Conclusions: Results suggest that CVD as a co-pathology contributes to TMEM106B accumulation in LATE cases. CVD may contribute to loss-of-function of TMEM106B through fibril formation, leading to increased TDP-43 pathology. As the development of TMEM106B fibrils is age-dependent, lysosomal loss-of-function may be implicated in the link between aging and dementia.

75

Thiophene-Based Ligand HS-84 Binding in Human PrP Proteinopathies

M Jacobsen [1], N Maynard [1], L Cracco [1], K Newell [1], R Vidal [1], T Klingstedt [2], P Nilsson [2], B Ghetti [1]; [1] Indiana University School of Medicine, [2] Linkoping University

Background: Current diagnostic methods for PrP proteinopathies include Real-Time Quaking-Induced Conversion (RT-QuIC) to detect misfolded prion protein (PrP). However, due to variability of the sensitivity and specificity of these assays between PrP proteinopathies, additional biomarkers are needed. Luminescent conjugated oligothiophenes (LCOs), such as the ligand HS-84, are potentially useful diagnostic methods. For Alzheimer disease (AD) pathology, HS-84 has been reported to bind to neurofibrillary tangles made of tau protein as well as the plaques and cerebral amyloid angiopathy (CAA) made of amyloid β (Aβ). Herein, we evaluate one thiophene based ligand, HS-84, and its binding affinity to human PrP proteinopathies

Methods: The Dementia Laboratory at Indiana University has an extensive collection of brains from individuals affected by PrP proteinopathies. Tissue sections of paraffin-embedded cerebellar cortex from cases of sporadic Creutzfeldt-Jakob disease (CJD) (MV 1-2 and VV2), Gerstmann-Sträussler-Scheinker disease (GSS) associated with PRNP mutation F198S, and PrP-CAA associated with PRNP mutation Q160X were studied. Multiplex immunofluorescence was carried out using HS-84, 3F4 primary antibody with an Alexa Fluor 647 secondary antibody, and DAPI.

Results: In sporadic CJD, both 3F4 and HS-84 stained the PrP plaques. In PrP-CAA associated with PRNP mutation Q160X, 3F4 and HS-84 colocalized in the PrP deposits in both the cerebellar cortex and leptomeninges. However, in GSS-F198S, HS-84 did not stain diffuse plaques and rarely stained cored plaques.

Conclusions: The findings of positive staining using HS-84 in PrP-CAA with PRNP mutation Q160X, but not in GSS with the PRNP mutation F198S may be consistent with potential structural differences of the amyloid filaments in the two different dominantly inherited amyloidoses. Additional studies are needed to better define the chemical basis of the affinity of HS-84 with amyloids originating from three different proteins.

76

Neuropathologic Findings in a Rare Case of Alpers-Huttenlocher Syndrome at Autopsy
L Robinson, J Suddock, E Abreo; Oklahoma Office of the Chief Medical Examiner

Background: This case involves a 24-year-old male with a past medical history significant for epilepsy and Alpers-Huttenlocher syndrome (AHS) who was found unresponsive in bed. Per medical records, he had a neurostimulator with associated electrode leads surgically implanted within right temporal aspect of the cranium. His seizures were reportedly well-controlled through neurostimulator device monitoring and anti-seizure medications.

Methods: At autopsy, the external and internal examinations, apart from the pertinent intracranial findings, were unremarkable. Grossly, the liver parenchyma appeared normal with microscopic sections showing subtle architectural disorganization, ballooning degeneration, and scattered hepatocytes with hypereosinophilic cytoplasm lacking observable nuclei.

Results: Neuropathologic examination revealed encephalomalacia of the bilateral temporal lobes, remote infarct of the right temporal lobe, subacute infarct of the left temporal lobe, arteriolosclerosis, and diffuse cerebral atrophy. Microscopic sections of the right temporal lobe demonstrated laminar necrosis, underlying marked gliosis, and cavitary white matter loss. Sections of the left temporal lobe showed scattered hemosiderin-laden macrophages, focal acute hemorrhage, and perivascular lymphocytic infiltrates. Scattered, hypereosinophilic neurons predominated the hippocampal CA1 regions. The cerebellum showed Purkinje neuronal loss, Bergman gliosis, and hypereosinophilic neurons involving the Purkinje cell layer and dentate nucleus.

Conclusions: AHS is an autosomal recessive condition caused by a mutation in the gene that encodes for mitochondrial DNA polymerase gamma (POLG) leading to combined cerebral cortical and hepatic degeneration. Patients usually present within the first 2 years of life with an overall reported incidence rate of ~0.002%. Initial clinical presentation typically involves debilitating seizures and developmental stagnation with gradual development of dementia, blindness, spasticity, and liver failure. Macroscopic examination of the brain commonly appears unremarkable. Microscopically the changes are more widespread involving astrocytosis, vacuolization, and neuronal loss throughout the cortical ribbon and deep grey nuclei. In cases of severe hepatic failure, Alzheimer type II astrocytes can be prominent.

77

Histopathological Features Associated with Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS)

J Opara, M Davis, M Weiss, T Bird, D Child, C Latimer; University of Washington

Background: Cerebellar Ataxia with Neuropathy and Vestibular Areflexia Syndrome (CANVAS) is a rare neurodegenerative disorder marked by progressive ataxia, severe neuropathy, and vestibular dysfunction, caused by a biallelic AAGGG repeat expansion in intron 2 of the replication factor C subunit 1 (RFC1) gene on chromosome 4. Although a few neuropathological studies have been performed, describing cerebellar and vestibular ganglion degeneration and demyelination of the dorsal columns and peripheral nerves, the underlying pathophysiology and clinical-pathological correlations remain poorly understood.

Methods: Here, we present the clinical and pathological findings from a patient with genetically confirmed CANVAS. Post-mortem neuropathologic exam of brain and spinal cord included extensive evaluation of the cerebellum with staining for p62, GFAP, calbindin, IBA-1, and Bielschowsky silver stain along with expanded assessments for hyperphosphorylated tau and TDP-43 in the cerebral cortex, brainstem, cerebellum, basal ganglia, and spinal cord.

Results: The patient's initial symptoms included chronic cough, dysphagia, dysarthria, falls, progressive ataxia, neuropathy, autonomic dysfunction, and intermittent horizontal diplopia. Genetic testing revealed a biallelic AAGGG repeat expansion in the RFC1 gene. Microscopic examination revealed features of cerebellar neurodegeneration, including mild loss of Purkinje neurons, axonal swellings, and Bergman gliosis. Tau pathology in a pattern most consistent with progressive supranuclear palsy (PSP) was also identified. Additionally, TDP-43 proteinopathy was observed in the ventral horn neurons of the spinal cord, characterized by skein-like inclusions as seen in motor neuron disease.

Conclusions: This case is the first histologic observation of combined tau and TDP-43 proteinopathy in CANVAS and adds to a growing literature on the clinical and pathologic heterogeneity of this disease. Further research is needed to understand the pathogenic role of RFC1 mutations and their potential link to these proteinopathies, which could offer new insights into the pathophysiology of CANVAS as well as other neurodegenerative diseases with overlapping features.

78

Microglial Heterogeneity in Alzheimer's Disease, Dementia with Lewy bodies, and LATE-NC

R Shahidehpour, A Bachstetter, P Nelson; University of Kentucky College of Medicine

Background: Microglia exhibit substantial phenotypic diversity in Alzheimer's disease (AD) and related dementias (ADRDs), engaging in complex (but incompletely understood) interactions with pathological hallmarks such as Aβ plaques, neurofibrillary tau tangles (NFTs), Lewy bodies, and TDP-43 proteinopathy. Historically, research on histomorphologic microglial alterations in AD-type dementia has been largely restricted to the medial temporal lobe (MTL), partly because of the MTL's early and severe involvement in AD neuropathologic changes (ADNC). While studies have established an association between dystrophic microglia—characterized by fragmented and beaded processes—and tau pathology in the MTL, it remains unclear how dystrophic microglia are distributed outside of the MTL and in non-ADNC dementing disorders. Here we expanded the scope of investigation and included non-MTL regions impacted by various ADRDs.

Methods: Using rigorous analyses of post-mortem human brain tissue representing multiple common ADRD neuropathological subtypes and severities, we assessed the regional distribution of histopathologically-defined microglial phenotypes, including ramified, hypertrophic, and dystrophic microglia. The cases that were evaluated were from the University of Kentucky AD Research Center autopsy cohort, and included ADNC, Lewy body disease (LBD) and limbic predominant age-related TDP-43 encephalopathy neuropathologic changes (LATE-NC) cases and controls.

Results: Dystrophic microglia were not exclusively observed in the hippocampus but were instead observed in multiple brain regions affected by dementia-driving pathologies. The presence of dystrophic microglia was highly correlated with markers of iron dysregulation, suggesting that microglia may be influenced by small hemorrhages or some other source(s) of pathologic iron deposition. Furthermore, dystrophic microglia were particularly abundant in areas exhibiting tau pathologic accumulation, less so in LBD and less still in LATE-NC cases, indicating tropism between dystrophic microglia and tauopathy.

Conclusions: Our study provides insights into the implications of microglial heterogeneity, highlighting their regional specificity and morphologic features in association with pathology across multiple neurodegenerative diseases.

79

Prolonged Survival in Cerebellar Variant Multiple System Atrophy with Parkinsonian Features and Co-Existing Lewy Body Disease

S Etemadmoghadam [1], A Ghaseminejad-Bandpey [2], M Keating [2], C Gaona [2], A Gonzalez [2], C Corbett [2], O Ogunbona [3], M Dopler [2], K Clarke [2], K Li [4], J Parker-Garza [2], B Danner [2], M Alhneif [2], M Habes [5], K Bieniek [3], S Seshadri [2], M Flanagan [6]; [1] Glenn Biggs Alzheimer's Institute, University of Texas Health Science Center at San Antonio, San Antonio, [2] Glenn Biggs Alzheimer's Institute, University of Texas Health Science Center at San Antonio, San Antonio, [3] Glenn Biggs Alzheimer's Institute & Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at San Antonio, San Antonio, [4] Neuroimage Analytics Laboratory and Biggs Institute Neuroimaging Core, Glenn Biggs Institute for Neurodegenerative Disorders, University of Texas Health Science Center at San Antonio, [5] Neuroimage Analytics Laboratory and Biggs Institute Neuroimaging Core & Research Imaging Institute, University of Texas Health Science Center at San Antonio, [6] Glenn Biggs Alzheimer's Institute & Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at San Antonio, San Antonio

Background: Multiple system atrophy (MSA) is a progressive α-synucleinopathy classified into MSA with cerebellar ataxia (MSA-C) and MSA with parkinsonism (MSA-P), based on predominant motor symptoms. Disease duration from onset to death ranges from 6–9 years. Comorbid pathologies in MSA are not commonly reported.

Methods: We present a case of MSA-C with overlapping MSA-P features and co-existing Lewy body disease (LBD) in a 63-year-old man with a prolonged 16-year clinical course. Comprehensive brain analysis followed the Biggs Institute protocol, which included sampling 23 regions per CERAD guidelines, staining with phosphorylated-α-synuclein (pSYN64), AT8, pS409/410, 4G8, and H&E, and assessment of Alzheimer disease neuropathologic change (ADNC) regardless of the final diagnosis. LB509 and Gallyas staining, and genetic testing were also performed.

Results: Loss of balance began at 48, followed by wide-based gait, slurred speech, and autonomic dysfunction 3.5 years later. Tremor and dysphagia developed, but no memory, visuo-spatial, or sensory deficits were noted. Antemortem and postmortem neuroimaging supported a clinical diagnosis of MSA-C. The patient passed at 63, surviving 16 years. Gross examination showed attenuation and discoloration of cerebellar white matter with severe cerebellar and brainstem atrophy. Histopathology confirmed a diagnosis of mixed olivopontocerebellar atrophy and striatonigral degeneration, characterized by pSYN64 and LB509 immunopositivity within glial cytoplasmic inclusions (GCIs), dystrophic neurites, and neuronal inclusions across limbic and cerebellar regions. Additional findings included low ADNC, severe cerebral amyloid angiopathy, and amygdala predominant and limbic/transitional LBD. Gallyas was positive in GCIs but negative in LBs. Genetic testing detected no repeat expansion mutation or sequence alteration associated with the Complete Ataxia Evaluation.

Conclusions: Given the limited reports on comorbid pathologies in MSA, determining their clinical significance remains challenging. In this case, the prolonged clinical course prompts consideration of whether the co-occurrence of LBD may have influenced disease progression; however, its impact remains uncertain.

80

Isolated Astrocytic Tau Pathology at Cortical Sulcal Depths: Is it "AR"TAG?

D Priemer [1], G Kovacs [2], D Perl [1]; [1] The Uniformed Services University School of Medicine, [2] University of Toronto

Background: The latest iteration of the consensus agreement chronic traumatic encephalopathy (CTE) diagnosis requires a neuronal phosphorylated tau (ptau) lesion of cortical sulcal depths which may or may not involve astrocytes. Astrocytic ptau at cortical sulcal depths, alone, is insufficient for CTE but rather it is generally suggested that this be categorized within the spectrum of Aging-Related Tau Astrogliopathy (ARTAG).

Methods: We present 3 post-mortem brain examinations of individuals aged 61 years and younger whose history included traumatic brain injury, including a 61-year-old male with a history of semi-professional football play, multiple motor vehicular accidents, and multiple fights, a 54-year-old male with a history of school-year participation in football, baseball, and basketball and multiple falls, and a 52-year-old male with a history of glioneuronal tumor and multiple neurosurgeries.

Results: Comprehensive brain sampling and assessment with ptau immunohistochemistry (AT8 antibody) revealed one or more lesions characterized by ptau-immunoreactive, subpial thorny astrocytes at cortical sulcal depths. No pathognomonic CTE lesion was observed in any of the cases. Further types and patterns characteristic of ARTAG in elderly individuals were similarly not observed.

Conclusions: ARTAG is considered a pathology of elderly individuals with multiple characteristic patterns not confined to cortical sulcal depths, but rather with a predilection for the cerebral base (e.g., amygdala, periventricular at the temporal horn of the lateral ventricle, etc.). The individuals presented here are younger than regularly reported for ARTAG, and the subpial astroglial ptau accumulation is limited to cortical sulcal depths. This supports the notion that some lobar subpial ARTAG might be related to local mechanical compression, including traumatic impacts. We raise the question whether these isolated lesions should be distinguished from ARTAG seen in elderly. The opinions or assertions expressed herein are those of the authors and do not reflect the official policy/position of Uniformed Services University or the Department of Defense.

81

Feasibility Assessment for Evaluation of Cerebellar Pathology in Huntington Disease

J Opara [1], A Sayyadi [2], D Child [3]; [1] University of Washington, [2] Univeristy of Washington, [3] Univerisity of Washington

Background: Huntington disease (HD) is a fatal, autosomal-dominant neurodegenerative disorder caused by a CAG trinucleotide repeat expansion in the huntingtin gene (HTT) on chromosome 4. While chorea is a hallmark symptom, HD presents with diverse motor, cognitive, and behavioral phenotypes, suggesting broader neuropathologic involvement. Although striatal medium spiny neurons (MSNs) are the primary site of neurotoxicity, recent studies highlight cerebellar Purkinje cell degeneration in a subset of individuals, implicating the cerebellum in HD pathogenesis. However, the relationship between Purkinje cell loss and symptom variability remains poorly understood. The aim of this study is to delineate cerebellar pathology and its association with clinical phenotypes in HD.

Methods: This study leverages post-mortem brain tissue from the UW Brain Repository and Integrated Neuroscience (BRaIN) lab, including 16 HD donors and matched controls. Tissue sections from the bilateral anterior and inferior cerebellar lobes and cerebellar vermis were stained with calbindin and HTT. Match striatal sections were stained with DARPP-32 to assess MSNs. Whole-slide images were captured using the Leica Aperio system for digital pathology analysis. Using the Halo suite, statistical analyses were conducted to assess correlations between neuron densities, HTT inclusion burden, and clinical phenotypes.

Results: Preliminary data from digital pathology analysis is consistent with previously reported Purkinje cell loss in Huntington disease. Findings also implicate Purkinje cell loss occurring independently of striatal medium spiny neuron degeneration and in a stochastic pattern, supporting a contribution from intrinsic somatic expansion.

Conclusions: Understanding cerebellar pathology in HD is crucial for elucidating its contribution to disease heterogeneity. Our findings demonstrate that FFPE tissue is suitable for studying HD cerebellar pathology and suggest that Purkinje cell loss occurs independently of MSN degeneration, highlighting the cerebellum’s potential role in symptom variability. This insight may refine therapeutic strategies, emphasizing the need to consider broader neuroanatomic targets beyond the striatum.

82

A case of rapidly progressing limb-onset ALS with an intermediate ATXN2 repeat expansion

T Brown, L Chen; University of Minnesota

Background: Ataxin 2 (ATXN2) is a gene most commonly associated with spinocerebellar ataxia type 2 (SCA2). A CAG trinucleotide repeat expansion with over 34 repeats in the ATXN2 gene causes SCA2. Interestingly, intermediate size expansions (27-33 repeats) in SCA2 are a known risk factor for amyotrophic lateral sclerosis (ALS). Patients with ALS and an ATXN2 expansion were more likely to have limb-onset disease and a rapid clinical course than those with normal ATXN2 repeats.

Methods: We present the case of a 61-year-old woman who noted right foot drop in June 2023 followed by weakness of the right upper and later left upper and lower limbs, without pain or substantial positive or negative sensory symptoms. She underwent electrodiagnostic studies and was diagnosed with limb-onset ALS. Pertinent negatives were cognitive or behavioral symptoms.

Results: Through genetic testing, the patient was negative for C9orf72 expansion, but was found to have 30 repeats in ATXN2. She rapidly progressed to wheelchair level and passed away in July 2024. Postmortem neuropathological examination revealed no gross abnormalities in the brain. There was degeneration and loss of large motor neurons in the anterior horn of the spinal cord, lower cranial motor nuclei of the brainstem, and Betz cells in the motor cortex. pTDP-43 positive inclusions were present in the motor cortex and all spinal cord segments.

Conclusions: This patient had classic clinical and neuropathological findings of ALS. However, her clinical progression was significantly more aggressive than is typical for limb-onset disease. This can be explained by her 30 repeat expansion in ATXN2, a known disease-modifying risk factor for ALS. This case highlights the need for further investigation into the pathogenic effects of intermediate repeat expansions in ATXN2 and their role in ALS.

83

Neuroinflammatory and Vascular Changes in Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD)

G Uruk [1], F Mu Hui [1], R Gatto [1], R Reichard [2], J Whitwell [3], K Josephs [1]; [1] Department of Neurology, Mayo Clinic, Rochester, MN, USA., [2] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA., [3] Department of Radiology, Mayo Clinic, Rochester, MN, USA.

Background: Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are two distinct late-onset “4-repeat (4R) tauopathies” showing 4RT inclusions. Growing evidence suggests that chronic and sustained immune response is the driver of neurodegeneration in Alzheimer’s disease (AD) where microglia activation develops before tau aggregation. Though neuroinflammatory and vascular pathologies have been identified in other neurodegenerative disorders, PSP and CBD are yet to be evaluated. We aim to investigate the relationships between neuroinflammatory cellular morphology and vascular structural changes in PSP and CBD by multiplex immunostaining.

Methods: This study included neuropathological samples from three CBD, and six PSP neuropathologically confirmed cases; one healthy control (HC) totaling 10 cases. Among the 6 PSP cases, 3 were clinically diagnosed as PSP-Richardson (subcortical) and 3 as PSP-Speech/Language (cortical). Neuropathological specimens focused on grey (GM), white matter (WM) and meningeal areas from three regions: basal ganglia, occipital cortex, and the superior/middle frontal gyrus (S/M-FG). Immunohistochemical staining was performed with antibodies for glial fibrillary acidic protein (GFAP) and microglia/macrophages (Iba1/CD68). Lycopersicon esculentum lectin (Lectin) and endothelium (CD31) were used to identify vascular structures.

Results: CBD and PSP-cortical groups demonstrated an extensive increase in the number and activation of microglia/macrophages in basal ganglia, GM and WM of S/M-FG, and less severe involvement in the occipital cortex, while PSP-subcortical had prominent pro-inflammatory activation in basal ganglia, relatively mild GM S/M-MG, and subtle GM occipital cortex involvement, these cases showed minimal changes in WM S/M-MG and occipital cortex. Meningeal inflammation was profound in PSP-cortical but not in PSP-subcortical or CBD.

Conclusions: CBD, PSP-SL (cortical) and PSP-RS (subcortical) show distinct distribution patterns of the vascular and inflammatory pathology providing insight into the understanding of the pathophysiology and spectrum of clinical manifestations of 4R tauopathies.

84

Adult polyglucosan body disease neurodegeneration with associated liver disease: an autopsy study

K Jones, F Weaver, P Kishnani, R Koch; Duke University Health System

Background: Adult polyglucosan body disease (APBD), the adult-onset form of glycogen storage disease type IV (GSD IV), is a progressive neurodegenerative disease with polyglucosan accumulation that primarily involves the CNS, unlike childhood-onset GSD IV, with primarily liver involvement. Recent data suggest that some individuals with hepatic GSD IV in childhood may later develop adult-onset CNS-related neurological symptoms associated with APBD. Only 5 APBD autopsies have been published in patients with isolated CNS involvement.

Methods: This report describes brain autopsy findings from two APBD cases with personal or familial liver disease, both with confirmed pathogenic variants in GBE1.

Results: Case 1 was a Native Hawaiian male with liver disease from age 2 that resolved by age 20. In his 30s, he developed urinary hesitancy and gait disturbance and was diagnosed with ABPD. He died at age 47 from medically assisted death. Case 2, of Italian descent, had a brother who died at age 2 years from GSD IV with liver disease. At age 37, he began experiencing urinary urgency and unsteady gait and was diagnosed with ABPD. He died at age 55 years from respiratory failure secondary to aspiration pneumonia. Brain autopsies revealed extensive periventricular and subcortical white matter infarct-like cavitation with sparing of subcortical U-fibers and gray matter. Cerebellar vermian atrophy was noted. Histologic examination showed widespread astrogliosis in white matter and patchy gliosis in gray matter. Periventricular white matter and subcortical white matter showed rarefaction or cavitation. Rarefied parenchyma showed relative preservation of axons and myelin. Polyglucosan bodies were found throughout the brain, with concentrations highest in the subependymal region, pyramidal cell layer of the hippocampus, cerebellar gray matter, and pons, but no significant neuron dropout.

Conclusions: A better understanding of the relationship between GSD IV and APBD clinicopathologic progression is essential for improving patient management and efficacy and specificity of therapeutic interventions.

85

The Brain Bank for Aging Research (BBAR) protocol for amyotrophic lateral sclerosis (ALS)

S Murayama [1], Y Saito [2]; [1] Tokyo Metropolitan Insisute for Geriatics and Gerontology, [2] Tokyo

Background: BBAR contributed to a comprehensive study of amyotrophic lateral sclerosis (ALS) since its establishment in 1999.

Methods: We froze a half brain and a spinal cord after sampling small pieces of frontal, temporal and occipital cortex and precentral gyrus, anterior amygdala, posterior hippocampus, cerebellar dentate gyrus, midbrain, and the fourth and eighth cervical segments, the fourth, eighth and twelfth thoracic segments, the fifth lumbar segment and the second sacral segment of the spinal cord, which were fixed in 4% paraformaldehyde two overnights, sliced for paraffin embedding and the remaining in phosphate buffer with cryo- protection. About the fixed half brain, we obtained 8 mm thick coronal consecutive slices from the frontal pole to the anterior commissure and from the ampulla of corpus callosum to the occipital pole. From the remaining middle, we got an axial 8 mm thick slice through the anterior commissure (AC), sagittal consecutive slices dorsal to AC and coronal consecutive slices ventral to AC. TDP43, FUS, SOD1 and C9 were screened immunohistochemically and genomic study, confirmed by Western blot and Immuno electron microscopy. Phrenic and sural nerves were sampled for for ultrastructural studies. Biceps brachii and short peroneal muscles were frozen for histochemical studies.

Results: We examined the upper motor neuron system (UMN) including the precentral gyrus, the isthmus of corpus callosum, the posterior limb of the internal capsule, the cerebral peduncle, the medullary pyramid and the cervical, thoracic, lumbar and sacral corticospinal tracts, and the lower motor neuron system (LMN), including the trigeminal, facial and hypoglossal nuclei and the cervical, thoracic lumbar and sacral anterior horns. All examined cases of ALS- TDP 43 were sporadic, showed degeneration of both UMN and LMN, and were classified into TDP43 type B.

Conclusions: With this protocol, we supported clinical and basic researchers of ALS in Japan.

86

Neuropathologic and Ocular Vascular Anomalies in Advanced Ataxia-Telangiectasia

D Smirnov [1], L Kozanno [2], A Stemmer-Rachamimov [3], M Frosch [3]; [1] Mass General Brigham, [2] University of Chicago, [3] Massachusetts General Hospital

Background: The neuropathology of Ataxia-Telangiectasia (A-T) is primarily characterized by infratentorial degeneration, including cerebellar atrophy, posterior column and nuclear loss, and anterior horn cell degeneration. While conjunctival telangiectasias are a hallmark feature, vascular anomalies within the central nervous system have been rarely reported.

Methods: Here we present a case of a 31-year-old man with A-T who died of sepsis in the setting of aspiration.

Results: Neuropathologic examination revealed extensive vascular abnormalities within the cerebral white matter and spinal cord, including evidence of both venous and arterial involvement (but notably without the characteristics of arteriovenous malformations). Many lesions demonstrated evidence of prior hemorrhage with surrounding reactive gliosis, some with thrombosis and re-canalization, while others showed active inflammation and red blood cell extravasation. The white matter adjacent to many of these lesions contains scattered, large, highly atypical nuclei. A striking and previously unreported finding was the presence of large cavitary spaces ("lakes") observed both on antemortem imaging and postmortem neuropathologic examination. These cavities were associated spatially with vascular anomalies but were not directly contiguous with them and did not demonstrate evidence of a vascular wall or an endothelial lining. Based on imaging, these lesions had been present for some time, yet were not associated with significant hemosiderin deposition around the edges, raising the possibility that these reflect extravasation of plasma without significant numbers of red blood cells through some form of blood-brain barrier breakdown in those regions. Additionally, examination of the globes showed clusters of thin walled, dilated vessels in the bulbar submucosa, consistent with the characteristic conjunctival telangiectasia of the disease.

Conclusions: These findings highlight novel and underappreciated vascular pathologies in patients with advanced A-T, which likely contribute to the neurologic status, and which may become increasingly prevalent as therapeutic advances extend patient survival.

87

Neuropathology of micro- and nano-plastics in brain

E Bearer [1], M Garcia [2], N Adolphi [3], A Caprihan [4], M Campen [3], G Rosenberg [3]; [1] University of New Mexico Health Sciences, [2] University of New Mexico Healh Sciences Center, [3] University of New Mexico Health Sciences Center, [4] Mind Research Network

Background: Micro-nano-plastics (MNP) identified by chemical analysis are found in post-mortem brains from healthy individuals (Nihart et al., Nature Medicine 2025). Here we report discovery of abundant MNP in human subcortical white matter in cases of Binswanger's and Alzheimer's disease and new method to determine their location by histopathology.

Methods: Alignment of ante- to post-mortem MRI allowed examination of regions abnormal in life by histopathology.

Results: AD cases were positive for ABeta plaques, p-tau and neuritic plaques (CERAD). In contrast, Binswanger's had Abeta not in plaques and little p-tau. Neither disease had TDP43 or synuclein aggregates. Binswanger's had microinfarcts and microhemorrhages with minimal arteriolar sclerosis. Clusters of CD68-positive macrophages, loss of myelin and collagenosis of vessels corresponded to regions of WMH. Glossy brownish deposits that do not stain for heme appeared near blood vessels in regions with myelin loss and abundant macrophages. Ultraviolet microscopy in wave lengths specific for plastics revealed these brownish deposits to be MNPs. Pyrolysis-gas-chromatography/mass spectrometry revealed a concentration of 30,908µg plastics per gram of tissue in white matter of AD, and 21,441µg/g in Binswanger's–more than 5-fold above that of healthy brains (average=4,800µg/g). Cortical gray matter from both diseases also contained more microplastics than healthy brain. Negative stain electron-microscopy of isolated plastics found sharp-tipped nanofibrils < 2nm in diameter, and 0.5um to 5um in length.

Conclusions: We are exploring chemical, optical and ultrastructural analyses with various immuno-histology and heavy metal stains to detect the cellular context of these nanofibers and identify the types of plastics they represent. Many questions remain, such as the consequences of such non-biological material in the brain on endothelial cell integrity and blood brain barrier leakage, on activation of inflammatory mediators (matrix metalloproteinases), on macrophages and microglia, as well as on neurons and other glia, and their contribution to impairments of cognitive and motor functions.

88

Lipid metabolism during normal aging and age-associated neurodegenerative disease

A Ahamad [1], S Ge [2]; [1] Stony Brook Medicine, [2] Stony Brook University

Background: Aging is a multifaceted biological phenomenon involving a wide range of changes, including significant alterations in lipid metabolism. Hippocampus, a region of the brain critical for cognition and memory, is particularly vulnerable to the effects of aging and age-associated energy deficit leads to impaired cellular function, disrupted protein homeostasis, and altered circuit plasticity, collectively driving cognitive decline. Despite the recognized importance of lipid metabolism, there is a substantial gap in our understanding of the impact of aging and interplay between lipid metabolism, hippocampal function and neurogenesis. Neutral lipids, such as triglycerides, are stored within lipid droplets, specialized cellular organelles that play a key role in cellular bioenergetics.

Methods: To investigate the role of neutral lipids in the adult brain of aging mice, we used a lipophilic dye, Bodipy, to label neutral lipids and examined changes across the aging brain.

Results: We found a significant increase in neutral lipid levels in the adult brain of aging mice. Also, we found marked elevation in lipid content in aging brains compared to younger ones through electron microscopy. Our data showed that age-related changes in neutral lipid levels lead to reduced hippocampal neurogenesis. To better understand the functional implications of neutral lipids during aging, we conducted behavioral assessments, such as fear conditioning and open field maze tests. We found that variation in neutral lipid levels during aging were linked to memory deficits and anxiety-like behaviors in mice. Furthermore, our study revealed a notable increase in neutral lipids in an Alzheimer’s disease mouse model, further implicating neutral lipids in cognitive impairments.

Conclusions: In conclusion, our findings highlight the previously unrecognized role of neutral lipids in the adult brain during normal aging and in age-related neurodegenerative disease. These results suggest that neutral lipids may serve as promising therapeutic targets to mitigate memory and cognitive deficits associated with aging.

89

Interface astroglial scarring and an unclassified tauopathy with features of progressive supranuclear palsy and corticobasal degeneration

S Hasan, K Bharani, R Sobel; Stanford

Background: Interface astroglial scarring (IAS) of subependymal and subpial brain surfaces has been associated with remote traumatic blast exposures (BE) (Shively et al., 2016). War veterans with BE have exhibited early-onset dementia (EOD) and atypical brain lesion patterns compared to non-military populations, often presenting with brain polypathology (Iacono et al., 2020). Neurodegenerative tauopathies, characterized by pathological tau aggregates, include corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP)—two disorders often marked by discrepancies between clinical presentation, neuropathological findings, and uncertain pathogenesis (Koga et al., 2023). CBD typically presents with asymmetric parkinsonism and executive dysfunction, while PSP manifests as axial rigidity and poor dopaminergic response. Definitive diagnosis relies on distinct tau deposition patterns. Here, we present the case of a 72-year-old Air Force veteran with complex tauopathy and IAS.

Methods: Neuropathologic examination followed standard autopsy procedures, including H&E and IHC stains, to assess neurodegeneration and correlate findings with clinical history.

Results: Clinically diagnosed with atypical Parkinson's disease, the patient experienced rapid physical and cognitive decline over four years. Post-mortem examination revealed a brain weight of 1255 g. Phosphorylated tau immunohistochemistry (AT8) identified overlapping PSP, CBD, and mild Alzheimer's disease neuropathologic change (ADNC) (A1B1C1). PSP features included neurofibrillary tangles, coiled bodies, threads, and tufted astrocytes in the globus pallidus, subthalamic nucleus, substantia nigra, and putamen. CBD pathology included astrocytic plaques and grumose degeneration of the dentate nucleus. Immunostains for α-synuclein and TDP-43 were negative. Additionally, GFAP+ IAS was observed subependymally (ventricles, cerebral aqueduct) and subpially (inferior cortical, mammillary body, lateral cerebellar cortex, brainstem, and upper spinal cord), suggesting possible blast exposure.

Conclusions: This case complements prior observations, highlights neuropathologic overlap among tauopathies, and suggests that IAS-associated brain polypathologies may extend beyond veterans with EOD. Further research is needed to investigate the relationship between IAS and neurodegenerative pathologies and their role in disease progression.

90

C9orf72 Mutation in a Patient with Amyotrophic Lateral Sclerosis

E Salari, S Schwartz; Thomas Jefferson University Hospital

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting upper and lower motor neurons. Patients can experience many physical, often progressive symptoms, including muscle weakness, respiratory failure, and death. Prognosis is poor; most patients expire within a few years of diagnosis despite treatment. ALS is characterized by excessive deposition of protein in motor neurons (ex: TDP-43). Although most cases occur sporadically, C9orf72 mutations are seen in many familial ALS cases. We present a case of C9orf72-associated ALS.

Methods: Genetic testing revealed a heterozygous pathogenic mutation in the C9orf72 gene, c.-45+179_-45+184[>30]. An autopsy was performed. Gross examination revealed decreased brain weight at 990 g and some pallor of the locus coeruleus, but otherwise unremarkable brain and spinal cord. Sections of brain and spinal cord were taken for microscopic examination; staining for TDP43 and PHF-tau were performed in some sections.

Results: TDP43 positivity and a decrease in motor neurons were identified in the spinal cord and motor cortex. TDP43-positive skein-like inclusions were also identified in some areas. TDP43 positivity, TDP43-positive neurites, and decreased neuronal density were identified in the frontal cortex. Rare positivity of TDP43 was seen in the amygdala and hippocampus. The amygdala also showed rare cytoplasmic inclusions in dentate gyrus neurons. Tau-positive neurites, pre-tangles, and neurites were identified in the temporal cortex, amygdala, and hippocampus. Tau-positive neurites were identified in the frontal cortex. Decreased neuronal density was seen in the temporal cortex.

Conclusions: The mutation and clinical course were sufficient to confirm a diagnosis of C9orf72-related ALS. The autopsy results, including decreased motor neurons in the brain/spinal cord, TDP43-positive neurites/inclusions, and Tau pathology are consistent with the diagnosis. The patient’s picture and pathologic findings are compatible with C9orf72-related ALS and suggestive of an incipient TDP43-associated frontotemporal lobar degeneration process.

Posters: Infectious

91

Jamestown Canyon virus meningoencephalitis in a lymphoma patient following rituximab therapy with biopsy findings

D BeDell, M Folkertsma, A Venteicher, G Fitzpatrick; University of Minnesota Medical Center

Background: Jamestown Canyon virus (JaCV) is an orthobunyavirus transmitted by mosquitoes with rare human cases being documented throughout the United States and in Canada. Typically asymptomatic in immunocompetent adults, JaCV can cause meningoencephalitis and present with a variety of neurologic symptoms and even lead to severe illness and death in immunocompromised patients. Cerebrospinal fluid (CSF) often shows lymphocytosis with elevated protein and normal glucose. Diagnosis is made by detection of JaCV IgM in serum or CSF and confirmed by plaque-reduction neutralization testing to rule out cross-reactivity with other California serogroup viruses. Brain biopsy is rarely performed, and only two cases to date of diagnosed JaCV meningoencephalitis with histopathologic findings have been reported.

Methods: We review the literature and present biopsy findings in a fatal case of JaCV meningoencephalitis mimicking recurrent lymphoma in a 64-year-old man who underwent chemotherapy with rituximab for diffuse large B cell lymphoma of the colon six months prior. He presented with altered mentation, and MRI demonstrated predominantly cerebellar leptomeningeal enhancement and T2-signal abnormality, raising the differential of recurrent lymphoma, therapy-induced changes, and infectious leptomeningitis. The patient underwent cerebellar biopsy.

Results: Histology demonstrated partial Purkinje neuron loss associated with moderate microglial activation and scattered T-lymphocytes throughout the cerebellar cortex. No leptomeninges were present for evaluation, though perivascular T-lymphocytes suggest extension of inflammation along Virchow-Robin spaces. No microglial nodules, necrosis, or viral cytopathic changes were identified. Though biopsy findings were nonspecific, JaCV IgM was subsequently detected in the CSF, confirming the diagnosis.

Conclusions: Only two prior human JaCV cases with histopathologic findings have been reported. Our findings are similar to those previously described. This case highlights the importance of considering Jamestown Canyon virus, particularly in immunocompromised patients, as standard infectious disease panels may not identify the virus.

92

A case of cerebral immune reconstitution inflammatory syndrome (IRIS) in an HIV-positive patient

M Gulfo [1], S Kurt [2], S Qi Huang [2], F Sheikh [2], J Hua-fang Lin [3], R Fecher [2], R Yokoda [2], S Chin [2]; [1] Albert Einstein College of Medicine, [2] Montefiore Medical Center, [3] SUNY Downstate Medical Center

Background: Immune Reconstitution Inflammatory Syndrome (IRIS) describes an exaggerated inflammatory response that occurs toward a pre-existing antigen in the setting of immune system recovery. IRIS most commonly occurs due to rising CD4+ T-cell counts after antiretroviral therapy (ART) initiation in HIV-positive patients. It is typically self-limited, but permanent damage is possible, especially in the central nervous system (CNS). CNS involvement occurs in 1% of IRIS cases following ART initiation, but in up to 40% of cases in patients with opportunistic infections. IRIS is a diagnosis of exclusion with incompletely characterized diagnostic findings.

Methods: A 60-year-old male patient with a history of HIV infection and variable ART adherence, seizures, and hypertension presented with altered mental status after a fall and possible seizure. His diagnostic workup included neuroradiologic, neuropathologic, and clinical laboratory assessments.

Results: Initial MRI brain revealed over 15 ring-enhancing lesions and marked left frontal edema. Biopsy and histopathological analysis revealed no evidence of primary neoplasm, lymphoma, malignancy, abscess, or organisms. It revealed CD8+-predominant lymphoid proliferation with granuloma formation, necrosis, and marked reactive microgliosis, consistent with IRIS reports. The patient's viral load was undetectable and CD4+-cell count was 51, suggesting recent ART reinitiation. While tissue Toxoplasma gondii staining by two labs was negative, analysis detected T. gondii DNA in the same tissue and anti-T.gondii IgG in serum. Clinical stability and mild improvement in enhancing lesions on subsequent MRI brain followed empiric treatment with corticosteroids and TMP-SMX.

Conclusions: A diagnosis of IRIS was made by exclusion and supported by the case findings. The findings are consistent with latent T. gondii acting as an inciting antigen, but the role of other antigens cannot be excluded. This case highlights the need to further elucidate causes of IRIS, provides descriptive evidence to aid disease characterization, and emphasizes the need for early detection and treatment of IRIS.

93

A Tumor by Any Other Name: A Case of Pott's Puffy Tumor Caused by Frontal Sinus Fungal Ball

A Sandoval [1], F Stone [2], C Lucas [2], J Chiu [2], A Campbell [2], C Eberhart [2]; [1] Johns Hopkins Department of Pathology, [2] Johns Hopkins Hospital

Background: First described by Sir Pott in 1768, cases of frontal bone osteomyelitis with a subperiosteal abscess causing a circumscribed bump on the forehead are now known as Pott's Puffy Tumor (PPT). The etiology is commonly acute or chronic rhinosinusitis. The clinical presentation can be varied but commonly includes forehead swelling, headache, fever, periorbital edema, rhinorrhea, and neurologic changes.

Methods: Clinical, imaging, pathology, and microbiology records were reviewed.

Results: An afebrile 78-year-old male with a history of chronic sinusitis on moxifloxacin presented to the emergency department after weeks of left eye pain and headache. The patient had recently completed a 5-day course of steroids. On physical examination, his left eye showed significant periorbital edema, restricted upward gaze with intact extraocular movements, and decreased visual acuity. CT showed left frontal cellulitis with erosive changes through the orbital roof, a 2.2 cm subperiosteal abscess and associated preseptal cellulitis with low suspicion for cranial involvement. He underwent orbitotomy for orbital abscess drainage and endoscopic sinus surgery for removal of the frontal sinus fungal ball. On surgical debridement, the patient was found to have a sinus fungal ball and mucopurulent drainage. Microscopically, orbital contents showed inflammation and necrosis with scattered gram-positive cocci, while sinus contents revealed similar bacteria as well as densely packed septate fungal hyphae with predominantly acute angle branching. Bacterial culture eventually grew Streptococcus anginosus. Given concern for osteomyelitis, the patient was then treated with intravenous Ceftriaxone.

Conclusions: Orbital involvement occurs in less than a third of PPT cases and rarely results in permanent sequelae, but usually requires surgical intervention. Regardless, prognosis is favorable, with mortality having decreased from 60% to 3.7% in the antimicrobial era. However, given the potential for serious complications, such as orbital and intracranial involvement, early diagnosis and timely intervention remain critical in managing Pott's Puffy Tumor.

94

A fatal case of Acanthamoeba encephalitis

D Guptil, J DeWitt; University of Vermont Medical Center

Background: We present the case of an 85-year-old man with a medical history significant for Waldenstrom's macroglobulinemia on ibrutinib and rituximab with a course complicated by pancytopenia. He presented with multiple days of gait unsteadiness and increased cough with fever. MRI brain showed a right frontal lobe mass. Imaging findings were suspicious for a primary glial neoplasm, likely high-grade given the enhancement. Infectious work up was negative.

Methods: On histologic examination, there was marked reactive gliosis, parenchymal necrosis, prominent reactive vascular changes, hemorrhage, hemosiderin deposition, and an extensive perivascular and intraparenchymal mixed inflammatory infiltrate. Scattered throughout the tissues were rounded structures with hard, glass-like, wrinkled membranes, consistent with amoebic cysts. Further inspection revealed scattered enlarged, atypical appearing, cell-like structures with a vague nucleolus and bubbly cytoplasm, consistent with protozoal organisms. Final diagnosis was amebic encephalitis.

Results: The specimen was sent to the CDC who reported granulomatous amebic encephalitis (GAE) with immunostaining of trophozoites and cysts on a pooled amoeba and Acanthamoeba immunostains. Balamuthia immunostaining was negative. In follow up with the patient, he had reported recent use of saline nasal washes (Neti Pot). Unfortunately, he continued to deteriorate clinically and passed away 2 days after discharge to hospice (9 days after initial presentation).

Conclusions: Acanthamoeba transmission in GAE has been linked to nasal exposure to contaminated water (i.e. Neti Pot) primarily in immunocompromised patients. Acanthamoeba exists in two forms: trophozoites and cysts. The trophozoite stage is one of growth and reproduction while the cyst stage is characterized by cellular quiescence, commonly resulting in human infection via a double-layer cell wall, which gives cysts strong resistance to many harsh environmental conditions. GAE has a mortality rate of >90%, making it one of the deadliest infectious syndromes. The ability to convert into dormant and highly resistant cysts form limits effectiveness of available therapeutic agents.

95

No findings of neurodegenerative disease in a long COVID patient

C Hayes, S Rajan, M Morris, D Nauen, C Ho; Johns Hopkins Hospital

Background: Long COVID-19 patients experience prolonged neurologic symptoms such as fatigue, memory problems, and dysautonomia after resolution of the acute phase of illness. Several mechanisms have been proposed to explain this phenomenon, including vascular dysfunction, immune dysregulation, and persistence of viral infection. Some studies suggest that COVID infection may induce or accelerate Alzheimer disease pathology. The extent to which neurodegenerative pathology may contribute to the clinical presentations of long COVID is unclear.

Methods: Postmortem brain examination was performed on a 69-year-old woman diagnosed with long COVID by a neurologist. Pertinent clinical history was reviewed. Neurodegenerative disease workup including Hirano silver staining and immunohistochemical staining for beta-amyloid, phospho-tau, alpha-synuclein, and TDP-43 was performed.

Results: The patient died from perioperative complications of renal cell carcinoma. Prior to her death, she was experiencing long COVID symptoms including insomnia, blood pressure lability, paresthesia, and dizziness, which were improving with physical therapy and exercise. Postmortem neuropathologic examination revealed normal anatomical configuration and mild hydrocephalus ex vacuo. On hematoxylin and eosin stain, the basal forebrain demonstrated a rare neurofibrillary tangle (NFT) and Ammon's horn demonstrated scattered Hirano bodies and rare granulovacuolar degeneration. On silver stain, moderate NFTs were noted in the hippocampus and entorhinal cortex (Braak stage II/VI). However, no neuritic plaques were present. A beta-amyloid stain was negative. Alpha-synuclein and TDP-43 stains were also negative for cytoplasmic inclusions. The findings were consistent with primary age-related tauopathy (PART), a common diagnosis in aged brains.

Conclusions: We did not find pathology of Alzheimer disease, Parkinson disease or frontotemporal dementia in this case of long COVID. This study is limited by being a case report of which the presentations may not be entirely representative of the broad spectrum of long COVID. Nevertheless, our findings suggest that advanced neurodegenerative disease pathology does not contribute to the clinical symptoms in some long COVID cases.

96

Neuropathology of a Necrotizing Brain Abscess with Dematiaceous Mold: A Case Report of Cerebral Phaeohyphomycosis

J Dailey, M Punsoni; Brown University Health-Rhode Island Hospital

Background: Cerebral Phaeohyphomycosis (CP) is an invasive infection often presenting as a brain abscess, caused by melanized fungi or dematiaceous molds. The most common neurotropic pathogen to cause CP is Cladophialophora bantiana. We present a case of CP in an immunocompromised male with an irregular, rim-enhancing mass. Although ~70% of cases are fatal, this patient survived due to early recognition, prompt diagnosis and treatment.

Methods: A 60-year-old male status post renal transplant presented with chest pain and headache. MRI brain demonstrated a rim-enhancing mass in the left parietal lobe with edema and reduced core diffusivity. History revealed marijuana smoking with no history of gardening or mold in his home. Intraoperative findings described darkly pigmented brain tissue and abscess, which was aspirated and sent for gram stain and culture. Although the patient was initially somnolent, he showed clinical improvement later that day. MRI brain showed a small focus of residual enhancement.

Results: Microbiology showed septate hyphae on gram stain and black-green velvety colonies on sheep blood agar. On Sabouraud agar olive-grey to green colonies grew with a positive Calcofluor stain. Hyphae appeared pale brown, septate, with chains of oval conidia on lactophenol cotton blue. Tissue was sent for phenotypic analysis and DNA sequencing which confirmed C. bantiana. Microscopic evaluation revealed gliotic brain tissue with neutrophil rich microabscesses and necrotizing granulomas containing pigmented fungal hyphae and yeast like forms. Some fungal elements showed globose swelling. Melanin rich fungal walls were highlighted by Fontana Masson.

Conclusions: CP is a rare, commonly fatal infection, caused by dematiaceous molds, in this case, C. bantiana. Histopathology and culture are the gold standard for diagnosis. Early recognition with prompt and aggressive treatment are essential to ensure patient survival. Notably, at the 10 month follow up, the patient remained disease free.

97

Fatal Eastern Equine Encephalitis in a Medically Complex Patient: A Case Report and Literature Review

H Qiu, S Hoseini, V Chaturvedi, E Borys, G Kleinman; Westchester Medical Center

Background: Eastern Equine Encephalitis (EEE) is a rare, mosquito-borne arboviral infection with high mortality, particularly in immunocompromised individuals. The virus exhibits neurotropism, causing extensive encephalitic necrosis, perivascular lymphocytic infiltration, and microglial activation. Severe vasculopathy, neuronal loss, and systemic dysfunction contribute to poor outcomes. Understanding the pathological basis of disease progression is critical for improving diagnostic and therapeutic strategies.

Methods: A 64-year-old male with multiple myeloma, cerebrovascular disease, and hypertension presented with status epilepticus, respiratory distress, and obtundation. He received seizure control, broad-spectrum antibiotics, and antivirals. MRI showed acute infarctions and lumbar punctures revealed lymphocytosis. Encephalopathy panels were negative until EEE was confirmed by PCR. A brain autopsy assessed CNS involvement, comparing findings with reported cases to identify key pathophysiological patterns.

Results: A gross brain examination showed cortical congestion, edema, and hemorrhagic necrosis. Histopathology revealed perivascular lymphocytic cuffing, microglial nodules, neuronal dropout, and gliosis, consistent with viral encephalitis. Immunohistochemistry (IHC) demonstrated strong CD163 positivity and reduced NeuN expression, indicating widespread neuronal loss across the frontal lobe, hippocampus, striatum, thalamus, and brainstem. Plasma cell collections at the skull base were consistent with the patient’s multiple myeloma. EEE progresses rapidly, with mortality rates ranging from 30% to 70%. Survivors often experience lasting neurological deficits, including cognitive impairments and motor dysfunction. Immunosuppressed patients face additional diagnostic challenges, as highlighted in a similar case of a 63-year-old woman on rituximab for follicular lymphoma. Both cases exhibited extensive CNS involvement and rapid clinical deterioration despite treatment, emphasizing the need for improved diagnostic and therapeutic strategies in high-risk populations.

Conclusions: This is the first reported case of Eastern Equine Encephalitis (EEE) in a patient with multiple myeloma, requiring PCR testing for diagnosis due to the inability to produce detectable antibodies. The case underscores the heightened severity of EEE in immunocompromised patients, marked by rapid progression and extensive central nervous system involvement.

98

An Unusual Fungus In A Neurosurgical Specimen

R Rebbe [1], S Edminster [2], K Hurth [3], A Mathew [3]; [1] Keck Medical Center of USC, [2] USC/Los Angeles General Medical Center, [3] Keck School of Medicine of USC

Background: The patient is a 35-year-old male with medically intractable epilepsy who underwent multiple cranial surgeries of the left frontal lobe resulting in complex skull defects. He underwent implantation of left frontal neurostimulator; repair of left frontal-temporal and left frontal parasagittal skull defects with cranioplasty.

Methods: At surgery the infected hardware was removed and a 1.7 x 0.9 x 0.1 cm bloodstained fragment of tissue was found attached to a piece of hardware. The tissue was submitted for microscopic evaluation.

Results: Sections of the fibrous tissue attached to the hardware revealed the presence of fungal elements. Some of these fungal elements resembled conidia. While there were small, scattered areas of inflammation, increased inflammation was not observed in many regions containing fungal elements. The GMS and PAS fungal stains effectively highlighted the fungal components. Additionally, fungal PCR testing identified the presence of Alternaria species.

Conclusions: Alternaria are dematiaceous fungi that are commonly found in soil, plants, and the air. Although they are generally nonpathogenic to humans, they can lead to infections in immunocompromised individuals. This atypical case underscores the importance of submitting tissue associated with hardware for histological evaluation, even when the specimen is designated for 'gross examination only.' A month later, the patient exhibited purulent drainage. The epidural tissue submitted for histological analysis revealed signs of acute inflammation and necrosis. While both Gram and fungal stains returned negative results, microbiology cultures confirmed the presence of Klebsiella aerogenes. The patient was treated with antibiotics and antifungals.

Posters: If you're unsure, Other

99

Utilization of Process Record Slide (PRS) technology to facilitate harmonization of immunohistochemical reactions between laboratories.

G Fernandes [1], J Otero [2], J Phillips [3]; [1] Department of Cellular and Molecular Medicine, Florida International University, Herbert Wertheim College of Medicine, [2] Florida International University, Herbert Wertheim College of Medicine & Baptist Health South Florida, [3] University of California, San Francisco

Background: The reproducibility of immunohistochemistry in tumor tissue analysis remains a persistent challenge. Variability in staining protocols across laboratories continues to compromise diagnostic precision and prognostic reliability. We investigate inter- and intra-laboratory assays in p53 immunohistochemical staining of Glioblastoma samples, focusing on the role of Process Record Slide (PRS) technology in mitigating these discrepancies. PRS applies 0-100% concentration scale incorporating primary surrogate and secondary antibodies to generate a standardized curve for DAB precipitation.

Methods: Fifteen Glioblastoma samples were digitized at 40x magnification using Aperio Image Scope software and analyzed independently by pathology departments at The Ohio State University and the University of California, San Francisco. Feature extraction, including intensity and texture parameters was performed using the EBImage package in R, followed by UMAP dimensionality reduction and DBSCAN clustering analysis.

Results: Our results show significant differences in intensity and texture clustering patterns between laboratory tissue samples. Random forest classifier can determine which slide the primary antibody PRS standard derived from with low accuracy (Acc=49%, $p< 10^{-16}$), relative to an outside lab (Acc=58%, $p< 10^{-16}$), resulting in inconsistent slide generation. However, PRS scale could be identified from the appropriate lab for primary (Acc=82%, $p< 10^{-16}$) and secondary (Acc=79%, $p< 10^{-16}$) antibody, showing a reproducibility challenge. While we successfully classified positive signals into intensity categories using the standardized PRS scale (Acc >70%), discrepancies in concentration scaling remained across laboratory. Specifically, a 30% scale concentration in Lab 1 was correlated with 75% in Lab 2, showing the intensity differences caused by variations in staining protocols.

Conclusions: Our findings emphasize the urgent need for immunohistochemistry standardization to ensure reproducibility and consistency in slide-based diagnostics. PRS technology improves intra-laboratory consistency, however inter-laboratory protocol variability remains a barrier to achieving reproducibility and automation in pathology. Further investigation incorporating additional laboratories would validate the effectiveness of the PRS in harmonizing immunohistochemistry diagnosis.

100

Instituting a Brain Biopsy Protocol for Tissue Conservation at the University of North Carolina: How Effective Has It Been?

E Price, B Cho; University of North Carolina Hospitals

Background: Given the importance of ancillary testing in comprehensive neuropathologic workups, a protocol was implemented to optimize preservation of central nervous system (CNS) biopsies: splitting biopsies greater than 0.3 cm into multiple blocks and cutting five unstained slides of each block up front.

Methods: Ten months after protocol launch, cases utilizing the protocol were identified via electronic medical records. Biopsies not following the protocol within the same timeframe were identified from all CNS cases by searching diagnosis lines for “biopsy” and “biopsies” while excluding “excision” and “resection”. Cases were assessed for appropriate protocol use, to query sufficiency for diagnosis, and to record unstained slide utilization.

Results: Forty-nine CNS biopsy cases were identified in the 10 months since protocol launch. Twenty-eight cases used the protocol with 92.9% appropriate utilization; two uses of the protocol (7.1%) were retrospectively deemed unnecessary. Unstained slides were used in 88.0% of appropriately assigned cases with unstained slides created up front. Despite protocol adherence, tissue was insufficient for diagnosis in three cases; inadequate specimen quantity/quality was responsible for insufficiency in all three cases rather than suboptimal tissue utilization. Of the 21 cases that did not utilize the protocol within the same timeframe, two were insufficient for diagnosis. One case was insufficient due to specimen inadequacy; in the other, a more specific diagnosis was feasible had more tissue been conserved for ancillary testing.

Conclusions: After 10 months of utilization, no cases (0.0%) following protocol were insufficient for diagnosis due to suboptimal tissue conservation compared to one case (4.8%) of insufficiency amongst cases not utilizing the protocol. Despite the potential burden of preparing more unstained slides up front, the decreased rate of insufficiency and high frequency of unstained slide utilization are reassuring. Further education about appropriate protocol assignment is needed to more uniformly adopt this method in CNS biopsy cases.

Posters: Tumors: nonglial

101

"Ectopic" Embryonal Neoplasms of the Central Nervous System: Two Cases at a Single Tertiary Care Center

E Price, G Chamberlin, B Cho, D Trembath; University of North Carolina Hospitals

Background: Most embryonal neoplasms of the central nervous system (CNS) are thought to be geographically restricted based on their apparent cells of origin. Medulloblastomas, for instance, arise within the posterior fossa by definition, while pineoblastomas arise from the pineal parenchyma. However, the increasing utilization of methylation profiling has challenged these diagnostic criteria by occasionally identifying apparent cases of embryonal CNS neoplasms in unexpected locations.

Methods: Here, we address two such cases identified within the past year at one institution.

Results: A 3-year-old female presented with a right lateral ventricle mass without tumor in the posterior fossa or elsewhere in the CNS. Histologic and immunophenotypic features of this lesion were most concerning for an embryonal neoplasm. The lesion matched to the WNT-activated medulloblastoma methylation class. Molecular testing identified monosomy 6, and the neoplastic cells also harbored a hotspot missense variant in exon 3 of CTNNB1. A second 3-year-old female underwent resection of a cystic and solid mass in the anteroinferior right temporal lobe. The lesion's histologic characteristics and immunophenotypic profile were supportive of a high-grade neoplasm with embryonal features. Methylation profiling matched the lesion to the pineoblastoma methylation class. The patient was subsequently found to have a germline DICER1 mutation without additional lesions identified outside the CNS.

Conclusions: So-called supratentorial WNT-activated medulloblastomas are exceedingly rare, and tumors matching to the pineoblastoma methylation class which arise outside of the pineal region have not been documented to the authors' knowledge. Together, these cases pose interesting challenges to the current paradigm for classifying CNS embryonal neoplasms. We propose two possible explanations: Either medulloblastomas and/or pineoblastomas can arise outside their expected geographic range (e.g., due to abnormalities in embryologic development); or these embryonal tumors represent entirely new entities whose molecular characteristics are otherwise nearly indiscernible from classic medulloblastomas and/or pineoblastomas.

102

The First Reported Case of CNS Collision Tumor Comprising of Malignant Meningioma and Malignant Peripheral Nerve Sheath Tumor

A Khalili-Toosi [1], D Zieba [2], M Snuderl [3], R Pulinthanathu [2], J K Liu [2], A Baisre-De Leon [2], M Movahed-Ezazi [2]; [1] Rutgers University, [2] Rutgers, [3] NYU

Background: Collision tumors are rare and defined by two or more histologically distinct lesions occurring at the same site and growing adjacent to one another. Although uncommon, glioma and meningioma are primarily the most reported collision tumors of the central nervous system, followed by meningioma and metastatic tumors.

Methods: We present a case of a 69-year-old female with headache, nausea, vomiting, weakness and a history of recent fall. MRI imaging of the brain showed a large, heterogeneously enhancing, bifrontal mass with broad dural contact. A second lobulated component of the mass appeared heterogeneously enhancing, but not as avid as the main mass. Surgical resection was performed. Histology showed a meningothelial neoplasm invading brain tissue with additional atypical features. Immunostains revealed the tumor cells expressed SSTR2 and EMA. Upon further molecular testing, a TERT gene promoter mutation was present, upgrading the histologic grade 2 lesion to a WHO grade 3 malignant meningioma. Microscopy of the second component, showed a more spindled cell growth pattern with elongated nuclei and intervening collagen deposition. Tumor cells diffusely expressed BCL-2 and showed focal expression of CD34 and S100. The overall finding of this radiologically distinctive region of the mass was suggestive of a nerve sheath tumor. DNA methylation further classified this lesion as a malignant peripheral nerve sheath tumor, with a calibrated score of 0.86.

Results: Overall, intracranial collision tumors are rare and furthermore the concurrence of a malignant meningioma and MPNST has never been reported. Management is primarily surgical and further evaluated based on each tumor type involved. Utilizing DNA methylation can further assist in classifying more of these challenging cases.

Conclusions: We present the first reported case of a collision tumor of a malignant meningioma and malignant peripheral nerve sheath tumor of the CNS, that was further confirmed using DNA methylation classifier.

103

Carcinoma Metastasizing to Meningioma: A Case Series and Pathologic Insights

P Nguyen, C Slocum, M Umphlett, J Walker, N Tsankova, J Crary, T Richardson; Icahn School of Medicine at Mount Sinai

Background: Meningiomas, the most common primary intracranial tumors, can serve as recipients of tumor-to-tumor metastasis, a rare but clinically significant phenomenon. We present three cases of carcinoma metastasizing to meningioma, emphasizing histopathologic features and clinical diagnostic challenges.

Methods: We reviewed three cases of meningioma with metastatic carcinoma. • Case 1: A 71-year-old man with history of prostate cancer and a left frontal meningioma resected in 2006. In 2011, he presented with a recurrent left frontal mass. Histology revealed metastatic prostate adenocarcinoma within a meningioma. • Case 2: A 73-year-old woman with history of meningioma and urethral clear cell adenocarcinoma with prior brain metastasis, now developed a posterior falx mass. Histology confirmed a meningioma with focal metastatic adenocarcinoma. • Case 3: A 68-year-old woman with history of meningioma was admitted after a fall. MRI revealed a heterogeneously enhancing dural-based mass. Histology confirmed metastatic squamous cell carcinoma adjacent to an atypical meningioma.

Results: Adenocarcinomas exhibited infiltrative growth, while squamous cell carcinoma remained peripherally confined. Extensive vascular invasion was observed in metastatic prostate carcinoma. Two patients died shortly after diagnosis.

Conclusions: In this case series, all three patients had pre-existing meningiomas, two of which harbored infiltrating metastatic carcinoma, while one exhibited only adjacent metastatic spread. Notably, despite their oncologic histories, none of the cases had preoperative imaging suggestive of metastasis, reinforcing the challenge of detecting this phenomenon without histopathologic confirmation. The histologic pattern of metastatic infiltration varied among cases. Prostate and urethral adenocarcinomas exhibited an infiltrative pattern, intermingling with the meningioma, whereas the squamous cell carcinoma remained peripherally adjacent. This may suggests that tumor biology, including metastatic potential and tropism, may influence the manner in which carcinoma interacts with meningioma tissue. Additionally, the extensive vascular invasion observed in the metastatic prostate carcinoma provides further evidence supporting the long-established theory of hematogenous dissemination as a key contributing factor.

104

A rare case of intracranial ALK-Positive Histiocytosis with DCTN1-ALK fusion originally diagnosed as a meningioma

R Colbourn, A Banihashemi; Hospital of the University of Pennsylvania

Background: ALK-positive histiocytosis (APH) is a rare histiocytic neoplasm characterized by ALK immunoreactivity and frequently harbors ALK-gene rearrangements. The clinical spectrum involves presentations in a variety of organ systems, with central nervous system (CNS) involvement being an increasingly recognized entity. However, fewer than 25 CNS cases have been reported to date, with the majority of them harboring the KIF5B::ALK fusion. The paucity of reported cases makes the entity a diagnostic challenge and makes the full molecular spectrum of presentation of CNS APH not well known.

Methods: We present a case of a 31-year-old woman presented to our hospital seeking a second opinion on multiple large bilateral torcular extra-axial hypervascular masses status-post two prior resections of the right side torcular mass in her home country with reported pathology of Grade 1 meningioma and recently presented with significant interval growth of the left sided parafalcine tumor. The right parafalcine extra-axial mass was resected.

Results: Pathologic examination of this resection as well as internal review of the prior left-sided resection demonstrated a spindle cell neoplasm with trabecular and fascicular growth pattern, elongated nuclei and eosinophilic cytoplasm. Tumor cells showed diffuse ALK and histiocytic marker (CD68, CD163, IBA1) immunopositivity and negativity for meningothelial (SSTR2, EMA, PR), myogenic/myofibroblastic (Desmin, SMA, Myogenin, Caldesmin, HHF-35), melanoma/nerve sheath tumor (S100, SOX10), and solitary fibrous tumor (STAT6 and BCL-2) markers. Next-generation sequencing (NGS) confirmed the presence of a DCTN1-ALK fusion. Herein, we present to our knowledge the first case of intracranial ALK-rearranged hystiocytosis with DCTN1 as its partner gene.

Conclusions: This case expands upon the genetic diversity of reported CNS APH tumors. Furthermore, it highlights the importance of maintaining a broad differential diagnosis in extra-axial CNS tumors and using a combination of morphology, immunohistochemistry, and molecular approaches to reach potentially unexpected diagnoses.

105

Intracranial solitary fibrous tumor with myxoid features: a rare presentation

A Jones [1], M Lopes [1], S Patel [1], A Asthagiri [1], Z Abdullaev [2], K Aldape [2], C Fadul [1], M McCord [1]; [1] University of Virginia, [2] National Cancer Institute

Background: A 74-year-old male presented with sudden onset of blurred vision. Brain MRI revealed a 5.2 cm contrast-enhancing, hemorrhagic, lobulated mass arising from the planum sphenoidale. The patient underwent a right pteronial craniotomy. Near-total resection (90-95%) was achieved, with decompression of the right optic nerve and improvement in vision.

Methods: The specimen underwent neuropathologic workup for diagnosis.

Results: Histopathology showed a dural-based tumor composed of spindle cells with a prominent myxoid matrix and numerous pools of mucin. Immunohistochemistry (IHC) showed CD99 and FLI1 positivity with focal expression of desmin and CD163. Additional IHC was non-contributory. The tumor received a provisional diagnosis of “mesenchymal, non-meningothelial neoplasm.” It was sent to the National Cancer Institute for array methylation profiling, and matched to methylation class “Solitary fibrous tumor.” Subsequent STAT6 immunohistochemistry showed strong nuclear positivity, consistent with a NAB2::STAT6 fusion. The diagnosis was updated to “Solitary fibrous tumor with myxoid features.” Morphology was compatible with Marseille Grade 1. The patient received adjuvant radiation, and remains in good condition with stable follow-up imaging.

Conclusions: Solitary fibrous tumor (SFT) can occur in multiple locations, but is uncommon in the central nervous system (CNS), accounting for less than 1% of CNS tumors. SFT with predominantly myxoid morphology is exceptionally rare. A previous case series of 3 CNS SFTs included one myxoid SFT of spine (PMID 15926073). We identified only one additional reported case of intracranial myxoid SFT (PMID 16978216). Our case is unique in that it is the first CNS myxoid SFT with NAB2::STAT6 fusion identified by staining, and the first to confirm the diagnosis via array methylation profiling, to the best of our knowledge. This case highlights the value of DNA methylation profiling for correctly classifying rare morphologic variants of CNS tumors.

106

BCOR Expression In A High-grade Neuroepithelial Tumor With MN1::BEND2 fusion: A Diagnostic Pitfall

P Nisarga [1], B Rathore [2], P Hodjat [2], A Mishra [2], B Derinkuyu [2], R Graham [2], P de Blank [2], J Skoch [2], S Roy [2], D Leino [2], K Gupta [2]; [1] Cincinnati Children's Hospital Medical Center, [2] Cincinnati Children's Hospital Medical Center

Background: MN1-altered CNS neuroepithelial tumors (NET) present in younger individuals with a female predilection and favorable outcomes, however, cases with multiple recurrences have been reported. Essentially all MN1-altered NETs cluster within HGNET-MN1 tumors on methylation classifier. This group is heterogenous and primarily comprises of MN1-altered (MN1::BEND2 fusion) tumors, followed by tumors harboring EWSR1::BEND2, MAML1::BEND2 and TCF3::BEND2 fusions. The histological spectrum of HGNET-MN1 tumors include astroblastoma, primitive NET, ependymoma, or pleomorphic xanthoastrocytoma.

Methods: We describe a 3-year-old girl presenting with left-sided paralysis and seizures. Imaging revealed an ill-defined, hyperintense lesion (1.3 cm) in the right parietal cortex.

Results: Histology revealed a well-demarcated tumor with minimal infiltration, composed of sheets of oval/spindle cells with rich arborizing vasculature and scattered perivascular rosettes. The nuclei were round/oval with delicate chromatin, conspicuous nucleoli, and frequent mitosis (5-6 per 2 mm2). Perivascular hyalinization and stromal pericellular collagen deposition was conspicuous. Significant atypia/pleomorphism, necrosis and microvascular proliferation were not identified. Interestingly, the tumor demonstrated synaptophysin and widespread BCOR immunopositivity, patchy Olig-2 expression with high Ki-67 labeling index (20-25%). Expression of ATRX, INI1, BRG1, and H3K27me3 by immunohistochemistry was retained. The cells were negative for GFAP, EMA, BRAF, H3K27M, p53 and L1CAM. While the positivity for BCOR prompted a diagnosis of BCOR-altered tumor, next-generation sequencing revealed an MN1::BEND2 fusion, confirming the diagnosis of HGNET-MN1 altered tumor. In addition, copy number losses of chromosomes 22q and X were detected, which are among the common recurrent alterations in this entity. At the 4-month follow-up, the patient showed no evidence of disease.

Conclusions: While BCOR immunopositivity is a feature of HGNET-BCOR ITD, to date, it has not been reported in MN1::BEND2 tumors. In the latter group, the fusion mediates promoter hypomethylation of the BCOR gene which leads to overexpression of BCOR, similar to the former group, and hence can pose to be a diagnostic confounder.

107

Extracranial Intracranial Mesenchymal Tumor with FET-CREB fusion: two case reports.
S Patel, T Pearce, D Marker; University of Pittsburgh Medical Center

Background: Intracranial mesenchymal tumor with FET::CREB fusion (ICMT) is a rare and recently described neoplasm that is characterized by fusions involving the FET family RNA-binding proteins to a CREB family transcription factor. This entity is diagnostically challenging due to the broad range of potential morphologies. Currently, the WHO defines this tumor as intracranial. Here we report two cases of extracranial ICMTs mimicking spinal meningioma.

Methods: Two extracranial tumors with FET::CREB fusions were identified. Both tumors were intradural/extramedullary and located in the spine.

Results: Case #1 is a female in her 5th decade who presented with a thoracic spinal tumor with multiple local recurrences. Her initial tumor was positive for EMA and vimentin. Initial molecular studies showed non-specific copy number changes and a low-confidence match to meningioma on the DKFZ classifier. The tumor was felt to be an unusual meningioma. Updated studies on the recurrence specimen showed a moderate confidence match to ICMT on the Bethesda classifier. Whole transcript sequencing confirmed the presence of an EWSR1::ATF1 fusion. Case #2 is a male in his 6th decade who presented with a cervical spinal tumor in 2016 with subsequent metastatic disease to regional lymph nodes. The tumor was EMA and pancytokeratin positive. Initial next-generation sequencing studies were negative. This tumor was also initially favored to be an unusual meningioma. Updated whole-transcript sequencing confirmed an EWSR1::CREM fusion. By methylation array, this tumor did not match on DKFZ, but did show a low-confidence match to ICMT on the Bethesda classifier.

Conclusions: These cases highlight the difficulties in diagnosing ICMT when these tumors present in extracranial locations and show atypical morphologic features. Extensive molecular testing is required to reach an accurate diagnosis and challenging interpretive pitfalls must be navigated. These cases provide additional evidence that ICMT can occur throughout the neuroaxis, and that the intracranial requirement may be unnecessary/misleading.

108

Loss of CDKN2A in a rare case of metastatic pituitary neuroendocrine tumor

J Peck, S Cathcart, A Yuil-Valdes, J Chen; Department of Pathology, Microbiology, and Immunology, University of Nebraska Medical Center, Omaha, NE

Background: Although pituitary neuroendocrine tumors (PitNET) account for 15% of intracranial tumors, metastatic PitNETs are extremely rare. We report a case of PitNET in a young female who experienced multiple extracranial metastases.

Methods: Hematoxylin and eosin staining and immunohistochemistry for the transcription factors and hormones were performed on the primary and metastatic tumors. A 50-gene next-generation sequencing panel was performed on the most recent specimen.

Results: The patient initially presented at age 26 with elevated prolactin and mildly elevated insulin like growth factor-1 (IGF1) and was found to have a 2.3-cm lesion in the sella and right cavernous sinus that was unresponding to cabergoline. A trans-nasal trans-sphenoidal near-total resection was achieved. Pathological examination of the mass revealed a PitNET/adenoma with diffuse PIT-1 and prolactin expression, focal growth hormone expression, rare thyroid-stimulating hormone expression, and an elevated Ki-67 labelling index of 8.6%. Five years later, laboratory surveillance revealed an elevated IGF1 level of >1000ng/mL. MRI sella showed no evidence of tumor recurrence, and chest CT revealed a well-circumscribed 4-cm hypodensity in the left paratracheal region. An endobronchial ultrasound-guided fine needle aspiration was performed and the cytopathological examination demonstrated a neuroendocrine tumor that was diffusely immunopositive for PIT-1 and growth hormone and weakly positive for prolactin, consistent with metastatic PitNET. Over the next two years, the patient underwent multiple resections for additional metastases including a 1.6-cm mass in the right lower lobe of the lung, a 3.1-cm mass in the right axilla, and a recurrent 6.5-cm mass in the left neck. A 50-gene sequencing panel performed on the recurrent left neck mass revealed CDK2NA copy number loss without other pathogenic/likely pathogenic variants.

Conclusions: This rare case of metastatic PitNET highlights the importance of improving classification for potentially aggressive PitNETs. In this particular case, CDKN2A loss may be associated with tumor progression.

109

A rare congenital case of HMGA2::NCOR2-positive giant cell tumor of cranial bone; acquired histologic features to diagnostic KPGCT/XGET.

P Nisarga [1], K Gupta [2], B Turpin [2], R Redline [3], S Szabo [2]; [1] Cincinnati Children's Hospital Medical Center, [2] Cincinnati Children's Hospital Medical Center, [3] Case Western Reserve University School of Medicine

Background: A unique subset of giant cell tumors, harboring HMGA2::NCOR2 fusions, have histologically been recognized either as “keratin positive giant cell tumors” (KPGCT) or as “xanthogranulomatous epithelial tumors” (XGET), due to the characteristic keratin positivity of epithelioid mononuclear cells and frequently extensive xanthogranulomatous features.

Methods: Case report and literature review (47 cases)

Results: We report on a congenital cranial tumor, affirming extension of the spectrum to congenital cases of this entity. A term female neonate, on DOL8, was diagnosed with a 3.9 cm enhancing left occipital bone mass, with soft-tissue and posterior cranial fossa extension (CT/MRI). Histologically a giant cell-rich tumor, with ovoid-spindled mononuclear cells, numerous osteoclastic giant cells (OCGC) and Touton-like giant cells (TLGC), brisk mitoses (18/10HPF), it was diffusely positive on histiocytic markers, though lacked appreciable xanthomatous features or keratin-positivity. While HMGA2::NCOR2 fusion-positive (RNA-sequencing), histologically it did not quite fit the diagnosis of KPGCT or XGET. However, 6 months later, post-chemotherapy final resection, the residual tumor did show xanthomatous features and expressed AE1/AE3 and CAM5.2. At 11-months, only a small non-enhancing lesion remained on imaging. Tabulated literature review of 47 patients (aged from 10 days – 87 years), in bone (19/41) and subcutis (22/41), reported mostly circumscribed tumors (10/10), with frequent OCGC (24/24), TLGC (12/24), OCGC+TLGC (8/24), keratin positivity (37/37) and xanthomatous features (17/25), commonly in the presence of TLGC. Fusion between exons 3-4 for HMGA2 and exons 14-20 for NCOR2 are most commonly reported.

Conclusions: Here we (1) affirm an extended age-range of this entity to congenital cases, (2) describe histologic “evolution” of the tumor, initially lacking telltale histologic hallmarks of keratin-positivity and xanthogranulomatous features, but acquiring them over time on therapy – while a diagnostic pitfall, a reflection of histologic nature and evolution of the tumor; and (3) tabulate and visualize (in heat-maps) the relevant features from the literature.

110

Pineal melanocytic neuroectodermal tumor of infancy (MNTI)/ anlage tumor (PAT): a diagnostic challenge

E Guney, I Caliskan, V Tang, K Mirchia, M Pekmezci, S Cha, K Aldape, A Bollen, A Perry, P Samghabadi; University of California, San Francisco

Background: Pineal melanocytic neuroectodermal tumor of infancy (MNTI) or anlage tumor (PAT) is a very rare histologic diagnosis with primitive and melanin-containing neuroectodermal and ectomesenchymal components, without any distinct genetic alterations, and DNA-methylation profiling (DNAMP) matching to choroid plexus tumor, pineoblastoma or group-3 medulloblastoma. MNTI/PAT is a diagnostic challenge due to rarity and overlapping histologic and molecular features with other entities.

Methods: -

Results: A 7-month-old female patient presented with reduced left arm movement, lethargy and vomiting. MRI showed an 8 cm heterogenous frond-like enhancing mass with blood products and calcifications appearing to originate from the body of right lateral ventricle but also involving both the pineal region and cerebellum. On MR imaging, a choroid plexus carcinoma was favored. Histopathology showed a hypercellular neoplasm comprised of nests of small round blue cells with nuclear hyperchromasia, molding and scant cytoplasm. Scattered clusters of retinal pigmented epithelium cells were seen. The intervening stroma was fibrous with focal chondromyxoid features. No well-formed rosettes, neurocytic components or rhabdoid cells were identified. Tumor cells showed patchy immunoreactivity to synaptophysin, pancytokeratin and CK7. HMB45 was positive in clusters of pigmented retinal epithelium. INI1 and BRG1 stains showed retained expression. Transthyretin, GFAP, OLIG2, Melan-A, desmin, myogenin, EMA, CK20, CD99, LIN28A, GAB1, and Prussian blue were negative in tumor cells. Next-generation-sequencing demonstrated no pathogenic or likely pathogenic single nucleotide variants, small insertions/deletions, or structural variants in any of 529 genes tested. Chromosomal copy number analysis revealed a balanced diploid genome. DNAMP matched to Medulloblastoma group 3. A final integrated diagnosis of MNTI/PAT was rendered.

Conclusions: As previously reported and as seen in this case, diagnosis of MNTI/PAT is a diagnostic challenge with remarkable clinicopathologic and genomic overlap with other entities.

111

Adult medulloblastoma: pleural metastasis following 10 years of remission in a 39-year-old male patient

A Kollasch-McGarvey, J Persons, K Eschbacher; University of Iowa Hospitals and Clinics

Background: Medulloblastoma is an embryonal tumor of the central nervous system, often arising within the posterior fossa. Although medulloblastoma is the most common malignant pediatric brain tumor, it is rare in adults. Large-scale studies of adult medulloblastoma are scarce, so current treatment paradigms often emulate pediatric treatment standards, despite distinct molecular characteristics and clinical considerations in adult patients. Herein we present a case of metastatic medulloblastoma in a 39-year-old male patient, highlighting advancements in molecular classification of medulloblastoma that provide valuable insights for targeted therapy.

Methods: We performed histologic, immunohistochemical, and molecular analysis of a pleural-based mass biopsy from a 39-year-old male patient with a remote history of medulloblastoma diagnosed at age 27 and a recent history of papillary thyroid carcinoma with lymph node metastasis and concern for osseous metastasis. Genome-wide DNA methylation was performed at the National Cancer Institute at the NIH. These findings were then correlated with the patient's initial medulloblastoma resection, clinical history and imaging from the time of initial diagnosis to the present, and next generation sequencing results.

Results: Microscopic examination of the biopsy revealed sheets of small round blue cells expressing synaptophysin and INSM1 while negative for keratin, TTF-1, OTP, and PAX-8. Tumor cells demonstrated cytoplasmic expression of GAB1, patchy nuclear and cytoplasmic expression of YAP1, cytoplasmic expression of beta-catenin (negative pattern), and no p53 overexpression. Next generation sequencing demonstrated two variants of potential clinical significance in PTCH1 and a variant of potential clinical significance in the TERT promoter. By methylation profiling, the tumor matched to "Medulloblastoma, SHH-activated, subclass 4" with a high confidence score from all classifiers.

Conclusions: Together with the patient's history, the morphology, immunophenotype, and molecular characteristics of the tumor were consistent with metastatic medulloblastoma, SHH-activated and TP53-wildtype. Based on these molecular features, the patient is now receiving targeted therapy with vismodegib, a SHH pathway inhibitor.

112

Case report of KRAS mutation in pituitary adenoma: a marker of aggressive behavior?
C Chen, M Milani, C Ozutemiz, P Mroz, N Godse, M Sharma, G Fitzpatrick; University of Minnesota Medical School

Background: Pituitary adenomas are typically benign tumors arising from the pituitary gland, varying in size and hormonal activity. While most are not associated with specific genetic mutations, large scale sequencing studies in pituitary adenoma are limited. HRAS mutations have been described in aggressive lactotroph adenoma, though only recently was a KRAS mutation identified, also in an aggressive pituitary adenoma.

Methods: We present an additional rare case of an aggressive pituitary adenoma with a KRAS mutation. A 37-year-old man with intermittent headaches, left-sided visual changes, memory issues, and balance difficulties. Brain MRI revealed a large 9 cm mixed solid and cystic mass replacing the sella and clivus, encasing the carotid arteries, invading the sphenoid sinuses, and displacing the optic apparatus, as well as displacing the floor of the third ventricle superiorly.

Results: Biopsy and partial resection was performed. Histology showed a proliferation of monotonous tumor cells with a neuroendocrine cytologic appearance. Immunohistochemistry was diffusely positive for synaptophysin with rare cells positive for T-Pit. ACTH showed focal positivity, while other hormone and transcription factor immunohistochemistry was negative. Final pathology favored a corticotroph-type pituitary adenoma. A 127-gene targeted next-generation sequencing panel identified a KRAS G12D mutation, though the tumor did not match any methylation class by whole genome methylation profiling. At six month follow-up there has been mild interval enlargement of residual tumor.

Conclusions: Identification of a pathogenic KRAS mutation in this pituitary adenoma is rare, though previous reports of mutations in KRAS and other RAS family genes, notably HRAS, in pituitary adenomas have been skewed towards invasive tumors similar to this case. However, recent identification of KRAS mutations at low variant allele frequencies in unremarkable pituitary adenomas highlights the need for further investigation into the clinical significance and prevalence of KRAS mutations in pituitary adenoma.

113

Fourth Ventricular Choroid Plexus Adenoma with Atypical Hemorrhagic Presentation: A Histopathologic and Diagnostic Review

H Qiu, G Kleinman; Westchester Medical Center

Background: Choroid plexus adenomas (CPAs) are rare, benign neoplasms of the choroid plexus epithelium, comprising < 1% of intracranial tumors. They typically arise in the lateral ventricles in children and the fourth ventricle in adults. While CPAs often remain asymptomatic or cause hydrocephalus due to cerebrospinal fluid (CSF) overproduction, hemorrhagic presentations are exceedingly rare. We report an incidental fourth ventricular CPA in a hypertensive patient initially suspected of subarachnoid hemorrhage (SAH).

Methods: A 57-year-old hypertensive woman presented with acute-onset thunderclap headache following air travel. CT imaging suggested SAH; however, CT angiography revealed no aneurysm or vascular malformation. MRI identified a 2.8 cm well-circumscribed fourth ventricular mass. Histopathology showed an acinar and retiform growth pattern with stromal elastosis, near-complete pre-albumen positivity (~100%), GFAP adherence, and a low Ki-67 index (< 1%), confirming a WHO grade I CPA.

Results: Literature suggests CPAs rarely exhibit hemorrhagic complications, which are more commonly associated with choroid plexus carcinomas. The tumor's location may have contributed to the patient’s symptoms via CSF flow obstruction. While hypertension is a known risk factor for intracranial hemorrhage, no vascular abnormality or coagulopathy was identified. No syndromic associations (e.g., Li-Fraumeni, Aicardi, Gorlin, or familial adenomatous polyposis) were detected.

Conclusions: This case highlights the importance of comprehensive neuroimaging and histopathological evaluation in patients presenting with acute-onset headache and suspected SAH, particularly when initial vascular imaging is unremarkable. Given the rarity of CPA-related hemorrhagic presentations, further investigation is needed to elucidate potential mechanisms linking CPAs to cerebrovascular events. This report adds to the growing body of literature on incidental choroid plexus adenomas in adults and underscores the need for continued research into their clinical significance, natural history, and potential underrecognized manifestations.

114

An unusual high-grade intracranial sarcoma harboring EWSR1::CREM fusion

V Huynh [1], B Ebner [1], C Ida [1], A Raghunathan [1], J Jebastin Thangaiah [1], R Batiste [2], C Giannini [1], A Folpe [1], M Vizcaino Villalobos [1]; [1] Mayo Clinic, [2] Spectrum Healthcare Partners

Background: Gene fusions involving FET and CREB transcription factor families are the distinctive feature of a new provisional entity in the 2021 WHO Classification of CNS Tumors – intracranial mesenchymal tumor, FET::CREB fusion-positive (IMT). However, such fusions have also been described in a variety of mesenchymal neoplasms with a wide histologic and immunophenotypic spectrum and variable biologic behavior. We present the case of a 32-year-old woman who was undergoing workup for anemia and was found to have a 2.8 cm right frontoparietal dural-based, heterogeneously enhancing, partially calcified and hemorrhagic mass with associated edema and mass effect.

Methods: Histologically, the tumor was densely sclerotic with epithelioid and clear cell features and focal arrangement in cords and showed high mitotic activity (up to 7 mitoses/10 HPF; Ki-67 proliferation index of ~15-20%) and foci of necrosis. By immunohistochemistry, the tumor showed strong, diffuse, cytoplasmic MUC4 expression and partial expression of EMA. Desmin and OSCAR were focally positive. A sarcoma targeted next-generation sequencing gene fusion panel identified an EWSR1::CREM fusion.

Results: The morphologic features and immunophenotype prompted consideration for sclerosing epithelioid fibrosarcoma (SEF); however, desmin and OSCAR are typically negative in SEF and EWSR1::CREM fusion is rare. Although IMT would be consistent with the EMA and desmin positivity and EWSR1::CREM fusion, the morphologic features, mitotic activity, and necrosis were unusual. A descriptive diagnosis of high-grade sarcoma harboring EWSR1::CREM fusion was rendered.

Conclusions: Following surgery, the patient’s presumed paraneoplastic anemia resolved. This case illustrates the complexity and wide histopathologic spectrum of neoplasms harboring FET::CREB fusions including IMT, soft tissue clear cell sarcoma, and SEF-like tumors, and highlights the diagnostic challenge to achieve an accurate diagnosis in a subset of cases.

115

A Rare Pediatric CNS Embryonal Tumor with ATM Germline Mutation and Concomitant CUX1-RAF1 Fusion

T Alkayyali [1], L Klesse [2], D Swift [2], A Sengupta [2], V Singh [2], V Rajaram [2]; [1] UT Southwestern Medical Center, [2] Children's Health/UT Southwestern Medical Center

Background: Central nervous system (CNS) embryonal tumors not elsewhere classified (NEC) or not otherwise specified (NOS) lack specific molecular alterations or cannot undergo further molecular testing. Emerging entities in this group include BRD4::CREBBP and MYO5A::NTRK3 fusions. Here, we present a novel case of a CNS embryonal tumor with an ATM germline mutation and CUX1–RAF1 fusion.

Methods: A 6-month-old girl presented with left arm weakness. Imaging showed a partially cystic tumor in the right temporal lobe, thalamus, and midbrain, without metastasis. Biopsy showed an embryonal tumor, NOS, and treatment followed the ACNS0334 protocol with chemoradiation. Genetic studies identified a heterozygous ATM germline loss-of-function mutation (p.Ala1931Profs*7) and a CUX1–RAF1 fusion. Subsequent tumor debulking revealed areas of glioneuronal differentiation.

Results: BRAF or RAF1 fusions are often found in desmoplastic infantile ganglioglioma/astrocytoma (DIG/DIA), which can have undifferentiated embryonal-like foci. CUX1 regulates cell proliferation and influences the expression of DNA damage response genes, including ATM. Evidence suggests that decreased CUX1 expression promotes tumor development, while increased expression promotes tumor survival. Although the CUX1–RAF1 fusion is not characterized, similar fusions in BRAF have been reported as constitutively active, causing hyperactivation of the MAPK pathway, supporting its role in oncogenesis. Combined with germline ATM heterozygosity, whose expression is regulated by CUX1, this fusion potentially drives tumor development.

Conclusions: Inactivating CUX1 alterations may correlate with higher tumor grade and poor prognosis. The presence of CUX1 alteration in our case makes it distinct in that it behaved aggressively and, by consensus, managed as an aggressive embryonal tumor that potentially developed areas of differentiation. Further studies are needed to characterize CUX1 alterations in CNS oncogenesis. Some DIG/ DIA with embryonal areas can also behave aggressively. The possibility of associated germline or somatic mutations should be considered in those cases. This patient is clinically and radiologically stable with residual tumor 2.5 years post-treatment.

116

An Unusual Case of a Chordoma Arising in the Cavernous Sinus

S Schwartz, S Gargano; Thomas Jefferson University

Background: Chordomas are uncommon malignant tumors with notochordal differentiation, representing approximately 0.5% of primary CNS tumors. The vast majority of chordomas arise within the axial skeleton, most notably the skull base and sacrococcygeal region. Here, we present the case of a 31-year-old transgender woman with a six-year history of an imaging-documented, slowly growing cavernous sinus mass thought to be a meningioma, who presented with worsening headaches and retroorbital pain.

Methods: MRI brain and orbit demonstrated a 3.5-cm mass with likely enhancement centered within the left cavernous sinus. The patient underwent an endoscopic transnasal approach and intradural resection of the tumor.

Results: Neuropathological examination of the mass demonstrated a variably cellular neoplasm with foci of myxoid and chondroid features. A subset of the neoplastic cells demonstrated physaliferous features. Immunohistochemistry demonstrated the neoplastic cells to be positive for EMA, S100, cytokeratin CAM5.2, and brachyury and negative for GFAP, progesterone receptor, and SOX10. The Ki-67 proliferative index was approximately 1-2%.

Conclusions: This case represents an example of a relatively uncommon tumor entity presenting in an unusual location. It also highlights the importance of tissue diagnosis in fully characterizing CNS tumors, as imaging findings may be more suggestive of other entities and treatment may be delayed without an accurate diagnosis.

117

Single Health System Experience with Hormone Receptor Expression in Meningiomas

D Jackson, M Majeed, K Shiue, N Gatson, H Harmsen, W Bell; Indiana University

Background: Hormone receptor expression for progesterone (PR), estrogen (ER), and androgen (AR) is not assessed routinely in meningioma cases. While PR expression typically has an inverse relationship with tumor grade, this finding is not consistent. Less is known about expression of ER and AR implications on tumor behavior. Previous studies have associated ER expression with higher grade meningiomas and increased proliferation, while AR expression correlated with PR expression.

Methods: A retrospective review was conducted searching IU Health Pathology Laboratory database for diagnosis of “meningioma” from August 2024 through February 2025. All cases included immunohistochemistry (IHC) for PR, ER, and AR. Pathology reports were reviewed for patient age, sex, tumor grade, tumor location, initial diagnosis versus recurrence, expression of ER, AR, and PR, and molecular (Seq) results.

Results: 55 meningioma cases from 54 patients were identified. Mean age at time of diagnosis was 58 years (range: 22-81 years). Thirty-five (64.8%) patients were female, and 19 (35.2%) were male (female to male ratio of 1.8:1). Fifty-two (94.5%) cases were PR(+), 48 (87.3%) were AR(+), and 3 (5.5%) were ER(+). Thirty-five (63.6%) cases were Grade 1, 13 (23.6%) were Grade 2, and 4 (7.3%) were Grade 3. Many cases showed similar PR and AR expression patterns. While quantitative expression was not performed, no clear trend of decreasing expression of PR or AR was seen with increasing tumor grade.

Conclusions: Our initial data is similar to results in other studies with little to no expression of ER in meningiomas and comparable AR and PR expression. Further comparative analyses including patient comorbid conditions and treatment prior to and after surgery are planned. Assessment of ER, PR and AR hormone receptors may aid in determining if expression or co-expression of ER, PR and AR impact clinical tumor behavior and treatment.

118

Sarcomatoid primary CNS neoplasms with GLI1 alteration

S Stone, R Landvater, N Becker, K Conway, D Rottmann, S Camelo-Piragua; University of Michigan

Background: GLI1-altered mesenchymal tumors are a recently identified group of neoplasms harboring GLI1 amplifications or rearrangements, with a variety of primary sites described. These tumors have the potential for aggressive behavior including development of distant metastases. GLI1, a key regulator of the hedgehog signaling pathway, is frequently amplified in gliomas and rarely fused in glioblastoma.

Methods: We present two cases of sarcomatoid CNS tumors harboring GLI1 alterations.

Results: The first case, a 35-year-old male with an intradural extramedullary thoracic spine mass, was clinically suspicious for schwannoma. The second case, a 62-year-old male with multiple parietal lobe masses, was concerning for metastasis or abscess. Histologically, both tumors displayed a mesenchymal morphology with small ovoid-to-spindled cells, brisk mitotic activity, and alternating areas of hyper- and hypocellularity. Immunohistochemistry showed strong CD56 positivity and negative staining for GFAP, OLIG2, S100, and SOX10. GLI1 in situ hybridization confirmed overexpression. Molecular analysis of the first case, revealed an ACTB::GLI1 fusion, without molecular features of glioblastoma, and no match on DNA methylation profiling (CNS DKFZ). A diagnosis of “GLI1-altered mesenchymal tumor” was made. Molecular analysis of the second case showed GLI1 amplification (30x) and TERT promoter mutation without EGFR amplification or +7/-10 signature. There was a suggestive calibrated score of 0.7 for Glioblastoma, IDH-wildtype, mesenchymal type on methylation profiling, but no match. A diagnosis of “Sarcomatoid neoplasm most consistent with gliosarcoma” was rendered. No other primary lesions were identified in either case.

Conclusions: We report the first GLI1-altered mesenchymal tumor primary to the CNS. The second case highlights the unique diagnostic challenge these tumors pose in the CNS, given the high frequency of GLI1 amplification in glioblastoma. GLI1 overexpression should be interpreted with caution in sarcomatoid CNS tumors, where gliosarcoma and GLI1-altered mesenchymal tumor - both primary and metastatic - should be considered.

119

Molecular characteristics of metastatic meningioma: A case report in the era of cIMPACT-NOW Update 8

L Evans, K Galbraith, R Yoda; University of Washington

Background: Meningioma metastasis to extra-neural sites is an uncommon phenomenon, with purported risk factors including malignant histology and multiple recurrences. However, given the rarity of metastatic disease, our understanding of these risk factors is currently limited. Under recent cIMPACT-NOW update 8 guidelines, molecular findings play an even greater role in risk stratification of meningiomas. We present a patient with a recurrent spinal meningioma lacking definite histologic grade 2 features, found to have lung and liver metastases. Further studies revealed that the lesion warranted a designation of CNS WHO grade 2 by molecular criteria.

Methods: A 70-year-old male with a history of a C3-C5 meningioma, CNS WHO grade 1, status post decompressive laminectomies, biopsy, and radiation, presented 4 years later with imaging suggestive of recurrence, as well as multiple lung and liver masses. He underwent resection of the spinal mass and core needle biopsy of a liver lesion, with DNA methylation profiling performed on the spine lesion and next generation sequencing performed on the liver lesion.

Results: H&E-staining of both samples demonstrated a meningioma with < 1 mitosis/10 HPF and macronucleoli, without other atypical histologic features. Next generation sequencing revealed concomitant 1p and 22q loss as well as an NF2 mutation, without evidence of pTERT or CDKN2A/B alterations, sufficient for a CNS WHO grade 2 under new cIMPACT NOW guidelines. Methylation array demonstrated a consensus match to meningioma, subtype intermediate, subclass A with a high confidence score.

Conclusions: This histologically bland metastatic meningioma demonstrated CNS WHO grade 2-defining molecular features. This case supports a low threshold for molecular characterization of recurrent or clinically aggressive meningiomas. Further molecular characterization of these rare metastases is needed to better understand potential molecular risk factors.

120

Large cell/anaplastic Medulloblastoma with Marked Neuronal Differentiation in a Patient with PTPN11 Mutation

D Jackson [1], M Majeed [1], R Qaiser [1], A Lion [1], T Tihan [2], W Bell [1]; [1] Indiana University, [2] University of Miami

Background: Medulloblastoma is the second most common malignant pediatric brain tumor and may be associated with inherited cancer syndromes, including Gorlin syndrome and Li-Fraumeni syndrome, among others. Tumors are subdivided histologically into four subtypes – classic, desmoplastic/nodular (D/N), medulloblastoma with extensive nodularity (MBEN), and large cell/anaplastic (LC/A). While neurocytic or ganglion cell differentiation has been reported to varying degrees in medulloblastoma, particularly the D/N and MBEN subtypes, it is not commonly seen in the LC/A subtype. The clinical significance of this finding in the LC/A subtype is uncertain.

Methods: Our patient is an 11-year-old boy with history of attention-deficit/hyperactivity disorder diagnosed with LC/A medulloblastoma. MRI revealed a 2.7 cm mass centered in the inferior fourth ventricle with CSF dissemination. Following resection, pathology revealed an embryonal neoplasm with brisk mitoses, nuclear molding, cell wrapping and pronounced areas of neuronal and ganglionic differentiation. Immunostaining showed tumor cells were synaptophysin(+) and YAP1(-). GAB1 was equivocal. Beta-catenin showed no nuclear staining. NeuN was strongly positive in areas of neuronal differentiation.

Results: Molecular testing revealed MYCN amplification, 1q gain, 7p gain, and germline mutation in the PTPN11 gene [heterozygous variant, c.175A>G (p.Thr59Ala)]. Methylation class was medulloblastoma, non-WNT/non-SHH, group 3. Histology, immunostaining, and copy number alterations were consistent with group 3 medulloblastoma. However, the PTPN11 germline mutation was unexpected and not a common finding in patients with medulloblastoma and led to subsequent diagnosis of Noonan syndrome.

Conclusions: We report a unique case of LC/A medulloblastoma showing significant neuronal differentiation not typically seen in this subtype. Additionally, a PTPN11 germline mutation was found, which has been reported in one other patient with medulloblastoma diagnosed with Noonan syndrome. The presence of the PTPN11 mutation may be related to the development of medulloblastoma in Noonan syndrome patients.

121

Two Cases of Metastatic Urothelial Carcinoma Involving Posterior Fossa

D Jackson [1], M Majeed [1], M Pease [1], A Acosta [1], B Mobley [2], W Bell [1]; [1] Indiana University, [2] Vanderbilt University Medical Center

Background: Brain metastases remain the most common adult brain tumors with lung, breast, and melanoma being the most frequent primary malignancies. Metastases of urothelial carcinoma (UC) to the central nervous system (CNS) are rarer occurrences, involving the brain, skull, spinal cord, or bony vertebra. While the brain is the most common site, the cerebellum is affected less often than the cerebrum. Bony involvement, particularly the skull, is reported even less than the cerebellum.

Methods: Patient 1 is a 78-year-old male diagnosed with pT4a urothelial carcinoma of the bladder, plasmacytoid variant, status post cystectomy/ileal conduit in 2020 and unknown adjuvant therapy status. Four years later, he presented with headaches and balance issues. MRI revealed a 3.0 cm left cerebellar hemispheric heterogeneously enhancing mass. Patient 2 is a 62-year-old male diagnosed with pT2 urothelial carcinoma of the bladder, status post neoadjuvant chemotherapy and radical cystectomy in 2022. Two years later, he presented with persistent headaches. MRI revealed a 6.6 cm heterogeneously enhancing mass within the occipital skull, extending into the posterior fossa and scalp.

Results: Chest, abdomen, pelvis imaging in both patients was negative for other lesions. Following brain mass resection, pathology revealed metastatic urothelial carcinoma in both patients. Patient 1's case showed focal plasmacytoid and signet-ring appearances. Immunostaining showed tumors were positive for CK7, GATA3, thrombomodulin, and p63.

Conclusions: These two cases contribute to growing literature examining UC brain metastases. Both cases involved the posterior fossa with one tumor arising within cerebellar parenchyma and the other arising from the skull and pushing on the cerebellum. Interestingly, the patient with lower pT stage presented sooner with metastasis and a more aggressive lesion, suggesting lower pT stage may not correlate with less aggressive behavior. Larger analyses including UC treatment regimens are required to truly understand the behavior of these CNS metastases.

122

Therapeutic effects of 40Hz light stimulation in 3xTg-AD mice by modulating cellular autophagy

z gu, Y fu, H cao, Y huang, C zuo, Y song, X chen, F wang; Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology

Background: Background: Alzheimer's disease (AD), the most common cause of dementia, now affects more than 30 million people worldwide, lacking effective and curative therapies. Light flickering at 40 Hz has shown great power in attenuating AD pathologies, especially in reducing Aβ deposition, but the underlying mechanisms are still unclear.

Methods: Methods: 3xTg-AD mice were treated with 40 Hz light stimulation at different illumination levels for 42 days. The Cognitive dysfunction of mice was evaluated by the Novel object recognition test and the Morris water maze test. The brain tissues were collected for in-depth mechanistic studies. Aβ levels, autophagy function, apoptosis and neuronal survival of 3xTg-AD mice were investigated. To further explore whether autophagy plays an essential role in the efficacy of 40 Hz light stimulation, an autophagy inhibitor 3-methyladenine (3-MA) was used. The cognitive function and pathological processes were examined as before.

Results: Results: we found that dysfunctional autophagy occurred early in 4-6 months 3xTg-AD mice. Only 40Hz (1100-1500 lux) stimulation significantly enhanced autophagy, reduced Aβ levels, and improved memory deficits in the visual cortex and hippocampus of 3xTg-AD mice. After the administration of autophagy inhibitor, 3-MA, 40Hz (1100-1500 lux) stimulation could not delay the decrease of hippocampal Aβ levels, reverse the neuronal damage, and could not improve the cognitive function of 3xTg-AD mice.

Conclusions: Conclusions: These results suggested that 40Hz (1100-1500 lux) stimulation is a promising therapeutic intervention and may exert its effects by modulating the cellular autophagy in the early stages of AD.

123

Histologic, immunophenotypic, and molecular characterization of CNS Neuroblastoma, FOXR2-activated, in a 5-year-old male patient

F Ogaban [1], K Eschbacher [2]; [1] University of Iowa, [2] University of Iowa Hospital & Clinics

Background: CNS neuroblastoma, FOXR2-activated, is a rare, newly recognized tumor type in the 2021 WHO Classification of CNS Tumors. There is limited epidemiological and prognostic data regarding these tumors. Recognition of characteristic histologic and immunohistochemical features of this tumor is beneficial for pursuing appropriate ancillary testing.

Methods: A retrospective review of the electronic medical record and case analysis was performed, including histologic characterization by H&E and a targeted panel of immunohistochemical stains. Molecular characterization including copy number analysis by chromosomal microarray, targeted next generation sequencing, RNA sequencing panels, and DNA methylation profiling was completed.

Results: A 5-year-old male patient presented with a 1-week history of decreased right arm movement. Brain imaging demonstrated a large, slightly hyperdense mass with central calcifications in the left temporo-parietal region without evidence of drop metastases. A left craniotomy and subtotal tumor resection were subsequently performed. Intraoperative smear preparations demonstrated a small round blue cell tumor. Histologic sections showed variable morphology and cellularity. Much of the tumor was composed of cells with hyperchromatic nuclei and high nuclear to cytoplasmic ratios. By immunohistochemistry, the tumor cells were diffusely positive for Olig2 and SOX-10, while largely negative for GFAP and vimentin. The tumor cells co-expressed multiple neuronal markers. NKX2.2 was positive. The composite DNA methylation profile indicated a consensus match to CNS neuroblastoma, FOXR2-activated. Following his surgical procedure, the patient received proton craniospinal radiation therapy with concurrent chemotherapy. He is currently undergoing maintenance chemotherapy.

Conclusions: The differential diagnoses for this case encompassed high-grade glioma and other CNS embryonal tumors. NKX2.2 expression may be a diagnostic pitfall in this tumor type. Most FOXR2 rearrangements described in this tumor cannot be detected by standard RNA sequencing panels. Thus, combined histologic and immunophenotypic findings were useful in narrowing the differential diagnosis and directing ancillary testing.

124

The monocyte-macrophage marker CD163 is highly expressed by meningioma

A Kollasch-McGarvey, A Bellizzi, O Lopes Abath Neto; University of Iowa Hospitals and Clinics

Background: CD163 is a 130-kDa transmembrane protein receptor associated with the monocyte-macrophage lineage. In some malignancies such as breast and colorectal carcinomas, aberrant expression of CD163 portends more aggressive tumor behavior. Meningiomas have also been demonstrated to express CD163 in medical literature, though reports are scarce. There is limited published information exploring the potential prognostic implication of CD163 expression in meningiomas. This study aims to evaluate the relationship between CD163 expression in meningiomas and patient outcomes after initial resection and comment on potential utility in employing CD163 immunostaining in the routine workup of meningiomas.

Methods: We performed immunohistochemical staining for CD163 on a cohort of 177 meningiomas (94 WHO grade 1; 66 WHO grade 2, 17 WHO grade 3) resected at the University of Iowa between 1998-2015 and assigned each tumor sample an average H-score based on the percentage and intensity of staining as assessed by three pathologists. Each corresponding patient's electronic chart was then reviewed to collect clinical data and calculate progression-free survival (PFS). H-score was compared with tumor grade and PFS using the Mantel-Cox log-rank test, and Kaplan-Meier survival curves were generated from the data.

Results: All meningiomas expressed CD163 (Median = 104, SD = 57 for grade 1; Median = 84, SD = 61 for grade 2; Median = 74, SD = 46 for grade 3). Average PFS was 193, 185, and 30 months for grades 1, 2, and 3, respectively. There was no statistically significant relationship between CD163 H-score and meningioma grade or PFS.

Conclusions: Based on this work, we assert that although meningiomas do express CD163, there is no correlation between CD163 expression and prognosis. However, CD163 is reliably positive in meningiomas, even more so than SSTR2, and could be a useful alternative as a sensitive, albeit nonspecific, marker for meningiomas in laboratories without access to SSTR2 immunostain.

125

A slow progressive neuroepithelial tumor with a MN1-PATZ1 fusion in a young adult

J Redding-Ochoa, L Chen; University of Minnesota

Background: PATZ1(POZ/BTB and AT hook containing zinc finger 1) is a tumor suppressor gene in chromosome 22q12.2, encoding a transcription factor with chromatin remodeling roles leading to transcriptional repression. Brain tumors with PATZ1 fusion were described recently as neoplasms with sarcomatous or neuroepithelial morphology, and in association with EWSR1 or MN1 as fusion partners. This case presentation aims to bring into discussion a novel category of brain tumors.

Methods: We describe a case of a 27-year-old man with a 17-year history of a circumscribed supratentorial mass initially diagnosed as a low-grade ganglioglioma, surgically treated and showing recurrence on 2 occasions over the next 17-year timelapse. Assessment of the last tumor resection prior to death was performed with conventional histological and immunohistochemical methods. Molecular characterization included next- generation sequencing, chromosomal microarray and DNA methylation analyses.

Results: The tumor showed a predominant primitive morphology alternating with areas of glial and mesenchymal differentiation. Chromosomal microarray analysis showed homozygous loss of CDKN2A/B, loss of chromosomes 1p and 11, gain of chromosomes 1q and 8, and most remarkably, chromothripsis of 22q11.23q13.31 (disrupting MN1 and NF2). Next-generation sequencing panel showed a MN1-PATZ1 rearrangement that resulted in the fusion of the N-terminal portion of the MN1 protein with the C-terminal portion of PATZ1, including multiple zinc finger regions. Remarkably, DNA methylation-based tumor classification did not match to CNS HGNET-MN1, or any other methylation class on the current classifiers. Despite resection and adjuvant chemoradiation, the clinical course was complicated by drop metastasis and further motor impairment leading to the patient’s death.

Conclusions: A subset of slow-growing pediatric CNS tumors with sarcomatous and neuroepithelial morphology is defined by recurrent PATZ1-MN1 fusion. Chromothripsis of chromosome 22q11 was found in association to the MN1 alteration, supporting prior published observations about chromothripsis as the main driver for gene rearrangement.

126

Intrasellar Plasma Cell Neoplasms

R Cecchi, K Conway, R Landvater; Michigan Medicine

Background: Patient one is a 74-year-old with a 6-7 week history of itchy watery eyes and double/blurred vision. Progressed to peripheral field cut in his left eye, with exotropia and ptosis. A 4.9 cm pituitary mass was encroaching on to the optic chiasm and abutting the left optic nerve. Patient two is a 77-year-old male with a 3 month history of persistent headaches in left frontal region and 2-3 week history of diplopia. A 35 mm sphenoid and sellar mass was causing left fourth nerve palsy. Follow-up PET shows extensive osseous, paraspinal, and pleural soft tissue masses. M-protein identified as IgG lambda at 0.3 g/dL.

Methods: N/A

Results: Both cases are elderly males with histories suggestive of pituitary abnormalities. Intraoperative analysis favored diagnoses of pituitary adenomas, with representative images of the frozen section slides provided. Permanent H&E sections show slightly more clarity as to the lineage of the cells, with confirmation on immunohistochemical stains seen by positivity of CD138. Both cases were negative for the usual pituitary panel.

Conclusions: Plasma cell neoplasms are a rare intrasellar neoplasm, corresponding to approximately 45 cases of in the literature. The presentation can be challenging, as headache and diplopia are two common symptoms that are also observed in the more common pituitary adenomas. Additional hurdles can be seen on frozen section slides, where the overlapping morphological features can make the diagnosis challenging in the high pressure frozens environment. The knowledge of this entity is important for accurate diagnosis as additional studies to check for disseminated involvement is key for further treatment. Radiotherapy is the treatment of choice, with chemotherapy followed by autologous peripheral blood stem cell transplant if disseminated, or possible surgery if localized. In conclusion, intrasellar plasma cell neoplasms are rare occurrences that warrant consideration in cases where the presentation is non-functioning pituitary.

127

Mesenchymal Chondrosarcoma with Extensive Intracranial Involvement

J Persons, M Tanas, M Samuelson, K Eschbacher; University of Iowa Hospitals and Clinics

Background: Mesenchymal chondrosarcoma is a rare, relatively fast-growing sarcoma that is molecularly defined by HEY1::NCOA2 fusion. Although this tumor can occur throughout body sites, many arise in the head and neck, often presenting with symptoms of mass effect. This report describes a case of mesenchymal chondrosarcoma with extensive intracranial involvement, diagnosed at the time of autopsy. The decedent was a 29-year-old woman who was brought to the emergency department after being found unresponsive following a recent history of headaches, nausea, and somnolence. Physical exam demonstrated fixed, dilated pupils and marked proptosis of the right eye. Imaging revealed a large intranasal and intracranial mass with signs of impending herniation. Brain death was pronounced soon after.

Methods: A complete autopsy was performed. Sections of the tumor were selected at the time of autopsy and submitted for histologic and immunohistochemical evaluation.

Results: Autopsy examination demonstrated a large mass eroding through the cribriform and right orbital plates and involving the bilateral nasal cavities, bilateral frontal sinuses, frontal dura, and anterior cranial fossa. Microscopically, the mass showed a fascicular arrangement of monomorphic spindle cells with occasional islands of hyaline cartilage. Other areas demonstrated many staghorn vessels with perivascular arrangements of small round blue cells. Mesenchymal chondrosarcoma, solitary fibrous tumor, and monophasic synovial sarcoma were considered. Tumor cells showed diffuse HEY1 positivity and were negative for other markers tested.

Conclusions: Morphology and immunophenotype were consistent with mesenchymal chondrosarcoma. Mesenchymal chondrosarcomas in this anatomical region can arise from the craniofacial bones, soft tissue of the sinonasal tract or orbit, or from intracranial sites including the meninges. The tumor most likely arose from within the sinonasal tract; however, given the large size of the tumor and extent of involved structures, a specific site of origin could not be definitively determined. Although excision can be curative, survival for mesenchymal chondrosarcoma is overall poor.

128

Central Nervous System Presentation of Classic Hodgkin Lymphoma: A Two Case Series
A Schmidt, C Syposs; University of Rochester Medical Center

Background: Classic Hodgkin lymphoma (CHL) primarily affects lymph nodes, particularly those above the diaphragm. It consists of malignant mononuclear Hodgkin cells and multinucleated Reed-Sternberg cells in a complex inflammatory microenvironment. Extranodal involvement can be seen particularly in advanced disease, and seldom can involve the central nervous system (CNS), including the brain, meninges, or spinal cord. While extremely rare, CHL can present within the CNS, either as primary disease or the presenting sign of advanced disease.

Methods: We reviewed two cases, analyzing histologic sections, immunohistochemistry, and clinical data.

Results: Case 1: A 75-year-old female presented with sinus pain and weakness. MRI demonstrated a 3 cm frontotemporal lobe mass with associated edema. CT showed multiple mildly enlarged lymph nodes of the abdomen and chest up to 1.3 cm. The mass was resected and the histology and immunophenotype was diagnostic of CHL. Case 2: An 18-year-old male presented with new onset seizures. MRI demonstrated a 4 cm frontal lobe mass with a possible dural tail. The mass was resected and similarly was diagnostic of CHL. PET scan showed multiple small, non-composite, supradiaphragmatic lymph nodes (SUV 3.0-6.5).

Conclusions: These cases illustrate CHL with CNS involvement in patients without prior diagnosis. Both patients exhibited mild nonspecific lymphadenopathy, which could indicate either CHL or another process. Particularly in case 2, this could be compatible with early stage CHL with metastasis to the CNS or primary CNS disease. Following a diagnosis of CHL, additional diagnostic material is rarely obtained, making a diagnosis of primary versus secondary disease particularly challenging. While these cases are very rare, they highlight the importance of considering CHL in the differential in a wide range of patients. In patients without a prior diagnosis, lymphadenopathy may serve as a diagnostic clue.

129

Anaplastic Meningioma with Sarcomatous Transformation and Extracranial Metastasis

L Kulumani Mahadevan [1], L Canbeldek [2], C Slocum [2], N Tsankova [2], T Richardson [2], J Walker [2], M Gupta [2], J Crary [2], W Fan [3], M Umphlett [3]; [1] Ichan School of Medicine at Mount Sinai, [2] Mount Sinai Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, [3] Mount Sinai West, Icahn School of Medicine at Mount Sinai, New York, NY

Background: Anaplastic meningioma is a rare but highly aggressive subtype with a high recurrence rate and rare extracranial metastasis (< 1 in 1,000 cases). While meningiomas originate from arachnoid cap cells, sarcomatous transformation complicates diagnosis, requiring molecular testing. This case highlights the diagnostic and molecular complexities of anaplastic meningioma with extracranial metastasis.

Methods: Case Description A 74-year-old male presented with a two-week history of left-sided headache, right neck pain, nausea, vomiting, and weakness. Imaging revealed a 2.6 cm left occipital intraparenchymal mass with nodular peripheral enhancement, suspicious for neoplasm. Histopathologic evaluation demonstrated a pleomorphic spindle and epithelioid cell neoplasm with necrosis, high mitotic activity (21 mitoses per 10 HPF), and unequivocal brain invasion. Immunohistochemistry was non-specific, with patchy SSTR2a and smooth muscle actin positivity, negative for EMA and PR with high Ki-67 proliferation index (70-75%). Next-generation sequencing identified an NF2 p.F119del mutation, supporting anaplastic meningioma. DNA methylation profiling suggested a mesenchymal neoplasm but lacked a definitive match. One month post-resection, PET/CT identified hypermetabolic lesions in the rib, vertebrae, and iliac bone. Biopsy confirmed metastatic disease, morphologically and immunophenotypically similar to the primary tumor.

Results: Discussion: Sarcomatous meningiomas resemble high-grade mesenchymal neoplasms, necessitating molecular studies for diagnosis. Extracranial metastases occur mainly in high-grade meningiomas but have been reported in grade 1 cases. NF2 and BAP1 alterations are implicated in metastatic meningiomas. NF2 mutations, while common in meningiomas (40-60%), schwannomas (60%), and mesotheliomas (30-50%) are rare in other malignancies, with isolated cases in hepatocellular, renal cell, lung carcinoma, and leukemia.

Conclusions: This case highlights the need for comprehensive molecular testing in anaplastic meningiomas with sarcomatous features. Although rare, extracranial metastasis can significantly impact patient management. Clinicians should maintain a high index of suspicion and consider full-body imaging in cases of anaplastic meningioma to enable early detection and timely intervention.

130

Morphological and Immunohistochemical Diagnosis in a Case of Metastatic Meningioma to the Lung

M Bouthim [1], M Curtis [2], S Schwartz [2]; [1] University of Minnesota Medical School, [2] Thomas Jefferson University

Background: Anaplastic meningioma is an aggressive brain tumor with strong propensity for recurrence and locally aggressive behavior, accounting for approximately 1-3% of meningioma cases. In rare cases, extracranial metastases have been described. We present the case of an 82-year-old man who underwent brain imaging after suffering a mechanical fall with head injury.

Methods: MRI brain demonstrated a 3.3 cm dural-based extra-axial mass in the right posterior parafalcine region. The patient subsequently underwent right parietal craniotomy and resection of the mass, followed by radiation therapy. Six months later, he re-presented with altered mental status, vomiting, and fever. CT chest revealed bilateral pulmonary emboli in addition to bilateral upper lobe nodules, prompting a biopsy of a 2-cm spiculated left upper lobe nodule.

Results: Neuropathological examination of the resected brain tumor demonstrated an anaplastic meningioma, WHO grade 3. Immunohistochemistry demonstrated negative staining for progesterone receptor, positive staining for vimentin, and partial staining for desmin, supporting the diagnosis. GFAP, OLIG2, and S100 demonstrated positive staining in entrapped glial cells in addition to positive neurofilament staining in entrapped axons. Next-generation sequencing identified NF2 and TERT promoter mutations consistent with the diagnosis of an anaplastic meningioma. Pathological examination of the lung biopsy demonstrated a spindle cell neoplasm with areas of necrosis. Immunohistochemistry performed on the lung specimen showed patchy positivity for cytokeratins AE1/AE3 and CAM5.2, and negative staining for CD34, p40, and SOX-10.

Conclusions: This case underscores the aggressive nature of anaplastic meningiomas and their potential for extracranial metastasis. It highlights the role of histopathology, immunohistochemistry, and molecular sequencing in distinguishing anaplastic meningioma metastases from other malignancies such as sarcomas and sarcomatoid or poorly-differentiated carcinomas, thereby guiding appropriate diagnosis and management. Metastatic disease should be considered in the differential diagnosis of a patient with new extracranial lesions and a history of WHO grade 3 meningioma.

131

A Rare Case of Xanthomatous Meningioma in a 47-Year-Old Female

A Schurr, S Schwartz; Thomas Jefferson University Hospital

Background: Meningiomas are the most common primary intracranial tumor and often present with symptoms arising from mass effect. The rare xanthomatous subtype of meningioma presents similarly and is characterized by foamy histiocyte-like cells admixed within the neoplasm. Here, we present a case of a 47-year-old female with a history of intermittent headaches who presented to the Emergency Department with two days of severe headache with associated nausea and photophobia.

Methods: MRI of the brain revealed a 6.9 cm suspected extra-axial mass in the right frontal region with vascularization and associated midline shift. Mass effect on the falx and right lateral ventricle was also noted. The patient subsequently underwent a right frontoparietal craniotomy for tumor resection.

Results: Gross examination revealed a tan-yellow to orange soft, lobular mass with a focally translucent gelatinous cut surface. Neuropathologic examination of the mass demonstrated an epithelioid neoplasm with predominantly whorled architecture and monomorphic cells. There were also intranuclear pseudoinclusions, prominent nucleoli, and rare mitotic figures, consistent with meningioma; admixed with the meningothelial component were areas with increased intratumoral inflammatory infiltrates and numerous cells with smaller nuclei and abundant foamy cytoplasm. Immunohistochemistry demonstrated positive immunoreactivity for EMA and patchy positivity for progesterone receptor; the foamy cells were positive for CD68. These findings were consistent with the diagnosis of xanthomatous meningioma, WHO grade 1. Next-generation sequencing was also performed, which revealed no mutations in the genes analyzed.

Conclusions: This case represents an example of a rare tumor entity with classic microscopic findings. Xanthomatous meningiomas exhibit the class features of a typical meningioma, but their unique incorporation of tumor cells with lipid-filled cytoplasm and central nuclei should not be mistaken for histiocytic inflammation. The presence of metaplastic elements within meningiomas should be considered in cases with unusual appearances, though the distinction between metaplastic and anaplastic meningiomas should be verified with further workup.

132

The Brain is a Big Place: A Ventricular Mass with Important Lessons
W Humphrey, J Rechberger; Mayo Clinic

Background: A 70-year-old female with a long-standing history of balance difficulties, nystagmus, and photophobia experienced a fall while running. Imaging of the head revealed a partially calcified mass occupying the fourth ventricle measuring 3.2 x 2.9 x 3.1 cm. The lesion exhibited mixed solid and cystic components, with patchy contrast enhancement, suggestive of a low-grade, slow-growing neoplasm compressing the cerebellar vermis and brainstem.

Methods: Histopathologic examination showed circumscribed mass demonstrating well-developed papillary architecture composed of fibrovascular fronds covered by a single layer of uniform cuboidal to columnar epithelial cells with round to ovoid, monomorphic nuclei and extensive psammomatous calcifications. Mitotic activity was absent. Associated with the tumor were large, nodular areas of chondromyxoid matrix containing foci of osseous metaplasia, variable amounts of fibrillary material, and peripherally surrounded by palisading spindle to epithelioid cells.

Results: Final diagnosis: Choroid plexus papilloma (CNS WHO grade 1) associated with calcifying pseudoneoplasm of the neuroaxis (“CAPNON”).

Conclusions: The case offers examples of two important entities in central nervous system (CNS) pathology. First, choroid plexus papilloma, an intraventricular papillary neoplasm derived from choroid plexus epithelium with very low or absent mitotic activity. The second important entity present in this case is that of calcifying pseudoneoplasm of the neuroaxis (“CAPNON”). CAPNON is a rare, benign process characterized by a calcified, fibro-osseous lesion with a chondromyxoid matrix and varying amounts of spindled, epithelioid, fibrous, meningothelial, and giant cells. While incompletely understood, CAPNON is believed to represent a reactive process that can arise anywhere in the CNS in association with inflammatory, degenerative, vascular, and neoplastic processes. Furthermore, this case demonstrates the importance of identifying the histopathologic features required for the diagnosis of CNS WHO-defined entities while also understanding the non-specific physiologic responses of the CNS to a variety of insults, and being able to integrate the findings with the appropriate clinical-pathologic correlations

133

TERT promoter mutation in Metastatic Papillary Thyroid Carcinoma Presenting as a Dural-Based Mass

M Majeed [1], D Jackson [2], C Takahashi [2], M Pease [2], N Gatson [2], H Harmsen [2], W Bell [2]; [1] Indiana University / School of Medicine, [2] Indiana University School of Medicine

Background: Metastatic papillary thyroid carcinoma to the brain is exceedingly rare. TERT promoter mutations are more frequent in metastatic thyroid tumors than primary thyroid tumors. Limited studies in distant metastases of thyroid carcinoma suggest an increased risk association with TERT promoter mutations. This is in agreement with the CNS WHO 2021, where the detection of TERT promoter mutation would upgrade primary brain tumors such as gliomas and other tumors such as meningiomas.

Methods: A single case review including imaging techniques, surgery and pathology. Histologic evaluation included hematoxylin and eosin, PAS, immunohistochemistry for cytokeratin, thyroglobulin, EMA, PR, SSTR2A, PAX-8, and TTF1 in addition to next generation sequencing (NGS).

Results: The patient is a 58-year-old female with a past medical history of goiter. At age 52 was a suspicious thyroid lesion was found on CT chest and thyroid ultrasound. She then underwent partial thyroidectomy and was diagnosed with papillary thyroid carcinoma. At age 58, she developed headache and blurry vision. MRI brain with contrast showed a 2 cm single, homogenously enhancing dural-based lesion along the right occipital pole. Resection of this mass was performed. Pathologic examination showed a poorly differentiated neoplasm with multiple lumens containing eosinophilic, colloid-like secretions mimicking pseudopsammoma bodies seen in secretory meningiomas. Neoplastic cells were diffusely positive for cytokeratin, thyroglobulin, focally positive for PAX-8 and TTF1, and negative for EMA and PR. SSTR2A was weak and focally positive. NGS revealed TERT promoter, NRAS Q61R, and ATM K2756 mutations.

Conclusions: TERT promoter mutation has been an increasingly interesting target for its role in tumor cell immortality and metastasis in general, but also in central nervous system tumors. This case report adds to the pool of cases where TERT promoter mutation is detected in a metastatic thyroid carcinoma, and it may play an essential role in the aggressive behavior and distant metastasis of thyroid carcinoma.

134

Malignant Peripheral Nerve Sheath Tumor with Osteosarcomatous Differentiation in a Vestibular Schwannoma: A Case Report

D Lombardo [1], D Buehler [1], Z Morris [1], K Aldape [2], J Helgager [1]; [1] University of Wisconsin Hospitals and Clinics, [2] National Institutes of Health, National Cancer Institute

Background: Vestibular schwannoma management includes observation, radiation, or surgery based on size, symptoms, and coexisting conditions. Transformation into a sarcoma, most often malignant peripheral nerve sheath tumor (MPNST), is an exceptional event and usually occurs in the setting of prior irradiation. The mechanisms of this transformation are incompletely understood. We present a case of a 62-year-old man with a vestibular schwannoma, which was treated with fractionated stereotactic radiation therapy (FSRT) one year before surgery but continued to grow after therapy. Resection showed progression to a high-grade MPNST with heterologous osteosarcomatous differentiation. The patient's history is notable for on-going treatment with alectinib, an ALK inhibitor, for metastatic ALK-fusion positive lung carcinoma.

Methods: Clinical history, histopathology, and results of targeted next generation sequencing (NGS) and DNA methylation profiling, are presented.

Results: Histopathology revealed a precursor schwannoma transitioning to a high-grade spindle cell sarcoma arranged in fascicles in a fibromyxoid stroma, with areas of malignant osteoid. Immunohistochemistry demonstrated loss of expression of nerve sheath tumor markers SOX10 and S100 and selective loss of H3 K27me3 nuclear expression in the sarcoma including the osteosarcomatous component, consistent with progression to high-grade MPNST. NGS detected an EGFR p.G796S gain-of-function mutation and CDKN2A/CDKN2B/MTAP deep deletion. By DNA methylation profiling, the tumor clustered with MPNST. No NF2 mutations were detected.

Conclusions: This case documents, with comprehensive molecular studies, an MPNST with heterologous osteosarcomatous differentiation arising from a vestibular schwannoma in the setting of prior FSRT. A brief discussion of this phenomenon in the context of other such cases reported in the literature will be undertaken. While the etiology may be related to prior irradiation, a short timeline between FSRT and tumor progression raises an intriguing question of the potential role of an EGFR p.G796S mutation, a known ALK-inhibitor bypassing alteration, in the development of this progression.

135

An ATRT in a 75 yo female

J Fullmer [1], C Schukow [2], J LLenos [2]; [1] Corewell Health, [2] Corewell Health William Beaumont University Hospital

Background: ATRT's are high grade malignancies of the CNS that normally occur in children but rarely can present in adults. This is a 75 yo female who presented with progressive blurry vision, pituitary dysfunction, and found to have a large (2.9 cm) central skull base mass extending to bilateral cavernous sinus (with likely invasion) and suprasellar cistern radiographically thought to be a pituitary macroadenoma. However intraoperatively it was found to be very vascular and encasing/infiltrating into the carotid artery so full resection was not possible and it was debulked. It also had a malignant appearance intraoperatively.

Methods: Conventional H&E, IHC staining, methylome profiling at the NCI

Results: Examination of H&E stained sections revealed markedly hypercellular tumor with moderate pleomorphism. Increased mitotic activity but IMO histology alone doesn't give a clear diagnostic impression. A variety of immunostains were performed (including but not limited to GFAP, synaptophysin, cytokeratins, CD20, CD45, SALL4, and ERG) and were negative. CD34 was positive but INI-1 expression was lost. As ATRT in a 75 yo is indeed unusual we sent it for methylome profiling and it did cluster with high confidence to ATRT, MYC subtype.

Conclusions: ATRT in a 75 yo is unusual and to our knowledge cases of anyone this old having ATRT have been reported.

136

CAPNON: A Rare Case with Long-term Follow-up

T Auen [1], J Boxerman [2], C Yu [3], D Cielo [3], D Anthony [3]; [1] University of Nebraska Medical Center, [2] Rhode Island Hospital, [3] Warren Alpert Medical School of Brown University

Background: Calcifying pseudoneoplasms of the neural axis (CAPNONs) are rare, benign lesions that may occur anywhere in the central nervous system. Less than 100 cases are reported in literature, and their etiology and natural history are not well understood. We present a unique case of CAPNON followed over 18 years. The patient was a 32-year-old male with seizures, who had a biopsy at presentation and was followed with regular MRI. After 18 years, increase in the lesion size was followed by gross total resection and allowed for definitive diagnosis.

Methods: Gross, microscopic, and immunohistochemical findings were diagnostic of CAPNON. A literature search for CAPNONs was performed with a focus on intra-axial temporal-based lesions as seen in our case. Ours is one of thirteen similar cases. Of note, there is a male dominance (10 M, 3F) with a calculated mean age of 34.6 years, many presenting with seizure activity (9 of 13; 69%), and most opting to undergo complete surgical resection (12 of 13; 92%).

Results: Microscopic features included extensive calcification within a fibro-osseous and chondromyxoid matrix. Scattered inflammatory cells and vascular proliferation were prominent, and the perimeter of the lesion showed brain tissue with gliosis. Immunohistochemistry demonstrated EMA positivity in arachnoid cells and GFAP expression in adjacent brain tissue.

Conclusions: CAPNONs are rare and have characteristic gross and microscopic findings. The prognosis is excellent following resection, and more investigations along with reporting of cases may allow additional insight into their unknown etiology.

137

Histologic, immunophenotypic, and molecular characterization of a case of chondroid synoviocytic neoplasm

K Higham-Kessler, M Tanas, A Isaacson, K Eschbacher; University of Iowa

Background: The category “chondroid synoviocytic neoplasm” (CSN) is recently proposed to describe a subset of calcified chondroid mesenchymal neoplasms (CCMN) with frequent FN1 fusions and a predilection for the temporomandibular region. CSN shares features with both CCMN and tenosynovial giant cell tumor, which may produce diagnostic uncertainty. Despite aggressive histologic features, the clinical behavior appears relatively indolent, with at most local invasion and low rates of post-resection recurrence.

Methods: Electronic medical record review and case analysis were performed, including histologic characterization by hematoxylin and eosin stained sections, targeted immunohistochemical stains, and molecular characterization (RNA-Seq based gene fusion panels and CISH).

Results: A 47-year-old man with history of chronic traumatic encephalopathy followed by MRI was incidentally found to have a heterogeneously enhancing, extra-axial mass in the right inferior temporal fossa, appearing to arise from the temporal bone. The mass was resected, including the involved portion of the temporal bone. It was adherent to, but had not invaded, dura. Histologically, the tumor consisted of polygonal epithelioid cells with eccentric nuclei and abundant eosinophilic cytoplasm admixed with osteoclast-type giant cells. Foci of associated eosinophilic matrix resembling osteoid or chondroid matrix were noted along with aneurysmal bone cyst-like changes. Immunohistochemistry revealed the neoplastic cells to focally express SMSA, CD68, and clusterin. They were additionally positive for CSF1 mRNA by CISH and negative for all additional markers tested, including H3G34W, S100 protein, desmin, cytokeratin AE1/AE3, ERG, CD30, and CD163. RNA sequencing revealed an FN1::TEK fusion transcript. MRI approximately 15 months following original resection was concerning for recurrent/residual tumor. The patient underwent repeat resection with consonant pathology.

Conclusions: The combined histologic, immunophenotypic, and molecular findings support a diagnosis of CCMN. The presence of synoviocytic differentiation would place this tumor within the proposed subcategory of chondroid synoviocytic neoplasm.

138

Meningioangiomatosis versus intraparenchymal meningioma with meningioangiomatosis-like growth pattern

I Caliskan [1], S Perez [1], A Putnam [2], G Chamyan [3], K Mirchia [1], J Van Ziffle [1], A Perry [1]; [1] University of California San Francisco, [2] Primary Children's Hospital, UT, [3] Nicklaus Children's Hospital, FL

Background: Meningioangiomatosis (MA) is widely viewed as a hamartomatous or malformative lesion and in most sporadic cases, no genetic alterations are found. However, rare examples with copy number alterations, mutations resembling pediatric or adult meningioma have been reported. In contrast, it has also been documented that a wide variety of both meningothelial and non-meningothelial neoplasms may spread along Virchow-Robin spaces yielding a histology closely mimicking MA.

Methods: Herein we report two MA-like cases with associated genetic alterations.

Results: Patient 1 is a 10-year-old boy with new-onset seizures, headaches, nausea, and vomiting. MR imaging showed a multicystic right temporal juxtacortical lesion. Patient 2 is a 16-year-old girl with epilepsy, autism, and germline SHANK2 mutation. MR imaging showed a T2-hyperintense frontal lobe lesion. The pathology in both showed classic features of MA with variable cellularity and hyalinization, diffuse vimentin staining, and focal weak positivity for SSTR2A and PR. Next generation sequencing demonstrated a frameshift NF2 mutation accompanied by monosomy 22q (including the NF2 gene locus) and 17q gain in patient 1. A partial 22q loss including the NF2 locus was identified in patient 2. Patient 1 was assessed by DNA methylation profiling (DNAMP) and did not match to any known entities. DNAMP results for patient 2 are pending.

Conclusions: MA with demonstrable genetic alterations is rare and the etiology remains controversial. One possibility is that of an intraparenchymal meningioma without a discernible mass, but rather a pure perivascular growth pattern. An alternate interpretation is that a subset of MA-like lesions could have a preneoplastic or neoplastic nature. Additional studies with larger cohorts are needed to further resolve this question.

139

Uncommon Cutaneous Presentation of a CNS Tumor

J Eberle-Singh, R Thomas; Thomas Jefferson University Hospital

Background: Meningiomas are proliferations of meningothelial cells, generally associated with intracranial meninges. Cutaneous meningiomas are rare tumors, often in children and young adults, usually in the head and neck. Three types are recognized: Type I is a congenital form arising from developmentally displaced arachnoid cells; Type II develops along the course of cranial nerves; Type III are tumors of the arachnoid that extend into the skin.

Methods: We report a cutaneous meningioma of the forehead masquerading on imaging as a primary osseous tumor.

Results: A woman in her mid-forties presented with a five-year history of a right forehead lesion, initially asymptomatic, with new onset headache and facial pain, and numbness and paresthesia overlying the lesion. She reported alternating periods of no growth and significant growth, with rapid growth over the previous eight months. Physical examination revealed a broad-based firm mass protruding from the right forehead. The neurological examination was normal. CT imaging demonstrated a 2 cm exophytic soft tissue lesion with associated ossification, involving the right frontal bone. No intracranial component was identified. An osseous neoplasm was suspected and a biopsy performed. Histology revealed a monomorphic population of cells with round-to-oval nuclei, fine chromatin and moderate cytoplasm, interspersed bundles of collagen and mature adipose tissue, and no features of malignancy. Immunohistochemistry was positive for EMA and PR; negative for SOX-10, HMB-45, S-100, ERG, ASMA and CAM5.2. The diagnosis was cutaneous meningioma, probably Type II.

Conclusions: While cutaneous meningiomas typically have a benign course, they can compress adjacent structures and show focal destruction of bone, thus mimicking an osseous tumor as in our case. Management typically includes complete surgical resection with negative margins to minimize the likelihood of local recurrence. Awareness of this rare entity helps in the differential diagnosis of lesions of the head and neck.

140

Cystic Choroid Plexus Papilloma in an Adult: A Diagnostic Challenge on Frozen Section: Case Report and Literature Review

A Cuevas Ocampo [1], C Soto Davila [1], O Arevalo Espejo [1], B Hartman [2], C Giannini [3]; [1] LSU Health Shreveport, [2] Ochsner LSU Health Shreveport, [3] Mayo Clinic

Background: Choroid plexus papillomas (CPP) are rare, benign neoplasms, accounting for 0.5% of all brain tumors. While most present as solid masses, cystic CPP (C-CPP) is uncommon, particularly in adults. This atypical presentation can pose diagnostic challenges, especially intraoperatively, when the papillary component is minimal or radiologic findings are misleading.

Methods: A 25-year-old woman with worsening headache, nausea, and vomiting underwent brain imaging, revealing a posterior fossa CSF-filled cystic lesion with obstructive hydrocephalus, initially interpreted as an arachnoid cyst. She underwent suboccipital craniotomy, with histopathological analysis, including frozen sections (FS), permanent sections (PS), immunohistochemistry (IHC), and electron microscopy (EM). A second opinion from Mayo Clinic was obtained.

Results: A 4 mm papillary lesion with fibrovascular fronds was seen only on FS, prompting an intraoperative diagnosis of CPP, which was met with skepticism by neurosurgeons. PS showed only a fibrous cyst wall lined by simple columnar epithelium, lacking a papillary component. IHC demonstrated identical staining in FS and PS, with positivity for CK AE1/AE3, CAM5.2, and CK7, focal positivity for GFAP, S100, and synaptophysin, and negative staining for EMA. Ki-67 index was 2%. EM confirmed a choroid plexus phenotype, revealing numerous apical microvilli. A second opinion from Mayo Clinic supported the C-CPP diagnosis, and a neurosurgery tumor board review identified a 0.4 cm enhancing nodule, correlating with FS findings.

Conclusions: CPPs are rare in the posterior fossa of adults and can present as cystic lesions, complicating diagnosis when the papillary component is minimal or absent. C-CPP should be considered in posterior fossa cystic masses, even when preoperative imaging and histology lack classic papillary features. To our knowledge, fewer than eight adult C-CPP cases have been reported in the medical literature.

141

Meningioma: The Good, the Bad, and the Proliferative.

J Dailey [1], A Nobee [2], M Punsoni [2]; [1] Brown University Health-Rhode Island Hospital, [2] Brown University Health

Background: Meningiomas, although typically benign, can vary in clinical progression. The Ki-67 index thresholds are not included in the WHO grading system, however, numerous studies show higher indices correlate with increased risk of recurrence. This study investigates the relationship of grade and Ki-67 in primary and recurrent meningiomas.

Methods: A 10-year retrospective review of pathology records (2015-2025) was conducted.

Results: We identified 494 cases from 466 patients (range: 14-90y; mean: 59y, 146 M, 336 F) with meningioma involving the brain (449), spine (42), and non CNS tissue (1), of which 37% lateralized to the right, 38% to the left with 6% in the midline. Intracranial meningiomas were most common in the anterior cranial fossa while spinal cases occurred most often in the thoracic region. There were 361 patients with grade I, 89 with grade 2, and 3 with grade 3 meningiomas with a Ki67 range of ≤4 to >20%, ≤4 to >40%, and >4 to >40% respectively. Six atypical cases showed Ki67 >40%. Forty recurrences, with a small subset (12.5%) with multiple recurrences, were identified and of those cases, grade 1 recurred in 5%, grade 2 in 15.7%, and grade 3 in 75% of cases. The average duration from original diagnosis to first recurrence was 124 months with the longest duration 273 months and the shortest interval in 5 months. Recurrent cases showed an elevated Ki67 of ≥ 4% in 75% of cases with a range of ≤4 to >20% for grade 1, ≤4 to >40% for grade 2, and >20 to >40% for grade 3 meningiomas.

Conclusions: Our retrospective showed a Ki67 of >4% in 75% of recurrent meningiomas, which supports the utility of Ki67 in predicting recurrence and influencing outcomes. However, the overlap of Ki67 range between grades, underscores the importance of integrating mitotic count and histologic grade for accurate stratification.

142

Calcifying pseudoneoplasms of the neuraxis (CAPNON) associated with Meningioangiomatosis in a Pediatric Patient. A Case Report

D Zieba [1], A Baisre de Leon [1], M Brady [1], C Guerrieri [2], M Movahed-Ezazi [1], L Tomycz [3]; [1] Rutgers-NJMS, [2] RWJ-Barnabas, [3] Rutgers-RBHS

Background: Meningioangiomatosis has been previously reported in the literature as a rare, benign, neurological vascular confluence with a collagenous component clinically presenting as seizure activity. Calcifying pseudoneoplasm of the neuraxis, CAPNON, is composed of a bony matrix and spindle cells. Here we present a case of the two rare entities colliding in a pediatric patient with a clear histologic demarcation.

Methods: The patient is a 13-year-old male with significant past medical history of chronic epistaxis since 6-years-old and anemia who presented to the emergency department with new onset seizures. The patient experienced 2 seizure-like episodes hours apart that same day. He was neurologically intact on examination and denied headaches. The patient had no history of epilepsy or neurofibromatosis 2, and the only significant family history was pediatric seizures in his paternal uncle. Imaging revealed a supratentorial lesion with coarse calcifications in the parasagittal left frontal lobe, with minimal extension in the adjacent parasagittal right frontal lobe. The initial differential diagnosis included arteriovenous malformation versus low-grade tumor, and pathology reports of the resected lesion confirmed meningioangiomatosis and CAPNON.

Results: The meningioangiomatosis demonstrated vasculature with positive CD34, rare EMA and PRA cells focused within the leptomeninges and superficial cortex. A trichrome stain consequently highlighted collagen in this component. In a distinctly separate sulcus, the leptomeninges demonstrated chondromyxoid matrix with spindle cells, most consistent with CAPNON. This area was diffusely positive for vimentin.

Conclusions: CAPNON is rarely diagnosed, and seldom reported in the pediatric population. Seizure activity is a common presentation of both CAPNON and meningioangiomatosis. To our knowledge, only one other case of CAPNON and meningioangiomatosis has been reported, however in an adult individual.

143

Intradiploic epidermoid cysts of the skull: Case report.

A Alkhotani, A Alkhotani; Umm Al-Qura University

Background: Epidermoid cysts are rare, benign, slow-growing lesions that account for less than 1% of all intracranial tumors. They are typically found in the cerebellopontine angle and suprasellar cistern, with the diploe being a less common and sporadic location. Intradiploic epidermoid cysts are typically located within the diploic space of the skull vault and may present with variable clinical manifestations depending on their size and location.

Methods: We report a case of a 43-year-old male with a history of right eye ptosis and gradual visual deterioration. His brain magnetic resonance imaging (MRI) reveals an extra-axial mass measuring 5.3 x 4.4 x 4.3 cm, with a heterogeneous T1/T2 signal and variable intrinsic T1 hyperintense signal changes over the right anterior inferior frontal convexity. This is associated with adjacent bony thinning, remodeling, and mild mass effect on surrounding structures. The patient underwent surgical resection of the mass.

Results: Histopathological examination shows a cyst wall lined by stratified squamous epithelium with keratin flakes, cholesterol clefts, and extensive mixed inflammation, with an absence of adnexal, endodermal, or mesodermal structures. The diagnosis of an intradiploic epidermoid cyst is made.

Conclusions: Intradiploic epidermoid cysts are rare, benign skull lesions that can mimic other skull lesions on imaging. Multimodal imaging, including MRI, and histopathological confirmation are essential for diagnosis. Surgical resection remains the definitive treatment, with an excellent prognosis in most cases.

144

Schwannoma with Extensive Xanthomatous Changes: A Case Report
A Alkhotani, A Alkhotani; Umm Al-Qura University

Background: Schwannomas are benign nerve sheath tumors composed entirely or nearly entirely of differentiated neoplastic Schwann cells, typically arising from peripheral, motor, sympathetic, or cranial nerves. They most commonly affect the vestibulocochlear nerve in the cerebellopontine angle. Conventional schwannomas are typically characterized by a classical biphasic pattern, with compact areas (Antoni type A) featuring nuclear palisading and loosely arranged areas (Antoni type B). These tumors generally do not present diagnostic challenges. However, rare histological variants, such as schwannomas with extensive xanthomatous changes, can pose unique challenges in diagnosis.

Methods: We report a case of a 36-year-old woman with a history of syncope and recurrent episodes of transient loss of consciousness over the past 5 days. Her magnetic resonance imaging reveals a large, heterogeneously enhancing mass in the left cerebellopontine angle, measuring 3.8 x 3.7 x 3.5 cm, extending into the left internal auditory canal. The tumor exhibits a complex appearance with both solid and cystic components, causing significant mass effect on surrounding structures. Obstructive hydrocephalus is noted. The patient underwent surgical resection of the tumor.

Results: The histological examination shows extensive xanthomatous macrophages that are immunopositive for CD68, intermingled with spindle-shaped tumor cells that have elongated nuclei, speckled chromatin, and eosinophilic cytoplasm. Mitoses and necrosis are not seen. The tumor cells are immunopositive for S100 and SOX10. The diagnosis of schwannoma with extensive xanthomatous changes is made.

Conclusions: Xanthomatous changes in schwannomas are a rare and intriguing histopathological finding that can complicate the diagnosis of these benign nerve sheath tumors and present a diagnostic challenge and distinguishingthem from other similar lesions is crucial for accurate diagnosis and appropriate management. Despite being a rare variant, the prognosis for schwannomas with extensive xanthomatous changes remains favorable, as these tumors are generally benign, and surgical resection typically results in a good outcome.

145

Distant metastases of an atypical meningioma presenting 14 years later after primary tumor resection: a case report and review of the literature

K Firde, I Akhtar, L Barry, A Bombonati, Y Rong; TUH

Background: Metastasis of meningioma in extracranial location is rare, occurring in less than 1% of cases. We present a case of atypical meningioma status post resection with intracranial recurrence followed by multiple radiation therapy and developed extracranial metastases 14 years later after the resection of the primary tumor.

Methods: A 68-year-old male with a history of parasagittal atypical meningoma (WHO grade 2) status post resection with intracranial recurrence followed by radiation therapy presented with 2 months of abdominal pain, early satiety and unintentional weight loss. Abdominal CT scan demonstrated a 21 x 18 x 14 cm left upper quadrant abdominal mass along the gastric fundus. Clinically gastrointestinal stromal tumor (GIST) was suspected. Hepatic and pulmonary metastatic lesions with multiple enlarged abdominal lymph nodes were also noted. A core biopsy of the abdominal mass demonstrated a meningothelial neoplasm with whorls, pseudo-intranuclear inclusions, prominent nucleoli, necrosis and scattered mitotic figures. Tumor cells were positive for CK AE1/3, Cam5.2, EMA (focal), vimentin, D2-40, E-cadherin, and somatostatin receptor 2a (SSTR2a), but negative for progesterone receptor (PR), GIST markers including CD117 (c-kit) and DOG-1 and immunomarkers specific for other primary sites including lung, liver, prostate, genitourinary and pancreatobiliary tract.

Results: Distant extracranial metastases of meningioma have been considered to be uncommon and mainly occur in malignant meningiomas (WHO grade 3). Several factors including invasion into the venous sinus, intracranial recurrence, high-grade histology and papillary morphology have been suggested to correlate with a higher risk for recurrence and distant metastasis. Among these factors, the WHO histological grading believes to be the most important factor to predict recurrence or metastases.

Conclusions: For patients with a history of meningioma, especially with multiple intracranial recurrence after surgical resection, a possible extracranial metastatic disease should be included in the differential diagnosis in the situation of suspected systemic lesions.

146

EBV+ Primary Central Nervous System Lymphoma in an Immunocompetent Patient

A Kenyon [1], L Kenyon [2], G Uppal [3]; [1] Mass General Brigham, [2] Cooper University Health, [3] Hackensack Meridian Health

Background: Primary central nervous system lymphoma (PCNSL) is a highly aggressive, rare form of non-Hodgkin's lymphoma (NHL) primarily seen in immunocompromised patients, especially those with HIV/AIDS. In immunocompromised patients, PCNSL is almost always related to an Epstein-Barr Virus (EBV) infection. In contrast, EBV+ PCNSL in immunocompetent patients is exceedingly rare with a yet to be fully elucidated pathogenic mechanism. Here we report a 65-year-old woman who presented to the hospital with persistent left-sided weakness and was found to have a right parasagittal parietal ring-enhancing lesion on brain MRI, concerning for a brain metastasis. The patient received dexamethasone and underwent craniotomy with tumor resection. Intraoperative frozen section demonstrated an extensively necrotic neoplasm which favored either a necrotic glioma or lymphoma.

Methods: Formalin fixed paraffin-embedded tissue, hematoxylin and eosin stain, immunohistochemistry (BCL-6, CD10, MUM1), and in situ hybridization (EBER) were utilized.

Results: Permanent sections were diagnostic of an EBV+ diffuse large B cell lymphoma (DLBCL), non-germinal center type, a rare entity in an immunocompetent patient.

Conclusions: EBV+ DLBCL is typically associated with individuals who are immunosuppressed, classically those with HIV/AIDS or secondary to immunosuppressive therapy, organ transplantation, or congenital immune dysfunction. EBV+ DLBCL of the CNS in an immunocompetent patient is extremely rare with only isolated reports in literature.

147

Intracranial solitary fibrous tumor with myxoid features: a rare presentation

A Jones [1], M Lopes [1], S Patel [1], A Asthagiri [1], Z Abdullaev [2], K Aldape [2], C Fadul [1], M McCord [1]; [1] University of Virginia, [2] National Cancer Institute

Background: A 74-year-old male presented with sudden onset of blurred vision. Brain MRI revealed a 5.2 cm contrast-enhancing, hemorrhagic, lobulated mass arising from the planum sphenoidale. The patient underwent a right pteronial craniotomy. Near-total resection (90-95%) was achieved, with decompression of the right optic nerve and improvement in vision.

Methods: The specimen underwent neuropathologic workup for diagnosis.

Results: Histopathology showed a dural-based tumor composed of spindle cells with a prominent myxoid matrix and numerous pools of mucin. Immunohistochemistry (IHC) showed CD99 and FLI1 positivity with focal expression of desmin and CD163. Additional IHC was non-contributory. The tumor received a provisional diagnosis of “mesenchymal, non-meningothelial neoplasm.” It was sent to the National Cancer Institute for array methylation profiling, and matched to methylation class “Solitary fibrous tumor.” Subsequent STAT6 immunohistochemistry showed strong nuclear positivity, consistent with a NAB2::STAT6 fusion. The diagnosis was updated to “Solitary fibrous tumor with myxoid features.” Morphology was compatible with Marseille Grade 1. The patient received adjuvant radiation, and remains in good condition with stable follow-up imaging.

Conclusions: Solitary fibrous tumor (SFT) can occur in multiple locations, but is uncommon in the central nervous system (CNS), accounting for less than 1% of CNS tumors. SFT with predominantly myxoid morphology is exceptionally rare. A previous case series of 3 CNS SFTs included one myxoid SFT of spine (PMID 15926073). We identified only one additional reported case of intracranial myxoid SFT (PMID 16978216). Our case is unique in that it is the first CNS myxoid SFT with NAB2::STAT6 fusion identified by staining, and the first to confirm the diagnosis via array methylation profiling, to the best of our knowledge. This case highlights the value of DNA methylation profiling for correctly classifying rare morphologic variants of CNS tumors.

148

Intradural Extraosseous Ewing Sarcoma in an Older Adult: A Case Report

H Ellsworth [1], H Bayne [2], H Ellsworth [3], E Karlovich [3], O Al Dalahmah [3], V Tikhomirov [4]; [1] Columbia University Irving Medical Center / New York Presbyterian Hospital, [2] University of Vermont, [3] Columbia University/New York Presbyterian Hospital, [4] University of Vermont College of Medicine

Background: Ewing sarcoma (ES) is a rare, highly aggressive malignancy that predominantly involves the long bones of the appendicular skeleton in children and adolescents. While ES primarily affects pediatric patients, extraosseous ES has been reported to occur more frequently in older patients and carry a worse prognosis. This report describes a unique case of extraosseous ES arising within the spinal dura of an older adult.

Methods: A 70-year-old female with a medical history of polymyalgia rheumatica, osteopenia, and right-sided piriformis syndrome presented with progressive right leg pain, intermittent left leg pain, and generalized pruritus. Physical and neurological examinations were within normal limits. MRI revealed a 1.9 x 1.4 x 0.9 cm ovoid mass intimately related to the intradural right L4 nerve root that demonstrated intense enhancement upon contrast administration. Two months after initial presentation, the patient underwent laminectomy with subtotal tumor resection, as dense adherence of tumor to the cauda equina prevented complete excision. Microscopic review of the tumor revealed sheets of small round cells with finely stippled chromatin, inconspicuous nuclei, and scant cytoplasm. The neoplasm was mitotically active with high (20-30%) Ki67 proliferation index, and displayed immunoreactivity for NKX2.2, FLI1, and CD99 with diffuse membranous staining. Cytogenetic testing via FISH analysis using EWSR1 (22q12) break apart probe demonstrated rearrangement in 92.5% of cells. RNA sequencing revealed a Type 2 EWSR::FLI1 fusion. These findings are consistent with ES.

Results: ES is a rare and aggressive malignancy primarily affecting pediatric patients that can also occur in older adults. Extraosseous ES can arise in unusual locations such as the spinal dura, and older patients with intradural disease may present with non-specific symptoms and challenging surgical management, delaying definitive diagnosis.

Conclusions: ES affects older adults in addition to pediatric populations. Intradural ES is a rare presentation of extraosseous disease and should be considered in a differential diagnosis.

149

Metastatic thymoma to brain parenchyma

J Fullmer [1], J Blumberg [2]; [1] Corewell Health, [2] Corewell Health William Beaumont University Hospital

Background: This is a 74 yo female with remote history of stable lung nodules and about 12 year history of (and I won't say this in initial slide as it would give it away) thymoma surgery at outside hospital. There was also a moderately suspicious thyroid nodule, 1.9 cm. She presented with headaches and some left upper extremity weakness. Eventual imaging discovered a 1.7 cm uniformly enhancing mass in the anterior right parietal lobe.

Methods: Conventional H&E histology and IHC, Methylome profiling at the NCI

Results: Examination of H&E stained sections revealed an epithelioid neoplasm with relatively monomorphic cells, no mitotic activity, and well demarcated border between tumor and surrounding brain. AE1/AE3, p40, CK5 and CK7 were positive while Claudin 4 was negative (so not supportive of carcinoma), as was CK20, GATA-3, TTF-1, PAX 8, SOX-10, thyroglobulin, INSM1, Synaptophysin, Uroplakin II, CD117, CD5, TDT, CD3, CD20, and CD1a. It was signed out as metastatic epithelial neoplasm with squamous differentiation and in comment noted this would be consistent with a thymoma but histology and IHC alone not specific. It was sent to Caris for sequencing and their panel favored thymoma. It was also sent for methylome profiling and did not match to any CNS classifier but with UMAP in pan-cancer background was closest to thymoma. Therefore, it is consistent with thymoma. The patient went to rehab and did well, not neoadjuvant therapy has been performed and the lung masses and thyroid mass has not been sampled.

Conclusions: Metastatic thymoma to the brain is uncommon but needs to be considered

150

Atypical meningiomas with diverse variants of unknown significance: a report of three cases.

S Sharma, M Toscano, E Shaver; VA Augusta Health Care System

Background: The current 2021 WHO classification recognizes three grades of meningioma.

Methods: We present three cases of grade 2 meningioma that underwent resection, histopathologic evaluation, and Next generation sequencing.

Results: Patients were 62, 74, and 54 years in age; two were males and one was female. Imaging showed extra-axial convexity masses involving the left temporal, parietal, and frontal regions. These ranged from 4.0 to 4.2 cm in greatest dimension and showed variable vasogenic edema, with one also showing left to right mid-line shift. Histologically, all three cases were WHO grade 2 atypical meningiomas based primarily on mitotic activity up to 7, 4, and 4 per 10 high power fields (respectively). Additional features included hypercellularity (3/3 cases), syncytial growth pattern (3/3), spontaneous necrosis (2/3), and prominent nucleoli (2/3). Ki67 labeling indices were 10%, 9%, and 11% (respectively). Next generation sequencing performed and interpreted at a reference laboratory showed low tumor mutational burden (TMB) and stable microsatellite instability (MSI) in all cases. NF2 mutations were seen in 2/3 cases. One case showed an EP300 mutation (albeit without any clinical stigmata of Rubinstein–Taybi syndrome). Additionally, all cases showed different variants of unknown significance which are described in various neoplasms but not in the WHO classification of meningiomas. These included MAPK1, FAT1, CCND3, ZFHX3, SLIT2, FANCD2, and JAK1 (many types of neoplasms); BCR, PLCG2, and SETBP1 (hematologic neoplasms; rarely reported in meningioma); SDHA (GIST and paraganglioma); SOX17 (gynecologic and GI neoplasms), and ERBB2 (breast and GI neoplasms).

Conclusions: Our limited study supports the reported dichotomy of atypical meningiomas based on NF2 mutations, but also shows variants of unknown significance which may benefit from further studies to evaluate any clinical significance.

151

An unusual case of late recurrence of atypical choroid plexus papilloma with intracranial and spine metastases in an elderly patient

O Tetteh [1], J Singh [1], R Ber [2], C Mau [2], B Donahue [3], T Daniels [4], B Cooper [4], J Zeng [1]; [1] SUNY Downstate Health Sciences University, [2] Maimonides Medical Center, [3] Maimonides Cancer Center, [4] NYU Langone Medical Center

Background: We report an unusual case of recurrent atypical choroid plexus papilloma (ACPP) in an elderly man with intracranial and spine metastasis. The patient is an 80-year-old man who was first seen in 2013 with complaints of dizziness and was found to have a fourth ventricular mass. The lesion was resected and the histopathology showed an atypical choroid plexus papilloma (WHO Grade 2). The patient received radiation therapy post-surgery with a two-year follow-up without any recurrence before being lost to follow-up. In 2024, the patient presented to the emergency department after a fall following more than two weeks of urinary incontinence, bilateral lower extremity weakness, and numbness. Imaging showed several enhancing lesions in third and lateral ventricles and in the cervical, thoracic, lumbar spine with cord compression. The resected tumors from both ventricle and spine exhibit similar morphology of florid papillary tumor lined by multi-layered or crowded atypical choroid plexus epithelium with increased mitotic activity up to 3/10HPF, consistent with recurrent atypical choroid plexus papilloma. Atypical choroid plexus papillomas are rare tumors and mostly occur in the pediatric population. To the best of our knowledge, the oldest reported case of ACPP was in a 62-year-old patient. The initial diagnosis in our patient was at age 68 years with recurrence 11 years later. No molecular studies were performed at the initial diagnosis. Molecular studies on the recurrent tumor revealed RAD54L R154W and CBL C384F subclonal alterations. No p53 mutation was identified. This piques an interest in looking at alterations in the more common pediatric cases to see if there are similarities and if these molecular signatures have a correlation with recurrence and metastasis. Potentially, these could be therapeutic targets which could provide adjuvant or alternative treatment for current standard management.

Methods: N/A

Results: N/A

Conclusions: N/A

Posters: Neurogenerative: FTLD/Lewy body/Parkinson

152

Clinicopathological characterization of vacuolar tauopathy associated with VCP D395G

R WATANABE [1], J Papatriantafyllou [2], K Maeda [3], G Aguirre [4], M Ando [5], B Benoit [6], M Grossman [4], D Irwin [4], B Kim [6], L Massimo [4], C McMillan [4], S Papageorgiou [7], T Shiraishi [8], Y Sugihara [9], E Suh [10], H Takashima [5], C Toro [11], V Van Deerlin [10], I Nasrallah [12], E Lee [6]; [1] University of Pennsylvania, [2] Medical Center of Athens, Memory Disorders Clinic and Day Care Center for 3rd Age 'IASIS', Athens, Greece, [3] Department of Neurology, Vories Memorial Hospital, Shiga, Japan, [4] Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, PA, USA, [5] Department of Neurology and Geriatrics, Kagoshima University, Graduate School of Medical and Dental Sciences, Kagoshima, Japan, [6] Translational Neuropathology Research Laboratory, Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, PA, USA, [7] 1st University Department of Neurology, Eginiteio University Hospital, National and Kapodistrian University of Athens, Athens, Greece, [8] Department of Rehabilitation, Higashi-ohmi General Medical Center, Shiga, Japan, [9] Department of Neurology, JCHO Shiga Hospital, Shiga, Japan, [10] Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, PA, USA, [11] NIH Undiagnosed Diseases Program, National Human Genome Research Institute, MD, USA, [12] Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, PA, USA

Background: Vacuolar tauopathy (VT) is a recently found autosomal-dominant genetic tauopathy harboring the VCP p.Asp395Gly variant. The pathologic tau protein accumulates in the frontotemporal neocortices due to the impaired tau disaggregation process involving VCP machinery, causing clinical frontotemporal dementia. However, the detailed clinical, radiological, and pathological features have not been well described due to the extremely rare occurrence of the disease.

Methods: We investigated the clinical, neuropsychological, physiological, laboratory, and radiological data and neuropathological findings in five symptomatic VT cases who met the diagnostic criteria for frontotemporal dementia (FTD). Radiological data included brain MRI (FLAIR and DWI sequences, n=5, including longitudinal tests for n=4) and nuclear imaging (99mTc-ECD SPECT, 99mTc-HMPAO SPECT, and 18F-FDG PET, n=1 each) for structural and functional evaluation. A longitudinal tau PET study was also obtained (n=1). Brain MRI was also collected from two pre-symptomatic carriers.

Results: All participants had heterozygous c.1184A>G, p.Asp395Gly in VCP. All symptomatic cases exhibited cognitive, behavioral, and/or language dysfunction, meeting the criteria for behavioral variant of FTD. Neuroimaging studies revealed marked bilateral frontal brain atrophy on MRI in all symptomatic cases (n=5), with progression over time (n=4). The occipital lobar diffusion hyperintensities were found in all cases. The longitudinal tau PET showed progressive

bilateral frontal tau deposition (n=1). Postmortem examination of three cases and brain biopsy of one case revealed abundant neuronal tau aggregates and neocortical microvacuolization. The neurodegeneration/tau deposition was inversely distributed with microvacuolization. Most neuronal tau aggregates resembled the neurofibrillary tangles in Alzheimer's disease, with less frequent cytoplasmic aggregates showing a rounded, compact appearance. Radiological changes were not evident in two pre-symptomatic carriers in their 20s.

Conclusions: This study reveals distinct clinical-radiological-pathological correlations in VT, expanding the early-onset frontotemporal lobar degeneration spectrum. Although the clinical VT phenotypes are common to other FTD syndromes, the occipital lobar diffusion abnormalities may distinguish them in clinical settings.

153

Alpha-Synuclein Oligomers and Visual Hallucinations in Dementia with Lewy Bodies: A Clinicopathological Study

H Sekiya, L Franke, D Ono, G Day, C Lachner, N Graff-Radford, P McLean, T Ferman, D Dickson; Mayo Clinic

Background: Visual hallucinations (VH) represent one of the core clinical features of dementia with Lewy bodies (DLB); however, the underlying pathology of VH remains incompletely characterized. While previous studies have focused on late-stage α-synuclein aggregates (i.e., Lewy-related pathology), recent attention has shifted to the toxicity of α-synuclein oligomers, which represent early-stage aggregates. This study aimed to elucidate the relationship between α-synuclein oligomers and VH in patients with DLB.

Methods: We examined 10 autopsy-confirmed patients of Lewy body disease who had been clinically diagnosed with DLB and prospectively evaluated. Patients completed neuropsychological assessment within three years of death and were evaluated for the presence of VH: five with VH and five without VH. Lewy-related pathology was detected using conventional phosphorylated α-synuclein immunohistochemistry, while α-synuclein oligomers were visualized using proximity ligation assay staining. We examined regions along the ventral visual stream involved in object recognition, including the primary visual cortex, visual association cortex, inferior temporal cortex, parahippocampal gyrus, amygdala, and nucleus basalis of Meynert. The pathological burden in each region was quantified as the percentage of stained area.

Results: There were no significant differences between patients with and without VH in age at death (VH 80±7 vs. non-VH 79±5 years; P=0.68), Braak neurofibrillary tangle stage (P=0.81), or Thal amyloid phase (P>0.99). Although Lewy-related pathology burden did not differ within regions between groups, α-synuclein oligomer burden in the parahippocampal gyrus was higher in patients with versus without VH (0.69% vs. 0.15%; P=0.04).

Conclusions: Patients with DLB and VH showed greater α-synuclein oligomer burden in the parahippocampal gyrus compared to those without VH. Our findings suggest that the accumulation of α-synuclein oligomers in the parahippocampal gyrus, a region involved in object recognition and identification, may contribute to the development of VH in DLB.

154

Prevalence of Chronic Traumatic Encephalopathy Pathology in Lewy Body Disease

L GOMEZ-ISAZA [1], M Luongo [2], M Morris [1], J Troncoso [1], T Zaikos [3]; [1] Johns Hopkins University School of Medicine, [2] Johns Hopkins University, School of Medicine, [3] University of California, Irvine

Background: Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease associated with repeated traumatic brain injury (TBI). It is characterized by the accumulation of hyperphosphorylated tau in neurons and astrocytes surrounding blood vessels at the depths of cortical sulci. While CTE has been extensively studied in athletes, its overlap with LBD is relatively unexplored. LBD commonly causes motor dysfunction, including an increased risk of falls and, in some cases, TBI.

Methods: We examined the brains of 155 autopsy-confirmed cases of LBD from the Johns Hopkins Brain Resource Center. Non-AD tauopathies were excluded. Immunostaining for phosphorylated tau (AT8) was performed on all cortical sections sampled in a standard neurodegenerative disease workup and evaluated for CTE lesions based on published NINDS/NIBIB criteria.

Results: The mean age of individuals in this cohort was 79 years with 69% male participants. Pathological staging of LBD was: 66% neocortical, 24% limbic, 6% brainstem, and 5% amygdala-predominant. Two individuals (1.3%) met the criteria for "definite" CTE, while 5 cases (3.2%) were classified as "possible" CTE. The average age of these individuals with definite/possible CTE was 78 years, with 86% male predominance. Of these, 71.4% had neocortical LBD and 28.6% had limbic LBD. With regards to co-pathology, 71.5% of these cases exhibited ADNC (57% high level, 14.2% intermediate), ARTAG was present in 32% of cases, and28% showed TDP-43 pathology.

Conclusions: These preliminary findings suggest that patients with LBD might have an increased risk of CTE pathology compared to the reported prevalence in the general population. The correlation of these findings with clinical data on reported head trauma and motor dysfunction is ongoing. While CTE in LBD is infrequent, it may impact disease progression in certain individuals. These findings highlight the need for further research to better understand the relationship between CTE and LBD, particularly in cases with mixed pathologies.

155

TDP-43 Proteomics of the Frontal Cortex in Lower Motor Neuron Disease and Frontotemporal Dementia

L Cracco [1], E Doud [2], R Rademakers [3], H Garringer [2], M Jacobsen [2], E Buratti [4], B Ghetti [2], K Newell [2]; [1] Department of Pathology and Laboratory Medicine, Dementia Laboratory, Indiana University, [2] Indiana University, [3] University of Antwerp, [4] International Centre for Genetic Engineering and Biotechnology (ICGEB)

Background: Immunohistochemical studies of the central nervous system in a patient with lower motor neuron disease and frontotemporal dementia revealed widespread TDP-43 deposits throughout brain and spinal cord. The etiology of this case is currently undetermined. Our aim was to characterize the molecular features of TDP-43 in the frontal cortex.

Methods: Sarkosyl-insoluble (S-I) TDP-43 was extracted from the frontal cortex. Immuno electron microscopy (IEM) with TDP-43 pS409/410 antibody (Ab) was carried out to determine the presence of fibrillary TDP-43 in the S-I fraction. IEM experiments were also carried out using polyclonal Abs targeting TDP-43 peptide sequences that contain phosphorylated serines (pS) 305, 369 or 375 to determine whether TDP-43 filaments were phosphorylated at these sites. Western blot (WB) was used to determine the TDP-43 biochemical profile, and mass spectrometry (MS) analyses were carried out to identify TDP-43 post-translational modifications (PTMs).

Results: IEM analyses revealed the presence of TDP-43 filaments in the S-I fraction; filaments were decorated with pS409/410 and pS305 Abs. The WB analysis with pS409/410 Ab showed that the TDP-43 biochemical profile in this case was similar to that observed in cases of FTLD-TDP Types A and B, except for a distinct relative abundance of C-terminal fragments in the 25–20 kDa range. MS analyses identified phosphorylation sites across all TDP-43 domains, predominantly in the prion-like low-complexity domain, along with additional PTMs, including citrullination. IEM experiments with pS369 and pS375 Abs are in progress.

Conclusions: The current findings indicate that, in this case, TDP-43 misfolded into filaments with abnormal phosphorylation at various sites, including S305 and S409/410, and underwent citrullination. Determination of the near-atomical structure of the TDP-43 fibrillar material is an essential step to determine whether TDP-43 filaments have a fold distinct from those previously reported.

156

RNA sequencing of amygdala in Parkinson's disease

C Tremblay [1], G Frosi [2], S Aslam [1], J Walker [1], A Intorcia [1], I Lorenzini [1], P Choudhury [1], C Adler [3], E Driver-Dunckley [3], S Mehta [3], H Shill [4], A Atri [1], Y Zeighami [2], T Beach [1], G Serrano [1]; [1] Banner Sun Health Research Institute, [2] Douglas Research Center, [3] Mayo Clinic Arizona, [4] Barrow Neurological Institute

Background: The amygdala is closely connected to the olfactory bulb and involved in olfactory processing as well. It is a particularly susceptible region that accumulates a-synuclein pathology in Parkinson's disease (PD). Our previous work revealed olfactory bulb gene alterations related to neuroinflammation, and neurotransmitter dysfunction to be associated with olfactory function. We aimed to extend this work and assess gene expression changes, affected pathways and co-expression networks by transcriptomic profiling of the amygdala in subjects with and without clinicopathologically defined PD.

Methods: Bulk RNA sequencing was performed on frozen human amygdala of 20 PD and 20 controls without dementia or any other neurodegenerative disorder, from the Arizona Study of Aging and Neurodegenerative Disorders.

Results: Differential expression analysis, corrected for age, sex and post-mortem interval revealed 40 significantly differentially expressed genes (DEGs) in PD. Downregulated genes were mainly related to altered hemoglobin expression while upregulated genes included inflammatory markers and glutamine transporter. Significantly enriched pathways were involved in oxygen and carbon dioxide transport, cellular oxidant detoxification and regulation of glutamine secretion. Cell enrichment revealed these genes to be mainly expressed in neurons. Co-expression network analysis using Weighted correlation network analysis (WGCNA) subsequently identified four significant modules correlated with both PD and premortem olfactory dysfunction which were involved in pathways related to neuroinflammatory processes, mitochondrial, endoplasmic reticulum and lysosomal dysfunction.

Conclusions: These preliminary results suggest cellular alterations in the amygdala related to mitochondrial dysfunction, altered oxygen homeostasis, oxidative stress, inflammation as well as glutamatergic neurotransmitter dysfunction that may contribute to neurodegeneration in PD.

157

Late-Onset Frontotemporal Lobar Degeneration TDP-43 Type A with Lewy Body Pathology and Protein Colocalization

A Ghaseminejad-Bandpey [1], S Etemadmoghadam [2], C Corbett [2], M Keating [2], A Gonzalez [2], O Ogunbona [3], M Dopler [2], K Clarke [2], J Parker-Garza [2], B Danner [2], M Alhneif [2], K Bieniek [3], S Seshadri [2], M Flanagan [3]; [1] Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Science Center at San Antonio, [2] Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases, University of Texas Health Science Center at San Antonio, [3] Glenn Biggs Institute for Alzheimer's and Neurodegenerative Diseases & Department of Pathology and Laboratory Medicine, University of Texas Health Science Center at San Antonio

Background: Frontotemporal lobar degeneration (FTLD) represents a group of proteinopathies characterized by the accumulation of tau, TDP-43, or FUS. FTLD is clinically associated with progressive declines in behavior, language, or executive function. FTLD usually affects individuals under 65 and is uncommonly associated with co-occurring pathologies. We describe the autopsy findings of an 81-year-old woman with a postmortem diagnosis of FTLD-TDP-43 type-A and Lewy body disease.

Methods: A Caucasian female presented with memory loss at age 74 with no signs of anxiety, disinhibition, or loss of empathy who stopped speaking 1.5 years before death at age 81. The clinical diagnosis was late-onset Alzheimer disease (CDR=3). Familial history of “Alzheimer-Pick disease” and early-onset dementia was noted. Gross examination revealed moderate frontotemporal lobar atrophy. Routine neurodegenerative disease neuropathologic assessments showed intra-cytoplasmic/nuclear phosphorylated-TDP-43 (pS409/410) accumulation in the upper cortical neuronal layers consistent with FTLD-TDP type-A but no Alzheimer’s disease neuropathologic change was present. Phosphorylated-α-synuclein (pSYN64) was observed in the limbic regions. Additional staining for LB509 and p62, in addition to multiplexed immunofluorescence with LB509 and pTDP-43, as well as pSYN64 and pTDP-43 was performed to assess intracellular protein colocalization. Pearson’s correlation coefficient (PCC) was used to quantify the protein colocalization from immunofluorescence stained slides.

Results: Both TDP-43 and LB509 separately labeled dense cytoplasmic inclusions and dystrophic neurites and showed strong colocalization. Colocalization was variable in the number of colocalized inclusions and neurites observed across brain regions. Colocalization frequency differed between cytoplasmic inclusions and neurites.

Conclusions: Colocalization of α-synuclein and TDP-43 may influence the clinical presentation, progression, and severity of the disease, which in this case was less aggressive than typically observed. Whether this colocalization had a protective role or represents an incidental finding requires further investigation.

158

Investigating Optic Nerve Alterations in Parkinson's Disease: A Histological and Protein Analysis Study

I Lorenzini, A Gonzalez, A Intorcia, A Shull, Z Wermager, J Walker, S Qiji, S Beh, R Arce, C Borja, M Cline, A Krupp, R McHattie, M Mariner, T Beach, G Serrano; Banner Sun Health Research Institute

Background: Parkinson's disease (PD) patients have non-motor symptoms that usually present earlier in the disease progression such as vision difficulties. We previously showed that phosphorylated alpha synuclein (pSyn), is found in the retina and optic nerve, while antemortem observations suggest that PD patients might have thicker optic nerves. In this study, we measured the thickness of optic nerves of PD participants and investigated the level of different proteins that could explain possible nerve enlargement.

Methods: Optic nerves collected at autopsy from 120 participants enrolled in the Brain and Body Donation Program (BBDP) program at Banner Sun Health Research Institute were fixed and paraffin embedded. Case selection included Alzheimer's disease dementia (ADD), PDs and controls. Paraffin sections were stained with hematoxylin and eosin, Masson trichrome (collagen), Verhoeff (elastin), Gomori (reticulin) and immunostained for glial fibrillary acid protein (GFAP), neurofilament (NF), CNPase for oligodendrocytes (OL), and pSyn.

Results: The optic nerve showed no significant changes in size across all groups, but dura mater or optic nerve sheath (NS) was significantly thickened in PD. This correlated with brain pSyn and tau densities, but not with age and sex. There were no significant differences in the percentage area occupied in the nerve proper or NS by NF, GFAP, and OL between groups. However, collagen seemed to be replaced by elastin in the NS of PD cases.

Conclusions: Our data suggests that the dura layer surrounding the optic nerve may experience changes during PD progression.

159

Asymmetric, Limbic-Predominant 4 Repeat Tauopathy with Pick body-like Inclusions discovered incidentally at autopsy – A Case Report

H Smith, M Mejia-Bautista, P Jamshidi, J Ahrendsen, R Castellani; Northwestern Memorial Hospital

Background: Frontotemporal lobar degeneration-tau (FTLD-tau) encompasses multiple entities defined by tau-positive neuronal and glial inclusions. The spectrum of preclinical pathologic findings in 4R- tauopathies is not well-characterized. Herein, we describe an incidental 4R-predominant tauopathy in an asymptomatic patient.

Methods: A 70-year-old male with history of aortic stenosis and recent valve replacement was hospitalized for management of methicillin-sensitive Staphylococcus Aureus bacteremia. His course was complicated by a right middle cerebral artery (MCA) territory infarct. He died due to complications of sepsis following thrombectomy. A complete autopsy was performed.

Results: Examination of the brain (1536 g) revealed a recent right MCA-territory infarct. Of note were marked atrophy and sclerosis of the left hippocampus and amygdala. Histopathologic sections revealed neuronal loss, gliosis, and numerous Pick-like inclusions throughout the left hippocampal formation and amygdala. Additional findings included rare balloon neurons in the left temporal neocortex, superficial microvacuolization of the left temporal lobe, cingulate, and inferior frontal gyrus, and rare Pick-like inclusions in the right hippocampus. Immunostains for tau (AT8) performed on all blocks labeled the Pick-like inclusions, neurofibrillary tangles and pretangles, threads, tufted astrocytes, and coiled bodies with the highest burden in the left mesial temporal structures and temporal lobe neocortex. The right cerebral hemisphere showed a similarly limbic-predominant tau distribution but with substantially lower burden. Left-predominant tau pathology was also noted in the subcortical nuclei and brainstem. The Pick body-like and glial inclusions exclusively labeled with 4R tau. β-amyloid, α-synuclein, and TDP-43 pathology were absent.

Conclusions: Records from multiple primary care visits described a high-functioning retired man with no cognitive, verbal, or motor symptoms. This asymmetric, limbic-predominant 4R tauopathy with Pick-like inclusions shows features of multiple FTLD-tau subtypes and highlights an extent of pathology that might be encountered in asymptomatic patients or “preclinical” disease.

160

Contribution of TAR DNA-binding protein 43 (TDP-43) and Annexin A11 in Frontotemporal Lobar Degeneration's Limbic Tau-PET Signal

R Gatto, G Uruk, H Youssef, R Reichard, V Lowe, J Whitwell, K Josephs; Mayo Clinic

Background: A subset of frontotemporal lobar degeneration (FTLD) is characterized by phosphorylated TAR DNA-binding protein 43 (pTDP-43) inclusions. Flortaucipir PET, which binds to paired-helical filament 1 (PHF-1) tau, shows uptake in some FTLD-TDP cases. Recently, a calcium-dependent phospholipid-binding protein, Annexin A11 (ANXA11), was identified in a subgroup of FTLD-TDP cases. Using a fluorescence flortacipir-PET analog (T726), we aim to determine whether some flortaucipir-PET uptake is related to Annexin A11 aggregations in FTLD-TDP.

Methods: This study included neuropathological specimens from eight cases; one (negative) control, one positive control with a high likelihood of Alzheimer's disease (hAD) without TDP-43, two cases with hAD and TDP-43, and four FTLD-TDP cases (one type A and three type C). Superior and middle temporal gyri (S/M-T) and hippocampus (HC) regions were stained with T726, PHF-1 tau, pTDP-43, and Annexin A11. Fluorescent confocal imaging was performed and overlap coefficients were calculated for each marker and region of interest.

Results: In the S/M-T region, as expected, there was a significant overlap between T726 and PHF-1 in all three AD cases and all three FTLD+TDP (type C) cases. ANXA11 uptake was seen in all FTLD-TDP type C cases in the S/M-T region. Little overlap was observed between T726 and pTDP-43 and between T726 and ANXA11 in these FTLD-TDP (type C) cases. In the HC's dental gyrus, we observed a significant overlap between pTDP-43 and ANXA11, as well as between T726 and pTDP-43 and between T726 and ANXA11 in all FTLD-TDP (type C) cases.

Conclusions: These results suggest that while some off-target binding of flortaucipir PET in FTLD-TDP could be due to the presence of other tau-positive co-pathologies such as primary age-related tauopathy or aging-related tau astrogliopathy, some uptake in FTLD-TDP (type C) may be related to ANXA11 and pTDP-43 bindings.

161

Corticospinal tract degeneration in frontotemporal lobar degeneration associated with phospho-TDP43 proteinopathy

R Castellani [1], D Mashoudy [2], T Gefen [2], M Mesulam [2], P Jamshidi [2]; [1] Northwestern University, [2] Northwestern University Feinberg School of Medicine

Background: Frontotemporal lobar degeneration with TDP-43 immunolabeling (FTLD-TDP) may be associated with ALS (e.g. type B) and/or corticospinal tract (CST) degeneration (e.g., type C, Josephs et al. Brain 2013;136:455-70). To examine the frequency and characteristics of the upper and lower motor neuron changes, we examined archival material at the Mesulam Center for Cognitive Neurology/Northwestern University Alzheimer's Disease Research Center diagnosed with FTLD-TDP type B (n = 10) or FTLD-TDP type C (n = 26) at autopsy.

Methods: The cases were characterized by immunohistochemistry according to Northwestern University Neuropathology Core protocol and classified according to Mackenzie et al (Acta Neuropathol 2011;122(1):111-113). The medulla at the hypoglossal nucleus was immunonstained for phospho-TDP-43, neurofilament, and CD163, along with luxol-fast blue. CST degeneration was characterized as negative, equivocal, or present per Josephs et al.

Results: No were diagnosed with ALS during life. 4 cases showed increased C9orf72 inserts (all type B).Of the 10 FTLD-TDP type B cases, 6 (60%) showed equivocal or greater CST degeneration (2 equivocal, 4 definite). Of the 26 FTLD-TDP-Type C cases, 17 (65%) showed equivocal or greater CST degeneration (12 equivocal, 5 definite). PhosphoTDP-43 immunohistochemistry demonstrated soma immunolabeling of hypoglossal neurons in 8 out of 10 cases. 3 of these 10 cases with inclusions in the soma showed no CST degeneration (differing from Josephs et al). None of the 26 FTLD TDP-C cases showed immunolabeling of the soma of hypoglossal neurons, although novel dot-like neuropil labeling was noted within or near the hypoglossal nucleus in 10 of the 26 FTLD TDP-type C cases.

Conclusions: These results demonstrate that TDP type B and type C show similar frequencies of CST degeneration and can be dichotomized based on changes in the medulla. The recognition of the high frequency of corticospinal tract involvement may prompt increased vigilance and earlier rehabilitation of motor function.

162

Early-Onset Sporadic Lower Motor Neuron Disease and Frontotemporal Dementia Associated with a TDP-43 Proteinopathy of Unknown Etiology

K Newell [1], D Clark [2], F Unverzagt [2], M Jacobsen [2], M Majeed [2], L Cracco [2], R Vidal [2], H Garringer [2], R Rademakers [3], B Ghetti [2]; [1] Indiana University School of Medicine, [2] Indiana University School of Medicine, Indianapolis, IN, [3] University of Antwerp, Department of Biomedical Sciences, Antwerp, Belgium

Background: TDP-43 proteinopathy associated with lower motor neuron disease (MND) and frontotemporal dementia (FTD) has been reported in a small number of individuals carrying TARDBP variants. We report a case in which a TDP-43 proteinopathy involved gray and white matter of brain and spinal cord.

Methods: Clinical studies were carried out according to research protocols used for FTD and MND. For neuropathology neurohistological methods were used. Immunohistochemistry was carried out using antibodies to TDP-43, tau, amyloid-beta, and alpha-synuclein.

Results: A 55-year-old male presented with complaints of numbness and weakness in the left hand. EMG suggested denervation and an MRI revealed right temporal lobe atrophy. He suffered from rapidly progressive motor decline with muscle weakness, atrophy and fasciculations. Behavioral changes also appeared and disinhibition, loss of empathy, dietary compulsions, and obsession with professional baseball were noted. He was diagnosed with behavioral variant FTD and MND. Two years after presentation, he was still able to ride his bicycle and mow the lawn; however, he declined rapidly and was placed on hospice care. He died at age 59. Postmortem, the brain weight was 1232 grams with asymmetric atrophy of the frontal and temporal lobes. Atrophy involved frontal, temporal and insular cortices, caudate nucleus, amygdala, hippocampus, brain stem, and cerebellum. Substantia nigra and locus coeruleus were depigmented. A severe TDP-43 proteinopathy in gray and white matter of central nervous system and spinal cord was characterized by numerous intracytoplasmic TDP-43 inclusions in neuronal perikarya and neuropil, in oligodendrocytes and astrocytes. Inclusions were also numerous in lower motoneurons and axons of anterior roots. Muscle denervation was severe.

Conclusions: Although DNA studies intravitam did not reveal a genetic etiology, the observation of TDP-43 intracytoplasmic inclusions in neurons and glia in multiple CNS regions supports the hypothesis that the MND-FTD may be caused by an unidentified TARDBP variant.

163

Asymmetric Frontotemporal Lobar Degeneration (FTLD)-TDP-43 with concurrent FTLD-tau, Corticobasal Degeneration Subtype

K Wysong, W Pendlebury, J DeWitt; University of Vermont Medical Center

Background: Frontotemporal Lobar Degeneration (FTLD) is a heterogenous group of neurodegenerative diseases consisting of predominantly three categories based on underlying pathologic proteins including FTLD-Transactive response DNA binding protein of 43 kDa (TDP-43), FTLD-tau, and FTLD-fused in sarcoma (FUS). Corticobasal Degeneration (CBD) is a rare neurodegenerative tauopathy with variable clinical presentation which may present predominantly as a movement disorder or with largely cognitive symptoms in which CBD can be categorized within the FTLD-tau family of disorders. While different underlying pathologies underly these categories they are not mutually exclusive, and patients may exhibit mixed deposition patterns of these pathologic proteins.

Methods: Here we describe autopsy findings of a 64-year-old man presenting two years before passing for evaluation of progressive gradual changes in speech. Evaluation revealed difficulty with word finding, effortful speech delivery, and decreased auditory comprehension with cognitive testing significant for impaired working memory, processing speed, and verbal reasoning/fluency skills. Motor deficits were present including gait bradykinesia with reduced arm swing as well as subtle cognitive alterations in level of engagement and flattened affect. Of note the patient’s memory was intact with no signs of tremor, hallucinations, or changes in mood/personality.

Results: Neuropathologic examination during autopsy revealed cerebral atrophy with significant asymmetric degeneration of the right temporal lobe. Microscopic examination found extensive TDP-43 proteinopathy primarily affecting the right cortex and hippocampus consistent with asymmetric FTLD-TDP-43 type A. However, concomitant tauopathy was also present with diffuse involvement of both hemispheres, hippocampi, and subcortical white matter with tau-inclusions of the cerebellar dentate, substantia nigra, pons, medulla, thalamus and basal ganglia consistent with CBD.

Conclusions: Cases of mixed FTLD-TDP-43 and CBD have been previously reported. However, they are exceedingly rare with novel patterns of pathology that may modify each other and their phenotypic clinical presentation that possibly reflect an interaction between pathologic TDP-43 and tau highlighted in this case.

Posters: Trauma

164

Examining Sex Differences in Neuroinflammation Associated with Traumatic Brain Injury
L Chung, K Sytsma, A Feichtenbiner, J Opara, R Mittenzwei, C Keene, A Nolan; University of Washington

Background: Traumatic brain injury (TBI) is a significant public health issue, serving as a leading cause of disability. Despite growing awareness, much of the existing research on TBI has focused primarily on male cohorts, leading to a gap in understanding sex differences in its pathophysiology. A better understanding of sex differences can aid in the development of personalized treatments and accurate prediction of outcomes.

Methods: Our research investigates the role of chronic neuroinflammation in TBI and our findings so far identified prominent changes in microglia, including an increase in perineuronal satellite microglia, but not in astrocytes or phosphorylated tau (p-tau) deposition in the orbitofrontal cortex (OFC) of male brain donors with a history of remote TBI compared to controls. Taking these observations to a mouse model, these perineuronal satellite microglia are found to modify neuronal excitability but lose this ability after injury, possibly contributing to network hyperexcitability and behavioral dysfunction. In this study, we expanded our analysis to female brain donors.

Results: Using quantitative immunohistochemistry, our preliminary results reveal similar significant microglial activation as measured by the percentage area of staining for IBA-1, as well as increases in satellite microglia without prominent astrogliosis or p-tau deposition in female remote TBI compared to controls. Our mouse model also shows that female satellite microglia modify neuronal excitability, but preliminary data suggests a different regulatory mechanism that is less dependent on P2Y12 receptors.

Conclusions: In summary, microglial response is prominent across male and female remote TBI in the OFC, but the exact mechanisms of how microglia function may be different and will affect future targeted therapeutic development in TBI.

165

Two cases of unusual sulcal phosphorylated tau aggregates in donors with a remote history of traumatic brain injury

A Penev, J Opara, R Mittenzwei, D Child, C Latimer, D Keene, A Nolan; University of Washington

Background: The relationship between traumatic brain injury (TBI) and later features of tauopathy , especially regarding sulcal aggregates of phosphorylated (p-tau) is still unclear and currently evolving.

Methods: At the University of Washington, we have established strong relationships with the local medical examiners to obtain brain donation and better evaluate community-associated TBI with a range of exposures. In this Pacific Northwest Brain Donor Network, we have identified two unique cases with histories of remote head trauma that exhibit unusual sulcal accumulation of p-tau.

Results: The first case was a 63-year-old female with a motor vehicle accident over 40 years prior to death involving full-body injuries and a long hospitalization; increasing confusion and short-term memory issues were noted to be progressing in the years prior to death. The second case was a 65-year-old male with a history of head trauma including a motorcycle accident 8 years prior to death associated with a chronic intraparenchymal hemorrhage following the incident and subsequent seizures as well as contact sports exposure in high school football and combat exposure in the military. In both cases, Alzheimer’s disease neuropathological change was low with a Braak stage III and both exhibited patchy age-related tau astrogliopahy (ARTAG) and agyrophilic grain disease (AGD)pathology. In addition, unusual sulcal p-Tau aggregates were observed in the neocortex (inferior parietal lobule, superior frontal sulcus, middle frontal gyrus, and anterior temporal lobe). The sulcal p-tau was found in neurons, astrocytes, and interestingly coiled bodies. Immunohistochemistry for 3R and 4R tau revealed only 4R positive tau.

Conclusions: Given the coiled bodies and only 4R staining pattern, these sulcal lesions might represent an unusual sulcal agryophilic grain disease pathology associated with traumatic brain injury. Regardless, these findings suggest a wider range of sulcal tau deposition might occur in the context of TBI that is not compatible with chronic traumatic encephalopathy neuropathology.

Posters: Vascular/stroke

166 *NOTE:* Moved to a platform presentation.

Characterization of the ischemic penumbra using MRI and 3D histology: Proof-of-principle case analysis

R Nanjappa [1], A Ayyappan [2], R Verma [2], J Jayakumar [2], K Ram [2], R Rangaswami [3], M Sen [4], R James [4], A Manesh [4], G Varghese [4], D Nauen [5], R Folkerth [6], M Sivaprakasam [7]; [1] Sudha Gopalakrishnan Brain Center, Indian Institute of Technology, Madras, [2] Sudha Gopalakrishnan Brain Centre, Indian Institute of Technology, Madras, India, [3] Sri Ramachandra Institute of Higher Education and Research, Chennai, Tamil Nadu, India, [4] Christian Medical College, Vellore, Tamil Nadu, India, [5] Johns Hopkins University School of Medicine, Baltimore, MD, USA, [6] Icahn School of Medicine at Mount Sinai, New York, USA, [7] Indian Institute of Technology, Madras, Chennai, India

Background: Ischemic stroke remains a significant cause of morbidity and mortality, with limited rational therapeutic options, despite extensive modelling in experimental animals. Translational progress will require better cellular characterization directly in human tissue, particularly of the ischemic penumbra as potentially “salvageable” in the acute and subacute clinical setting. In this study, we present a comprehensive multimodal approach employing premortem and postmortem MRI for definition of the ischemic core and penumbra, followed by whole brain histology.

Methods: The specimen (69-year-old man with COVID-19 and a 20-day course of multiple strokes) was fixed, cryoprotected in graded sucrose, and sectioned at 20 µm, with serial standard stains and immunohistochemistry for HIF1α, fibrinogen, CD68, GFAP, collagen 4, and CD34.

Results: Based on gross examination, block face imaging and H&E staining, different regions of interest were identified for comparative analysis: (a) cortical region with subacute ischemic infarct core and penumbra (confirmed on MRI), with focal reperfusion haemorrhage; (b) focus of cortical region with spongiosis and acute neuronal changes; and (c) cortical regions without apparent ischemia. Digital 3D reconstruction of scanned histological sections enabled mapping of cellular changes across neuroanatomical regions. For the subacute infarct, the core was devoid of intact neurons and GFAP+ glia, and of CD34+ and collagen 4+ microvessels, but was densely infiltrated by CD68+ macrophages, as anticipated. In the peri-infarct (penumbral) regions, clasmatodendrosis (fragmented glial processes) accompanied perivascular fibrinogen deposition (blood-brain barrier insufficiency). The subacute infarct penumbra, the acutely ischemic occipital cortex, and, surprisingly, some “normal-appearing” cortical regions were notable for clear HIF1α immunoreactivity of neurons, glia, and even vascular wall cells.

Conclusions: We propose that our multimodal-multiscale approach bridges neuroimaging with neuropathology, offering novel insights into the spatial and temporal progression of ischemic stroke including the penumbra and “normal-appearing” areas, potentially amenable to therapeutic intervention. Additional cases are currently in process in our laboratory.

167

Distinct patterns of vascular smooth muscle degeneration in cerebral small vessel diseases: A large-scale 3D structural analysis

R Saito [1], K Tainaka [2], H Hayashi [1], M Ozawa [1], O Onodeara [3], A Kakita [1]; [1] Department Pathology, Brain Research Institute, Niigata University, [2] Department of System Pathology for Neurological Disorders, Bain Research Institute, Niigata University, [3] Department Neurology, Brain Research Institute, Niigata University

Background: Although vascular smooth muscle cell (VSMC) degeneration is a cardinal feature of cerebral small vessel diseases (SVDs), disease-specific patterns of VSMC loss remain unclear. This study attempted to clarify the spatial patterns of VSMC loss in hereditary and sporadic SVDs using 3D analysis.

Methods: The postmortem brains of patients with CADASIL and HTRA1-related SVD (HRSVD; n = 2 each), sporadic SVD (sSVD; n = 2), and controls (n = 4; 2 young, 2 old) were studied. We evaluated the percentage of segments showing smooth muscle actin (SMA) loss, categorized as main, sub-, and white matter branches in the frontal lobe, using 3D analysis of chemically cleared specimens.

Results: We identified 442 vascular units comprising 5582 segments. Quantitatively, in order of severity, total SMA loss was most severe in HRSVD (71.0%), followed by CADASIL (58.1%), sSVD (37.5%), and elderly controls (28.6%). The distribution of SMA loss predominantly involved the main branches exclusively in HRSVD, while in other SVDs, including elderly controls, sub-branches were predominantly affected. This finding was further supported by cluster analysis.

Conclusions: Our findings suggest that SVDs can be categorized on the basis of whether VSMC loss occurs predominantly in the main or sub-branches, possibly as a result of disease-specific pathomechanisms that might serve as therapeutic targets.

168

Diffuse Cerebral, Brainstem, and Cerebellar Fat Emboli Occurring in the Context of Abdominal Compartment Syndrome and Soft Tissue Injury

J Houpt [1], Y Li [1], E Tugaleva [2], R Jacques [1], L Ang [1]; [1] Department of Pathology and Laboratory Medicine, London Health Sciences Centre, London, ON, CA, [2] London Health Sciences Centre Department of Pathology and Laboratory Medicine

Background: Cerebral involvement by fat emboli is predominantly thought of as a complication of traumatic injury or surgical repair of long bones. However, it may also be encountered in other clinical circumstances including bone marrow transplant, sickle cell disease, pancreatitis, acute hepatic necrosis, cardiopulmonary bypass, and soft tissue injury. The mechanical theory of fat embolus formation suggests that fat globules are released into the venous system directly from the marrow in cases of long bone trauma. In contrast, the biochemical theory posits that free fatty acid release is mediated by an inflammatory response and may explain cases of fat embolism formation in other circumstances.

Methods: We report on a case of a woman in her 50s who developed abdominal compartment syndrome due to ascites and volume overload following an orthotopic heart transplant, necessitating several decompressive laparotomies. She unfortunately passed away days later in the context of multi-segmental small bowel necrosis.

Results: At autopsy, innumerable well-defined hemorrhagic foci were present throughout the bilateral cerebral, midbrain, pontine, and cerebellar white matter. Microscopically, these corresponded to an abundance of punctate hemorrhages with predilection for grey-white matter junctions. Most of these were centered around blood vessels containing round to ovoid clear spaces, some of which appeared multilobulated with intervening membranes. Fat content in these clear spaces was confirmed via osmium impregnation.

Conclusions: This case is a rare illustration of the neuroautopsy findings of diffuse cerebral fat emboli occurring in the absence of long bone trauma, and highlights the importance of considering non-traumatic fat embolus formation via alternate pathophysiological mechanisms.

Posters: Demyelinating/inflammatory

169

Neuropathologic findings in a case of GAD65+ Autoimmune Epilepsy with mechanistic insights from HD Visium Spatial Transcriptomics

A Denney [1], A Wohlfert [1], A Granholm-Bentley [1], A Piquet [1], K Jones [1], A Toland [2], S Guzman [1]; [1] University of Colorado Anschutz Medical Campus, [2] Children's Hospital Colorado

Background: Inhibitor signaling in the brain relies on GABA, catalyzed by glutamic acid decarboxylase-65 (GAD65). Low-titer GAD65 disease can be a diverse category of diseases, which include limbic encephalitis and autoimmune epilepsy. Notably, GAD65 autoimmune epilepsy is an important cause of refractory and recurrent seizures that are thought to be underdiagnosed among epilepsy cases. We hypothesize that complete neuropathologic characterization and spatial transcriptome profiling in autoimmune epilepsy will help us understand the pathogenesis of low-titer GAD65 disease.

Methods: Herein we describe a case of a 21-year-old woman with refractory seizures, later diagnosed with GAD65+ autoimmune epilepsy. She underwent a right temporal lobectomy, during which tissue from the hippocampus was biopsied for further analysis. The hippocampus was pathologically diagnosed as Hippocampal Sclerosis, ILAE type 1. The patient was later found to have a positive low-titer GAD65 autoantibody. IRB consent was obtained from Children’s Hospital Colorado and brain tissues were analyzed by immunohistochemistry and evaluated by a board-certified neuropathologist. Spatial transcriptomic analysis was performed on hippocampal tissue using 10X Genomics HD Visium platform.

Results: Hippocampal tissue showed diffuse T cell inflammation and heavy reactive microgliosis, as well as loss of pyramidal neurons in CA1 and CA4. Spatial transcriptome profiling identified several relevant canonical pathways such as significant inhibition of GABA and overexpression of glutamate, overall generating excitotoxicity and enriching for oxidative stress and cellular stress response pathways. The Class I MHC-mediated antigen processing canonical pathway was also significantly increased compared to normal control. Interestingly, the KEGG Pathway Analysis highlighted several viral entities following pseudo-bulking of the data.

Conclusions: This case emphasizes the role of GAD65 autoantibodies in disrupting hippocampal GABAergic signaling. Here we demonstrate for the first time the detailed spatial gene expression profiling within a hippocampus affected by autoimmune epilepsy, with viral entities potentially playing a role in propagating the underlying disease.

170

Consecutive brain biopsies illustrate the histological evolution of acute hemorrhagic leukoencephalitis

E Pai [1], F Jones [2], A Banihashemi [1], J Orthmann-Murphy [3], E Lee [1]; [1] Hospital of the University of Pennsylvania, [2] Mayo Clinic, [3] Hospital of University of Pennsylvania

Background: Acute hemorrhagic leukoencephalitis (AHLE), also known as Weston Hurst syndrome, is a rare fulminant encephalopathy, often preceded by viral infection, including COVID-19, or vaccination. Due to high mortality, diagnosis is usually made empirically based on clinical presentation allowing for early intervention, or at the time of autopsy. Brain biopsies for diagnostic purposes are rarely performed. Here, we present a case of AHLE with two consecutive biopsies, illustrating the histologic evolution of the disease.

Methods: A 31-year-old previously healthy female presented with 1 day of progressive fever, confusion, headache, blurry vision, and left-sided weakness, following recent upper respiratory symptoms. Neurological examination revealed inattention, left hemineglect, left homonymous hemianopsia, left hemiparesis, and left hyperreflexia with Babinski sign present. Meningismus was not observed. Brain MRI showed a rapidly evolving large gadolinium-enhancing right parieto-occipital lesion with a differential diagnosis including tumefactive demyelination, acute demyelinating encephalomyelitis (ADEM), hemophagocytic lymphohistiocytosis, or central nervous system (CNS) infection. Despite broad-spectrum antimicrobial treatment and high-dose steroids, the patient rapidly progressed to a comatose state due to worsening cerebral edema and herniation. On day 2, a brain biopsy was performed to guide clinical management. A second craniectomy was conducted on day 4 for decompression, with additional brain tissue collected for histological examination.

Results: The initial biopsy revealed early-stage AHLE, characterized by neutrophilic-predominant perivascular inflammation, blood extravasation following venular wall damage, and rare organized ball-like hemorrhages. The subsequent biopsy showed later-stage AHLE characterized by multifocal well-organized ball-like hemorrhages. This was accompanied by decreased neutrophilic inflammation, increased perivascular macrophage aggregates, and evidence of parenchymal damage, as indicated by myelin phagocytosis and spheroid formation around affected venules.

Conclusions: This case presents the first report of consecutive brain biopsies showing the histological progression of AHLE at different stages of the disease.

171

Amyotrophic lateral sclerosis in a patient with a 30-year history of multiple sclerosis

E Russler-Germain, R Schmidt, S Smith, A Cross, S Dahiya; Washington University School of Medicine

Background: Multiple sclerosis (MS) is a presumed autoimmune disease targeting central nervous system white and gray matter. Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease causing selective loss of upper and lower motor neurons. Accumulating evidence suggests immune-mediated mechanisms play a role in ALS neurodegeneration. Here, we report the case of a 65-year-old woman diagnosed with MS 30 years prior to ALS development. Her MS presented with dizziness. She was treated with glatiramer acetate for 5 years and natalizumab for 4 years, the latter stopped for recurrent sinusitis. She received rituximab infusions for 3 years, stopping due to bilateral lung infiltrates. Early 2021, the patient developed left foot drop progressing to right foot drop 6 months later, with no new lesions on brain/spinal cord MRI and physical examination suggesting peripheral nervous system dysfunction. Electrodiagnostic studies corroborated an ALS diagnosis. Genetic testing of ALS-associated loci was negative for pathogenic gene variants. The patient died from ALS in 2023.

Methods: Neuropathologic gross and microscopic evaluation of the dura mater, brain, and spinal cord were performed through autopsy.

Results: Gross and microscopic examination of the brain revealed numerous small white matter lesions consistent with inactive MS plaques. The spinal cord showed inactive MS plaques within the cervical dorsal columns and inferior thoracic lateral cord. Anterior horn motor neurons were decreased at all spinal cord levels, with rare Bunina bodies in remaining neurons. There was lateral corticospinal tract degeneration. Phosphorylated TDP43 antibody labeled inclusions within anterior motor neurons and glia, consistent with ALS. Finally, the hippocampus showed low-stage Alzheimer disease neuropathologic change (ADNC).

Conclusions: While there is no appreciable link between MS and ALS disease mechanisms, case reports of co-occurrence have emerged, including this patient. Further investigation may be necessary to resolve any possible relationship between MS and ALS pathologies and/or association of ALS development with MS therapies.

172

20-Year-Old Male with X-linked Adrenoleukodystrophy: A Case Report with Postmortem Findings

D Mack, S Chen, S Moore; University of Iowa Healthcare

Background: Adrenoleukodystrophy (ALD) is a rare X-linked peroxisomal disorder caused by mutations in the ABCD1 gene, a peroxisomal membrane transporter protein involved in the degradation of very long-chain fatty acids (VLCFA). ABCD1 mutations cause VLCFA accumulation in all tissues, with pathological changes primarily affecting the nervous system and adrenal glands. ALD phenotypes include cerebral leukodystrophy, myeloneuropathy, and adrenal insufficiency manifesting across a wide age range, without genotype-phenotype associations. Many individuals with ALD live into middle age, while others develop a rapidly progressive form of cerebral leukodystrophy resulting in death within 1-3 years of onset.

Methods: We report a 20-year-old male diagnosed with ALD at 18 months of age through familial screening. The maternally inherited ABCD1 variant is novel: c.1623G>C, p.A413P. He exhibited adrenal insufficiency during infancy. His disease remained stable until early adolescence when he developed loss of balance, frequent falls, spastic gait, weakness, and decreased sensation, bilaterally. A rapid, dramatic decline in motor function began at age 20 and progressed over 10 months marked by worsening sensorimotor deficits, leading to fatal aspiration pneumonia.

Results: Postmortem examination revealed characteristic lesions of ALD within the central and peripheral nervous system (CNS and PNS). Leukodystrophy with marked gliosis and perivascular inflammation was noted in the splenium, posterior limb of the internal capsule, midbrain, pons, medulla, and cerebellar peduncles. There was significant myelinated axon loss from the spinal cord, especially severe in the cervical dorsal columns and lumbar corticospinal tracts. Examination of peripheral nerves and muscle demonstrated distal greater than proximal neuropathic changes.

Conclusions: This case introduces a previously undescribed ABCD1 mutation in an individual with infantile onset, neurological progression in his teens, and rapid decline leading to death at age 20. Thorough autopsy examination of the CNS, PNS, and muscle demonstrated widespread lesions that add to the body of literature describing this heterogeneous disease.

Posters: Developmental/pediatric

173

Insights in underlying pathophysiology of brain malformations associated with VRK1-related syndrome derived from fetal neuropathology

S Brock [1], A Tessier [2], O Monestier [2], V Benoit [2], F Debray [3], L Ghassemi [4], K Van Berkel [5], F Vauthier [2]; [1] Department of Pathology, Universitair Ziekenhuis Brussel, Brussels, Belgium, [2] Institut de Pathologie et de Génétique, Gosselies, Belgium, [3] Metabolic Unit, Department of Medical Genetics, Sart-Tilman University Hospital, Liège, Belgium, [4] Department of Gynecology and Obstetrics, Hôpital Citadelle, Liège, Belgium, [5] Center for Medical Genetics, Reproduction and Genetics, Reproduction Genetics and Regenerative Medicine, Vrije Universiteit Brussel (VUB), UZ Brussel, Brussels, Belgium

Background: Biallelic variants in VRK1 have been described in patients with heterogeneous phenotypes with childhood or adult-onset of progressive upper and lower motor neuron disease. Prenatal onset and neurodevelopmental disorders associated with VRK1 have rarely been described in the literature. Here, we report the first fetal cases and first neuropathological examination of the brain in patients with pathogenic variants in VRK1.

Methods: Clinical data: Two fetuses of consecutive pregnancies of second-degree consanguineous parents presented with microcephaly prenatally during the early second trimester. Termination of pregnancy was performed for both cases.

Results: Post-mortem examination showed overlapping features including facial dysmorphisms, microencephaly, and brain malformations. These included agenesis of the corpus callosum; absent gyration and reduced neuronal density with a thin cortex, suggestive of a simplified gyral pattern; abnormal corticospinal tracts and fragmentation of the capsula interna; and dysmorphic basal ganglia and hippocampi. Whole exome sequencing identified a homozygous probably pathogenic variant in VRK1 (NM_003384.3, GRCh38):c.238C>G p.(Leu80Val) in both fetuses. The variant is located in a previously reported cluster close to the ATP-binding site. The parents were heterozygous for the variant.

Conclusions: Neuropathological examination in these cases give first insights in the underlying pathophysiological process of biallelic pathogenic variants in VRK1 in humans. Our findings are evocative of a combination of impaired neuronal proliferation, of a neuronal migration deficit, and abnormal axon guidance.

174

Histopathologic Characterization of Focal Cortical Dysplasia in DEPDC5-Related Epilepsy

J Newman [1], A Toland [2], S Guzman [2], H Vogel [1]; [1] Stanford Health Care, [2] University of Colorado

Background: Mutations in proteins involved in the regulation of the mTOR pathway have emerged as potential heritable causes of medically refractory epilepsy. Specifically, mutations in proteins which constitute the multimeric GATOR1 repressor complex, including DEPDC5, NPRL2 and NPRL3 have been increasingly linked to focal familial epilepsies. Despite the emerging importance of this epileptic mechanism, thorough histopathologic and immunohistochemical characterization of lesional DEPDC5-mutant cases are poorly described in the literature.

Methods: 3 cases of focal cortical dysplasia with confirmed pathogenic DEPDC5 alterations are identified: 2 cases from University of Colorado Anschutz Medical Campus and 1 case from Stanford Health Care. Histopathologic analysis of representative sections are performed and described in detail. Immunohistochemical studies for glial, neuronal, and inhibitory intraneuronal are performed and analyzed.

Results: Two of the three cases show focal cortical dysplasia type IIA, and the remaining case shows findings consistent with bottom-of-sulcus dysplasia. This is the first report of bottom-of-sulcus dysplasia associated with a DEPDC5 mutation. One case with focal cortical dysplasia type IIA shows a unique pattern of reduced and disorganized GABA inhibitory interneurons.

Conclusions: This series highlights the diverse array of potential histopathologic findings in cases of focal cortical dysplasia in DEPDC5 mutations, along with potential unique patterns. Neuropathologists should be keen on identification of these patterns, as epilepsy cases associated with mTOR regulatory protein mutations are emerging as an inheritable and potentially treatable form of epilepsy.

175

Exome Sequencing in a Grey Matter Heterotopia Cohort Identifies Novel Roles for Neurodevelopmental Genes.

M Lukacs [1], D Harris [2], C Prasad [2], C Walsh [2], J Neil [2]; [1] Brigham and Women's Hospital, [2] Boston Children's Hospital

Background: Grey matter heterotopias (GMH) are a group of neurodevelopmental disorders defined by nodules of ectopic neurons that result from the abnormal migration of neuronal precursors. These disorders, including Periventricular Nodular Heterotopia, Subcortical Band Heterotopia, and Subcortical Heterotopia, display a variety of neurological symptoms including epilepsy, developmental delay, motor delay, and cognitive impairment. Previous studies have identified over 146 causative genes and chromosomal loci associated with GMH indicating many diverse genes and molecular pathways are involved in the pathogenesis. However, up to 50% of cases of GMH remain without a genetic diagnosis and few therapies exist to treat the underlying pathology.

Methods: We performed exome sequencing in 158 individuals with GMH to identify causative genes.

Results: We identified a number of known causative variants in GMH (including DCX, FLNA, KLHL20, NEDD4L, KAT8, RNU4-2), as well as several previously identified neurodevelopmental genes (including AGO1, FRMDP4, and MORC2) that have not previously been associated with GMH.

Conclusions: Several of these candidate genes are involved in transcriptional repression and implicate this process in neuronal development and migration. These findings expand the role of these neurodevelopmental genes and imply an early role in neuronal migration.

176

A Practical Atlas of the Developing Human Brain for the Neuropathologist

R Risgaard [1], M Duran [2], K Han [2], S Salamat [2]; [1] University of Wisconsin-Madison, [2] University of Wisconsin School of Medicine and Public Health

Background: The ontogeny of the human brain is a remarkably intricate process that predominantly occurs in the prenatal period. This developmental trajectory is defined by a highly regulated cascade of morphogenetic and anatomical events that work in concert to generate one of the most sophisticated and computationally complex organs within the human body. The identification of “where”, “when”, and “how” things go awry in this process is the job of the Neuropathologist. The difficulty of this task, however, is underscored by the heterogeneous and asynchronous nature of maturation across diverse brain regions. This developmental heterochrony presents a formidable challenge in accurately characterizing pathological deviations from the normative neurodevelopmental sequence.

Methods: This study involves the analysis of >100 prenatal/neonatal autopsy cases ranging from 18-weeks of gestation to 6 months postnatal development. Analysis was performed on formalin fixed, paraffin-embedded tissue sections using H&E. Brain regions to be analyzed in this study include the cerebral cortex, striatum, thalamus, midbrain, pons, medulla, and cerebellum.

Results: Here, we present a summarized, H&E-based practical atlas of the major morphological and morphometric parameters of development and maturation across select brain regions. We highlight the relative thickness of layers of the developing cerebellum, along with the morphologic features of the pyriform cell layer as a key parameter for defining nervous system maturation.

Conclusions: This practical atlas of morphological parameters derived from H&E analysis of over 100 prenatal and neonatal autopsy cases provides a valuable resource for neuropathologists and researchers studying human brain development. By highlighting key parameters, this study offers critical benchmarks for assessing development and maturation. Our findings also underscore the importance of considering regional heterogeneity and developmental heterochrony when evaluating potential pathology. This work contributes to a more nuanced understanding of the complex prenatal and early postnatal neurodevelopmental processes with the goal of enhancing diagnostics of neurodevelopmental pathologies at autopsy.

177

Brain-restricted chromosome 1q gains underlies focal epilepsy with hyaline astrocytic inclusions

H Adle-Biassette [1], A DE MEULEMEESTER [2], M Scopin [2], S Lina [2], R Checri [3], C Nava [4], L El Khattabi [4], M DOLADILHE [2], S FERRAND SORBETS [5], G DORFMULLER [5], M CHIPAUX [5], S BALDASSARI [2], S BAULAC [2]; [1] Université de Paris Cité, service d'Anatomie Pathologique, AP-HP, Hôpital Lariboisière, DMU DREAM, Biobank BB-0033-00064, UMR 1141, INSERM, 75010, Paris, France, [2] Institut du Cerveau-Paris Brain Institute-ICM, Sorbonne Université, Inserm, CNRS, Hôpital de la Pitié Salpêtrière, F-75013 Paris, France, [3] Institut du Cerveau-Paris Brain Institute-ICM, Sorbonne Université, Inserm, CNRS, Hôpital de la Pitié Salpêtrière, F-75013 Paris, France; Department of Pediatric Neurosurgery, Rothschild Foundation Hospital EPICARE, 75019, Paris, France, [4] Department of Medical Genetics, AP-HP, Sorbonne Université, Hôpital de la Pitié Salpêtrière, F-75013 Paris, France, [5] Department of Pediatric Neurosurgery, Rothschild Foundation Hospital EPICARE, 75019, Paris, France

Background: Brain somatic mosaicism is an emerging cause of neurological disorders, including cortical malformations and epilepsy. Here, we aimed to identify the genetic basis of focal epilepsy with hyaline astrocytic inclusions, a distinct neuropathological entity.

Methods: We analyzed matched blood and surgically resected brain tissue from eight children with drug-resistant focal epilepsy and hyaline astrocytic inclusions using deep whole-exome sequencing, genome-wide copy number analysis, and fluorescence in situ hybridization (FISH). Laser capture microdissection of astrocytes was performed, followed by targeted sequencing.

Results: We identified brain-specific mosaic chromosome 1q gains in 6 out of 8 patients, which were absent in blood. Variant allele analysis revealed that these gains originated from maternal meiosis, suggesting subsequent loss from non-neural lineages through postzygotic rescue. The 1q gain was significantly enriched in astrocytes with hyaline inclusions.

Conclusions: We establish chromosome 1q gain as a genetic cause of focal epilepsy with hyaline astrocytic inclusions and demonstrate that brain-restricted mosaicism can arise through postzygotic rescue of meiotic errors. Our findings highlight tissue-specific mosaicism as a novel disease mechanism and suggest that astrocyte-specific chr1q gains contribute to epileptogenesis in this distinct clinicopathological entity.

178

Multimodal single-cell analyses of the early postnatal Down Syndrome brain

R Risgaard, ; University of Wisconsin-Madison

Background: Down syndrome (DS), resulting from genetic perturbations of chromosome 21, is the most common genetic cause of intellectual disability, accounting for approximately one-third of all mild to moderate intellectual disabilities in school-aged children. The cognitive phenotype associated with DS begins in early infancy and progresses to have significant consequences on long-term academic, occupational, and daily functioning. The early onset of these deficits suggests that alterations in neurodevelopmental processes occur during the initial stages of brain development in DS.

Methods: This study aims to elucidate the cellular and molecular correlates of cerebral cortical development and maturation in early postnatal DS, as a crucial step towards understanding the biological mechanisms underlying the cognitive and behavioral deficits observed in this condition. Recent advancements in multiomic single-cell and ATAC-sequencing technologies have emerged as powerful tools for investigating brain development in DS. These methodologies enable simultaneous profiling of gene expression and chromatin accessibility, facilitating the correlation between changes in regulatory elements and gene expression patterns.

Results: Here, we have profiled over 200,000 single cells from the early postnatal dorsolateral prefrontal cortex of postmortem brains affected by Down Syndrome and age-matched control samples. Our results demonstrate a broad homology of cell subtypes between trisomy 21 and control brains and identify non-neuronal cells as the most affected cell type in the early postnatal period.

Conclusions: Modern "multiomic" sequencing technologies provide unprecedented analysis of the complex gene expression and regulatory perturbations in the developing trisomy 21 brain, offering valuable insights into the underlying mechanisms of DS.

179

Friedreich ataxia is a hypoplastic and neurodegenerative disease

A Koeppen [1], J Mazurkiewicz [1], S Pelech [2], J Qian [1], C Sutter [3], P Feustel [1]; [1] Albany Medical College, [2] University of British Columbia, Vancover, BC, [3] Kinexus Bioinformatics Corporation

Background: One hundred fifty years have elapsed since Friedreich illustrated the lesion of the dorsal columns of the spinal cord, and trainees in neurology and neuropathology are still being taught that this lesion is the key to our understanding of Friedreich ataxia (FA). Measurements of spinal cord area and neuronal sizes in dorsal root ganglia (DRG), however, point to hypoplasia rather than degeneration. The disease also causes proliferation of satellite glial cells, inflammatory infiltration, and neuronophagia of the remaining DRG neurons.

Methods: Antibody microarrays; immunohistochemistry; double-label immunofluorescence; confocal microscopy

Results: Antibody microarrays show upregulation of phosphorylated KIT (KITpY936). On tissue sections, KITpY936 and its ligand, the stem cell factor (SCF) are increased in FA, which may be related to an unexpected over-expression of frataxin in satellite glia. The outstanding abnormalities of the dentate nucleus (DN) in FA are loss of large neurons and grumose reaction, a proliferation of GABAergic axonal terminals arising from Purkinje cells. Grumose reaction is also reactive with antibodies to mTOR and the mTOR-associated proteins Rictor and Raptor. The mTOR overexpression is unexplained but may be related to the proliferation of synaptic terminals in the DN.

Conclusions: Traditional neuropathology and recent proteomics support the conclusion that the pathogenesis of FA includes hypoplasia, superimposed inflammation, and selected proliferation of synapses.

180

Atypical Histopathology in a Surgical Case of Epilepsy Associated with Sturge-Weber Syndrome Complicated with Developmental Venous Anomaly

H Miyata [1], J Abe [2], R Honda [3], T Ono [3], S Miura [4], M Ito [4]; [1] Department of Neuropathology, Research Institute for Brain and Blood Vessels, Akita Cerebrospinal and Cardiovascular Center, [2] Akita University School of Medicine, [3] Epilepsy Center, National Hospital Organization (NHO), Nagasaki Medical Center, [4] Department of Pathology, National Hospital Organization (NHO), Nagasaki Medical Center

Background: Leptomeningeal angiomatosis in Sturge-Weber syndrome (SWS) is often accompanied by enlarged low-signals of the deep medullary veins, resembling developmental venous anomalies (DVAs), as seen on susceptibility-weighted magnetic resonance images (MRI); however, the co-occurrence of DVAs showing prominent vascular flow voids on T2-weighted MRI is relatively uncommon.

Methods: We present atypical histopathologic features observed in the surgical specimen from a 6-year-old girl with SWS suffering from early-onset intractable epilepsy associated with leptomeningeal angiomatosis and coexisting DVA in the left frontal lobe. Presurgical computed tomography and T2-weighted and contrast-enhanced MRI depicted the atrophic left frontal lobe with subcortical calcifications, subarachnoid enhancement, and DVA extending from the ipsilateral frontal periventricular white matter to the deep middle cerebral vein. She underwent resection of the left central and prefrontal regions and was seizure-free postoperatively.

Results: Histopathologic examination of the resected specimens revealed leptomeningeal angiomatosis, focal microscopic polymicrogyria, and cortical pseudolaminar sclerosis variably involving layers 2-3 or layer 4, i.e., FCD type IIIc. In addition to these findings characteristic of SWS, four atypical observations were noted: (1) nearly absent cortical calcification, (2) well-defined regions of fibrillary gliosis and prominent calcification surrounding the non-dilated veins in the subcortical white matter, (3) a focal cortical venous malformation, and (4) structural abnormalities in a proportion of arteries in the subarachnoid space, such as fibromuscular intimal thickening, degenerative internal elastic lamina, the irregular thickness of the tunica media, and foci of transmural calcification.

Conclusions: These findings, together with the organization of the intrinsic cerebral venous system, suggest that non-dilated white matter veins surrounded by calcified gliosis represent superficial medullary veins, and dilated veins represent deep medullary veins draining into the DVA and may serve as collateral venous drainage pathways to compensate for the dysplastic cortical and subarachnoid venous development. The arterial pathology may represent secondary regressive changes.

181

Caudal Pontomedullary Dysplasia (Brainstem Disconnection Syndrome) in a Term Neonate

S Belakhoua [1], S Karathanasis [2], F Dekio [2], M Snuderl [2], R Folkerth [3]; [1] NYU Langone Health, [2] NYU Grossman School of Medicine, [3] Icahn School of Medicine at Mount Sinai

Background: "Congenital brainstem disconnection" is exceedingly rare, with only single case reports available.

Methods: We report a term 2000g girl (< 3rd percentile), Apgars 5 and 8, with microcephaly, poor reactivity, right facial droop, and absent suck and gag reflexes. Magnetic resonance (MR) imaging showed absence of the pons, small cerebellum, and deficient vertebrobasilar system. Karyotype and chromosomal microarray were normal. She died at 20 days.

Results: Tetralogy of Fallot, vascular ring, abnormalities of right lung lobation and right ribs, and intestinal malrotation were found at autopsy. Brain examination (weight, 269g; < 5th percentile) showed open opercula and asymmetric temporal sulcation. The proximal pons had a globular shape, with cranial nerve (CN) roots I-III and V visible. A segmental "gap" extended to mid-medulla, which was hypoplastic. Cerebellar hemispheres were foliated, but small. Basal vessels were artifactually avulsed and could not be evaluated. Rostral to the "gap", microscopy showed hypoplasia of cerebral peduncles and pontine descending tracts; disorganized heterotopic bundles of axons traversing in a side-to-side or circumferential fashion in the tegmentum and across the roof of the fourth ventricle (reminiscent of displaced Probst bundles in callosal agenesis); CN nuclei and roots of III-V were visible. Caudal to the "gap", the pyramids were hypoplastic, but CN nuclei and/or roots V-VII, IX, X, and XII were visible. Heterotopic rhombic lip-type neurons were seen along the ventrolateral aspects of both rostral and caudal brainstem segments, although olivary, arcuate, and basis pontis nuclei were not recognizable as such. The cerebellum had normal Purkinje and granular layers; the dentate was globular. Spinal cord had thin lateral corticospinal tracts.

Conclusions: While homeobox gene defects have been postulated among the rare examples of "brainstem disconnection", we also entertain an early (5th gestational week) disruptive vascular event, since cellular components specified by known homeobox genes are present, but disorganized.

182

An autopsy case of hyaline protoplasmic astrocytopathy in a 17-year-old epileptic patient status post remote functional hemispherectomy

C Voyles, E Stalter, M Blessing, O Lopes Abath Neto; University of Iowa Hospitals and Clinics

Background: Hyaline protoplasmic astrocytopathy (HPA) is an underrecognized and incompletely understood disorder that has been reported in rare cases of refractory epilepsy, especially in Aicardi syndrome, as well as in other neurodevelopmental disorders, characterized by eosinophilic ameboid filamin A-containing inclusions in neocortical astrocytes.

Methods: We reviewed electronic medical records, performed gross examination of the brain, and examined H&E stained sections from multiple cortical and subcortical areas of both hemispheres. Immunohistochemical stains for GFAP, NeuN, OLIG2, PU.1, and neurofilament were performed for additional characterization.

Results: The patient was a 17-year-old male with a history of remote right functional hemispherectomy for refractory epilepsy, performed at age 6 months, with intellectual and motor disability, who died in the setting of pneumonia complicated by sepsis. Pathology from the early surgical resection specimen did not reveal HPA. Gross examination of the brain revealed asymmetric cerebral hemispheres due to a reduced volume of the right hemisphere, which contained a large area of cavitation spanning the frontal and temporal lobes and sparing the basal ganglia and thalamus, consistent with the history of functional hemispherectomy. Histopathological examination of sections from both hemispheres showed numerous haphazardly arranged astrocytes with eosinophilic ameboid to granular cytoplasm, variably distributed throughout all layers of the neocortex, and not present in deep gray matter structures. The inclusions were positive for GFAP and negative for NeuN, OLIG2, PU.1, and neurofilament.

Conclusions: In this autopsy case, hyaline astrocytic inclusions were diffusely distributed in neocortical areas but were not reported in the functional hemispherectomy surgical specimen 17 years prior, which suggests HPA may be a secondary process that develops as a later complication of epilepsy.

183

Congenital Brainstem Tumor: Novel Molecular Insights from a Fetal Case

Y Fisher [1], S Shinar [2], C Hawkins [3], E Miller [4], P Shannon [5]; [1] Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, ON, Canada, [2] Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [3] he Hospital for Sick Children, Toronto, ON, Canada, [4] The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada, [5] Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada

Background: Fetal brainstem tumors are rare, and obtaining adequate tissue for histology and molecular analysis is challenging. Herein, we present a case of a fetal pontine tumor detected by ultrasound at 32 weeks of a dichorionic diamniotic twin pregnancy. Fetal MRI revealed a large, expansile mass centered in the pons. Radiological differential diagnosis included diffuse midline glioma, or less likely, atypical teratoid/rhabdoid tumor or medulloblastoma.

Methods: At 35 weeks, feticide of the affected twin was performed, and an in-utero needle core biopsy of the brainstem mass was obtained. Histology, immunohistochemistry, next-generation sequencing (Illumina Nova-Seq 6000) and methylation profiling (Illumina Infinium Methylation EPIC array, DFKZ and NIH classifiers) were performed.

Results: Histology revealed an undifferentiated small round blue-cell tumor with a sheet-like growth pattern, focal infiltration and reactive astrocytosis. Immunohistochemistry showed diffuse synaptophysin positivity and retained INI-1 and BRG expression, supporting an initial diagnosis of medulloblastoma. Next-generation sequencing identified an in-frame deletion in exon 18 of PDGFRA (NM_006206.6, c.2522_2527delGAGACA, p.Arg841_Asp842del), involving the kinase domain. No oncogenic variants were found in IDH1, IDH2, TP53 or other cancer related genes. Methylation profiling classified the tumor as diffuse pediatric-type high-grade glioma, H3-wildtype, IDH-wildtype, RTK1 subtype. Subsequent immunohistochemistry confirmed GFAP positivity and H3 wildtype status.

Conclusions: Despite histological features resembling medulloblastoma, the non-classical location and radiological features prompted further investigations. The PDGFRA variant detected was previously reported, but not in CNS neoplasms. A missense variant at the same locus is a known oncogenic hotspot in several types of cancer, including pediatric diffuse glioma. Integration of histological and molecular features led to a final diagnosis of diffuse pediatric-type high-grade glioma, H3-wildtype, and IDH-wildtype. This case expands the spectrum of fetal brainstem tumors and underscores the role of molecular testing in refining the diagnosis in rare fetal CNS neoplasms.

Posters: Ophthalmic Pathology

184

Optic Pathway Glioblastoma/Malignant Optic Nerve Glioma (MONG) with Molecular Characterization in an Adult

H Highfield [1], K Sinicrope [2], D Sun [2], C Davidson [3]; [1] Norton Neuroscience Institute, CPA lab, Norton Healthcare, [2] Norton Neuroscience Institute, [3] Caris Life Sciences

Background: Optic pathway gliomas comprise the majority of lesions originating in the optic pathway for pediatric and adult patients. Pilocytic astrocytoma is the most common, comprising approximately 60% of lesions in pediatric patients and 38% of lesions in adult patients. Optic nerve glioblastoma is a rare, aggressive entity. Patients typically present with progressive decline of visual acuity, with a mean survival in adults of approximately seven months.

Methods: A 61-year-old woman without a clinical history of neurofibromatosis presented with vision loss in her left peripheral visual field that progressed to her right eye. MRI revealed a 2.5 x 1.9 x 1.3 cm solid, enhancing, circular lesion centered in the optic chiasm with involvement of the retro-orbital optic nerves and optic tracts abutting the infundibular stalk. The tumor was biopsied via a right parietal craniotomy.

Results: Sections show an infiltrative, high grade astrocytic neoplasm with foci of microvascular proliferation. Tumor cells are immunoreactive for GFAP and Olig2, with rare cells immunoreactive for p53. Tumor cells are negative for IDH1 R132H, and ATRX expression is retained. Up to 40% of tumor cell nuclei label with Ki67. NGS revealed a TERT promoter mutation, EGFR amplification (with EGFRvIII isoform), and homozygous deletion of CDKN2A/B, MTAP, and PTEN. The overall histopathologic and molecular profile of this tumor is consistent with Glioblastoma, IDH wildtype, CNS WHO grade 4. The patient was treated with palliative radiation and died approximately six months following diagnosis.

Conclusions: We present the molecular characterization of a rare optic pathway glioblastoma/malignant optic nerve glioma (MONG) with two defining molecular characteristics of IDH-wildtype Glioblastoma: TERT promoter mutation and EGFR amplification. To the best of our knowledge, this is the first reported NGS molecular profile for an optic pathway glioblastoma in an adult. Molecular characterization of these rare tumors may lead to improved tumor classification and patient treatment options.

185

CNS-like Ocular Tumors, A Series

A Gilani [1], A Toland [2]; [1] University of Colorado Anschutz Medical Campus, [2] University of Colroado Anschutz Medical Campus

Background: Many neuropathologists sign out a limited number of eye cases in their practices and/or ophthalmic cases may be handled by other subspecialty pathologists; yet, understanding the full range of tumors possible within the globe is important. We detail six tumors, seen in our practice, that were histologically similar to primary CNS tumors but instead presented within the eyeball itself.

Methods: Survey of in-house and consult ocular globe cases in our pediatric and adult practice since 2017. Standard immunohistochemical staining was performed with DNA methylation profiling in a single case. Cases of retinoblastoma or melanocytic tumors, although more common are not included in this series.

Results: One case each of solitary fibrous tumor (SFT), choroidal ganglioneuroma, massive retinal gliosis and hemangioblastoma and two of retinal astrocytic hamartoma were encountered amongst other ophthalmic cases, mainly retinoblastoma and melanocytic tumors. The SFT was clinically and radiologically confused with melanoma, while one of the retinal astrocytic hamartoma was clinically diagnosed as retinoblastoma and initially treated with intra-arterial chemotherapy. All cases manifested classic histological features and diagnoses were further confirmed by relevant immunohistochemistry (STAT6, TTF1, synaptophysin, GFAP and inhibin). One of the retinal astrocytic hamartoma cases received DNA methylation profiling. The patient with choroidal ganglioneuroma had a known germline NF1 mutation, while the germline TSC1/2 status of the patients with retinal astrocytic hamartoma was not available. All patients currently show no recurrence of their disease.

Conclusions: Tumors of the ocular neuroepithelium and dural coverings are identical to their CNS counterparts and can be confused clinically with the far more common intraocular tumors such as melanoma and Retinoblastoma. These cases serve as a reminder to neuropathologists of their occasional presentation within the ocular globe.

Posters: Peripheral nerve/muscle

186

A MICU1 mutation leading to adult-onset myopathy and cerebellar ataxia with unique pathologic and ultrastructural features

R Geyer, J Imitola, Q Wu; University of Connecticut School of Medicine

Background: Regulation of calcium influx is critical for proper mitochondrial function. This influx is regulated, in part by MICU1, a regulator of the mitochondrial Ca2+ uniporter, MCU. MICU1 mutations are associated with a disease known as myopathy with extrapyramidal signs, which is associated with a childhood onset of ataxia, variable other features (e.g. developmental delay, learning disability), and pathologic changes in skeletal muscle fibers and mitochondria. We report here a patient with a homozygous MICU1 mutation, cerebellar ataxia, cerebellar atrophy, and muscle weakness whose symptoms first presented at age 45.

Methods: Histological evaluation including H&E, histochemical and immunohistochemical stains. Electron microscope. Whole genome sequencing.

Results: Muscle biopsy revealed pathologic findings including variation in fiber size with atrophy of type II fibers, which has been previously observed in patients with MICU1 mutations. Our patient's muscle also showed several electron micrographic features not previously reported in patients with MICU1 mutations. Mitochondria are present in increased numbers, aggregate in the subsarcolemmal region, and have marked variation in size and shape with some mitochondria having excess or a concentric arrangement of cristae. Nuclear abnormalities include the presence of vacuolar and filamentous inclusions. Lastly, the sarcolemma has an indurated appearance.

Conclusions: Our findings represent the first case of a pathogenic MICU1 mutation leading to adult-onset disease with novel ultrastructural abnormalities.

187

Mitochondrial changes in muscle biopsies of patients with antisynthetase syndrome and other idiopathic inflammatory myopathies

A Murphy [1], G Mak [2], K Gordon [1], G Grafham [1], J Provias [1], M Tarnopolsky [1], J Lu [1]; [1] McMaster University, [2] University of Alberta

Background: Mitochondria are cytoplasmic organelles critical to cellular functions. In various diseases, mitochondrial dysfunction contributes to cell degeneration and death, often associated with variable inflammation. Targeting mitochondrial metabolism may provide a therapeutic approach for chronic inflammatory disorder. Mitochondrial abnormalities have been documented in inclusion body myositis (IBM), rarely observed in dermatomyositis (DM), and not reported in antisynthetase syndrome (ASS). This study aims to comparatively investigate muscle mitochondrial changes in patients with ASS, DM or IBM.

Methods: We examined skeletal muscle biopsies from patients diagnosed with idiopathic inflammatory myopathies (IIMs) according to the clinico-sero-morphological classification. Three IIM groups were studied: 16 patients with serologically-confirmed ASS (aged 28-77 years; median: 56), 16 patients with DM (aged 18-69; median: 42), and 11 patients with IBM (aged 52-82; median: 68). Histopathological and ultrastructural changes particularly in the mitochondria were systematically assessed.

Results: No significant age difference was observed between ASS and DM patients, while IBM patients were significantly older, possibly with more age-related mitochondrial changes. The serum creatine kinase levels, indicating muscle damage, were significantly higher in ASS compared to DM or IBM. Infrequent ‘ragged-red fibers” were found in 3/11 IBM and 2/16 ASS patients, but absent in DM patients. All groups showed variable ultrastructural mitochondrial changes including abnormal shapes in all patients and abnormal cristae in 16/16 ASS, 14/16 DM, and 11/11 IBM patients. Mitochondrial-associated, rod-like filamentous inclusions were found in 15/16 ASS patients, 9/11 IBM patients, and 6/16 DM patients ($p < 0.05$, DM versus ASS or IBM). Additionally, nuclear filamentous inclusions were identified in 5/16 ASS patients and 6/11 IBM patients but not found in DM patients.

Conclusions: ASS has prominent muscle mitochondrial abnormalities, like those in IBM and higher than those in DM patients. These abnormalities in muscular mitochondria may contribute to the pathogenic process of IIMs and present potentially targetable mechanisms for treatment.

188

Intracellular Amyloidosis in Peripheral Nerve and Skeletal Muscle Biopsies

G Grafham [1], G Mak [2], S Grant [1], A Murphy [1], S Baker [1], M Tarnopolsky [1], J Lu [1]; [1] McMaster University, [2] University of Alberta

Background: Amyloidosis is a multisystemic disease caused by abnormal deposition of amyloid fibrils typically in the extracellular matrix. The pathophysiological mechanisms driving cellular damage in amyloidosis remain poorly understood. This study aimed to investigate histopathological and ultrastructural characteristics of intracellular amyloid deposits in peripheral nerve and skeletal muscle biopsies.

Methods: We reviewed all cases of amyloidosis diagnosed through sural nerve and skeletal muscle biopsies at our institution, from 2000 to 2024, for evidence of intracellular amyloid fibrils. Biopsy specimens were routinely examined by histological/histochemical, and immunohistochemical stains, including Congo red for amyloid confirmation. Electron microscopy (EM) was also used to analyze the ultrastructural features. The distribution of amyloid deposits and other relevant features were systematically assessed.

Results: Amyloid deposits identified by positive Congo red staining and/or EM were found in 3 sural nerve and 5 thigh or deltoid muscle biopsies from 8 patients (aged 59 to 79 years) with neuromuscular disorders. Amyloidosis types were hereditary (ATTRv in 3 cases; AGel in 1 case), light-chain associated with multiple myeloma (2 cases), and unclassified (2 cases). All cases showed variable intracellular deposition of amyloid fibrils identified on EM, in addition to typical extracellular deposition. In the nerve specimens, intracellular amyloid deposits were seen within the blood vessel (BV) cells and Schwann cell bands of Büngner, with the latter forming distinctive, focally fibrillar inclusions. In the muscle specimens, amyloid deposits were confined to the BV cells, necrotic/degenerative myofibers, and peri-sarcolemmal areas with focal lobulation and/or destruction of myofibers.

Conclusions: This study demonstrates intracellular deposition of amyloid fibrils in peripheral nerve and skeletal muscle, suggesting that intracellular amyloidosis plays a significant role in cellular injury and dysfunction. Our findings provide new insights into the pathogenic mechanisms of peripheral nerve and skeletal muscle amyloidosis, advancing our understanding of the processes underlying amyloid-related neuromuscular disorders.

189

A complex diagnosis of nemaline myopathy requiring genetic testing and muscle biopsy correlation

A Jones [1], A Jones [2], V Smith [1], J Mandell [1]; [1] University of Virginia, [2] University

Background: A 3-month-old female born with hypotonia, weakness, feeding difficulties, and several congenital malformations underwent genetic testing for a suspected underlying myopathy. A complex genetic picture emerged, and muscle biopsy was performed for further diagnostic clarity.

Methods: Whole exome sequencing performed at Mayo Clinic was reviewed, and the muscle specimen underwent neuropathologic workup.

Results: Genetic testing was notable for compound heterozygous for two variants in the KLHL40 gene, c.557T>A (p.Leu186His) and c1153-3C>A. Additionally, a heterozygous mutation in RYR1, (c.10587C>G (p.Asp3529Glu)) was found. The pathogenicity of these variants was uncertain and their contribution to the clinical presentation was unclear. This necessitated additional workup via muscle biopsy. The muscle biopsy demonstrated rod-like inclusions and myopathic changes appreciable on both paraffin embedded and frozen tissue. A trichrome stain highlighted red/purple inclusions, and electron microscopy confirmed the presence of inclusions consistent with nemaline bodies. This was confirmed by ultrastructural analysis. Importantly, no central cores or targets were seen on NADH and SDH special stains or on ultrastructural analysis. Type II myosin immunohistochemistry (IHC) showed exclusivity of type I fibers; the remainder of the special stain and IHC panel was unremarkable.

Conclusions: Certain mutations in KHLH40 have been associated with nemaline myopathy 8, and mutations in RYR1 are associated with central core diseases, myopathy, and classically, malignant hyperthermia. Given the patient's complicated and non-specific clinical symptoms, determining the contribution of the identified genetic abnormalities to the phenotype was of utmost importance for accurate diagnosis. Our case is unique in that muscle biopsy findings were confirmatory of the presence of Nemaline myopathy, specifically related to mutations reported as variants of uncertain significance. The patient continues to improve with appropriate interventions.

190

Concurrent inclusion body myositis and sarcoid myopathy in a young patient

C Lee [1], K Quigg [1], A Stino [1], N Becker [1], K Conway [1]; [1]University of Michigan

Background: Rare cases have been reported of muscle biopsies showing simultaneous involvement of both sarcoidosis and inclusion body myositis (IBM). Most cases have occurred in older patients, leaving open whether the co-occurrence of disorders is related or coincidental. We herein describe muscle biopsy findings in a young patient showing concurrent diagnostic features of IBM and granulomatous inflammation consistent with sarcoid myopathy.

Methods: We review clinical history and findings from skeletal muscle biopsy processed in frozen and formalin-fixed, paraffin-embedded tissue as well as electron microscopy.

Results: The patient is a 41-year-old man with known sarcoidosis diagnosed based on enlarged mediastinal lymph nodes and splenomegaly as well as an elevated angiotensin-converting enzyme (ACE) level. He presented with five years of progressive proximal, primarily symmetric, upper and lower limb weakness. Panel-based genetic testing was negative for hereditary muscular dystrophies. Quadriceps biopsy showed an inflammatory myopathy with marked myopathic changes, endomysial fibrosis, lymphocytic inflammation, diffuse MHC class 1 expression, rimmed vacuoles, and accumulation of p62 and TDP-43 positive protein aggregates supporting a diagnosis of IBM. The biopsy also showed a large area of confluent granulomatous inflammation consistent with sarcoid myopathy. Electron microscopy additionally showed a prominent intranuclear inclusion composed of actin filaments with z-line formation.

Conclusions: The young age of this patient and presence both pathologies in the same muscle sample possibly suggests that IBM arose out of an immune-mediated process related to the patient's underlying sarcoidosis. Notably, electron microscopy showed a prominent intranuclear actin inclusion, somewhat atypical of the filamentous inclusions seen in IBM and more reminiscent of nuclear actin accumulation described in antisynthetase-syndrome related myopathy. While the findings in the biopsy and clinical history were not suggestive of antisynthetase syndrome, this ultrastructural feature raises the possibility that the patient's IBM is part of a broader "overlap" phenomenon or general inflammatory milieu.

191

Congenital Myasthenia with Unexpected Cytochemical, Immunohistochemical, and Electron Microscopic Findings

R Rebbe, K Moradi, S Beydoun, L Darki, A Mathew, K Hurth; Keck Medical Center of USC

Background: We report a 46-year-old Hispanic female with lifelong proximal muscle weakness and fatigability without ocular or significant bulbar symptoms.

Methods: She underwent a muscle biopsy.

Results: Histology revealed fat replacement and atrophy, along with fibers containing vacuoles, subsarcolemmal aggregates, and increased internalized nuclei. There was no significant inflammation. Involved fibers were predominantly Type 1. Aggregate material showed mixed NADH-TR activity, strong acid phosphatase, strong esterase activity, and was PAS positive. Aggregates were LC3 positive, and TDP43 negative. Muscle biopsy showed granular linear sarcolemmal positivity for C5b-9 (MAC) in the absence of MHC1 upregulation. Immunostain for dysferlin demonstrated marked sarcolemmal loss with retention of other sarcolemmal immunostains (sarcoglycan, dystroglycan, dystrophin). Electron microscopy demonstrated sarcolemmal folding, subsarcolemmal myelin whorls, tubular aggregates, and honeycomb structures. Genetic testing identified GFPT1 c.686-2A>G and p.Phe437Ile, c.1309T>A, pathogenic splice-site variant and variant of uncertain significance respectively, suggesting compound heterozygosity, and heterozygosity for pathogenic variant DYSF p.Ala927Leufs, c.2779del.

Conclusions: GFPT1 controls the flux of glucose into the hexosamine pathway, which catalyzes the formation of glucosamine 6-phosphate. Dysferlin, associated with the sarcolemma, is involved in muscle contraction and has been suggested to be involved in membrane regeneration and repair. Variants in either of their coding genes are associated with unrelated autosomal recessive myopathies. The biopsy suggests a mixture of pathological changes, possibly due to contributions from the multiple variants detected in GFPT1 and DYSF.

192

Limb girdle muscular dystrophy R28 in an infant. Expanding the spectrum of pathology
H Vogel, A Johnson, J Newman; Stanford University School of Medicine

Background: Autosomal recessive limb-girdle muscular dystrophy-28 (LGMDR28) is characterized by progressive weakness with an age of onset usually in the first decade, also into adulthood. Most patients have limited ambulation and respiratory insufficiency. Muscle biopsy findings are limited to two publications and range from unremarkable to nonspecific myopathic and dystrophic features.

Methods: A male infant was born at 40 weeks gestation; upon delivery, he was hypotonic and developed medication-respondent seizures. Creatine kinase was elevated to 7,500 in first days of life, which downtrended to 1,600 by discharge. He was re-admitted at 7 months of life for respiratory failure during RSV infection, and again noted to have significant hypotonia and proximal weakness requiring tracheostomy and gastrostomy tube placement.

Results: Nerve conduction studies and electromyogram demonstrated a myopathic process with mild irritative features. Chromosomal microarray was suggestive of first degree relative consanguinity. Genome sequencing revealed three variants of uncertain reported with possible myopathic features: D2HGDH, PLEC , and a VUS in HMGCR (c.1669A>T, p.T557S). Biochemical testing eliminated the D2HGDH variant as a candidate gene. While PLEC variants have known association with AR LGMD17 and epidermolysis bullosa, they are not disease causing and this patient had no skin findings or contractures. The mutant gene suspected to be disease causing for this patient was in HMGCR, resulting in a LGMD with neonatal presentation, although HMGCoA reductase activity was not assessed. Muscle biopsy at age 9 months showed dystrophic changes but was negative for multiple dystrophy-associated immunohistochemical studies. Frequent C5b-9 positive fibers were present. He experienced fatal hemorrhages, malignant hyperthermia and ADAMTS13 deficiency at 2 years of age. Autopsy confirmed dystrophic skeletal muscle as well as myocardial pathology consistent with dystrophy, and no cerebral dysmorphisms.

Conclusions: This case adds to the clinical and pathological spectrum of LGMDR28 by documenting neonatal onset and possible concurrent cardiac involvement.

193

Muscle building injection induced myositis

K Arkun [1], H Hamid [2]; [1] TUSM Tufts University Ned School, [2] TUSM

Background: 33-year-old male presented to emergency department with pain in right thigh. He has history of illicit testosterone and anabolic steroids injections with several past admissions for Inflammatory vs Infectious myositis. Was previously treated with steroids and antibiotics without improvement.

Methods: He is afebrile, without leukocytosis, normal CK and elevated CRP121. CT showed edema and concern for Infectious myositis and myonecrosis and hypoattenuating locules suspicious of injected material for bodybuilding. Pain and redness worsening necessitated IV antibiotics. MRI showed enhancement and no clinical improvement prompted muscle biopsy.

Results: H&E sections showed focal myonecrosis, fibrous replacement, fat necrosis, and sclerosing spaces, some hyalinized, some lined with macrophages along with chronic inflammation and rare giant cells. Surviving myofibers showed increased internal nuclei, internal splitting and whorled fibers, and checkerboard pattern and type 2 fiber predominance.

Conclusions: Bodybuilding injections can cause infectious myositis and muscle damage due to steroid effect, such type 2 predominance, and due to foreign body /oil induced reaction with hyalinized spaces /sclerosing lipogranulomatosis with fibrous tissue replacement and necrosis. Awareness of MRI and microscopy findings of injection myositis is important.

Posters: If you're unsure, Other

194

Pediatric Neurooncology Postmortem Research and the Children's Brain Tumor Network: Impact and Neuropathology Perspectives

M Blessing [1], B Frenkel [2], J Lilly [3], P Gustafson [4], J Stevens [5], K Yao [6], C Kopsidas [7], M Williams [8], T Torrescano [9], A Liljensten [10], C Campbell [11], A Backlund [12], N Diarra [13], D Dupal [14], J Mason [15], T Patton [15], C Stamy [16], M Frazer [17], M Hefti [18], A Resnick [15], K Eschbacher [18], M Santi-Vicini [19], M Koptyra [20], A Viaene [19]; [1] University of Iowa / Carver College of Medicine, [2] Children's Hospital of Philadelphia Center for Data Driven Discovery in Biomedicine, Gift from a Child, Children's Brain Tumor Network, [3] Children's Hospital of Philadelphia Center for Data Driven Discovery in Biomedicine, Children's Brain Tumor Network, [4] Swifty Foundation, [5] Seattle Children's Biorepository and Precision Medicine, Gift From A Child, [6] Seattle Children's Hospital, Gift From A Child, [7] Children's National Hospital, Gift From A Child, [8] Ann & Robert Lurie Children's Hospital of Chicago, Gift From A Child, [9] Orlando Health Arnold Palmer Hospital for Children, Gift From A Child, [10] Stanford School of Medicine Monje Lab, Gift From A Child, [11] Weill Cornell Medicine, Children's Brain Tumor Project, Gift From a Child, [12] Weill Cornell Medicine, Gift From A Child, [13] Children's Hospital of Philadelphia Center for Data Driven Discovery in Biomedicine, Children's Brain Tumor Network, [14] Children's Hospital of Philadelphia Center for Data Driven Discovery in Biomedicine, [15] Children's Hospital of Philadelphia Center for Data-Driven Discovery in Biomedicine, Children's Brain Tumor Network, [16] University of Iowa Stead Family Children's Hospital, [17] University of Iowa, [18] University of Iowa and Carver College of Medicine, [19] Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, [20] Children's Hospital of Philadelphia Center for Data Driven Discoveries in Biomedicine, Gift from a Child, Children's Brain Tumor Network

Background: Primary brain tumors remain the prevalent cause of pediatric cancer deaths. Postmortem donation protocols (PDP) are increasing in clinical trials and research efforts including molecular characterization and targeted therapy response, while honoring patient and family wishes. "Rapid" and institution-specific PDP exist; however, most collections stem from participation in national initiatives. Neuropathologists are increasingly ethically and professionally compelled to incorporate PDP into practice. This study describes the value and challenges of postmortem pediatric neurooncologic tissue collection, emphasizing neuropathologist perspectives.

Methods: De-identified data including demographics, tumor type, postmortem interval, and molecular results was requested from Children's Brain Tumor Network (CBTN), encompassing The Swifty Foundation and Gift from a Child. Postmortem interval (PMI) was compared to molecular testing success. A preliminary subset of CBTN PDP -participating neuropathologists were surveyed to ascertain benefits and challenges. IRB guidelines were followed.

Results: Thirty-four institutions participate in CBTN, resulting in 7,600 enrolled patients, 74,950 research samples, and 412 projects. 1,084 participants were deceased; 503 (46%) underwent PDP. PMI data was available from 8 institutions and 254 samples (44% DIPG/DMG H3K27-altered; 22% HGG; 9% MB; 25% other) and ranged from < 6h-6d (median: 12-24h). WGS was successful in 314/503 (PMI range: < 8 to >72h; (median: 12-24h). RNAseq was successful in 166/503 (PMI range: < 8 to >72h (median: 24-48 h). Cell lines were attempted in 38 (50% success in PMI < 24h; 30% success in PMI 24-72h). Neuropathologist benefit included receipt of molecular data, collaborative opportunities, and professional fulfillment; participation was optimized by implementing alongside other research protocols. Challenges included transportation, clinical workload, after-hours autopsy support, and PMI metrics.

Conclusions: Pediatric neurooncologic tissue is an invaluable clinical and scientific resource. Successful analysis including cell lines and potentially organoid development, crucial for drug discovery, is PMI-dependent. Neuropathologist involvement in PDP development minimizes PMI and maximizes participation, as does utilizing CBTN support.

195

Neuropathological Findings in Bongkrekic Acid Intoxication: A Case Series of Six Autopsies

K Chang [1], W Lin [2], Y Wang [2], T Weng [3]; [1] Department and Graduate Institute of Forensic Medicine, College of Medicine, National Taiwan University, Taiwan, [2] National Taiwan University Hospital, Taiwan, [3] National Taiwan University, Taiwan

Background: Bongkrekic acid (BKA) is a rare foodborne mitochondrial toxin produced by Burkholderia gladioli pathovar cocovenenans, affecting critical organs like the liver, kidneys, and brain, leading to potential fatal outcomes. Despite its clinical significance, neuropathologic changes associated with BKA intoxication have not been reported in English literature. In March 2024, an outbreak of BKA poisoning occurred in Taipei, Taiwan, resulting in six fatalities. This study investigates neuropathologic changes in individuals intoxicated by BKA by analyzing brain tissue from forensic autopsies.

Methods: Brain tissue from six individuals who died of BKA intoxication was obtained from autopsies. Neuropathologic examination was performed on formalin-fixed paraffin-embedded slides stained with H&E.

Results: The individuals aged 39 to 66 years (median 43). Time to death after consuming contaminated food varied from 2 to 75 days (median 38.5). Initial symptoms included abdominal pain, diarrhea, nausea, vomiting, and jaundice. All cases progressed to hepatic failure, renal failure, and shock. Neuropathologic examination reveals diffuse brain edema in all cases (100%, 6/6), with neuronal necrosis and loss in the neocortex (100%, 6/6). Neuronal necrosis and loss are also observed in the CA region and dentate gyrus of the hippocampus (100%, 3/3 with available tissue), the Purkinje cell layer, accompanied by Bergmann gliosis, and the granular cell layer and deep nuclei of the cerebellum (100%, 4/4 with available tissue). White matter demyelination is demonstrated by Luxol fast blue stain. Alzheimer’s type II astrocytes are evident in 3 of 6 cases (50%). Focal subarachnoid hemorrhage is present in one case. One case, who died 36 days after consuming contaminated food and showed brainstem dysfunction six days prior, also had acute hypoxic-ischemic encephalopathy and multifocal hemorrhagic microinfarcts.

Conclusions: Fatal BKA intoxication leads to extensive brain edema and widespread neuronal necrosis. Systemic conditions, including hepatic failure and hemodynamic disturbances, complicate and lead to additional neuropathologic changes.

196

Creating an AI-Driven Morphological Landscape of Meningiomas

M Ayad, K McCortney, C Horbinski, L Cooper; Northwestern University Feinberg School of Medicine

Background: Meningiomas are the most common brain tumors in adults, accounting for approximately one-third of primary intracranial neoplasms. Prognosis is largely based on tumor histology as defined by the WHO, which categorizes meningioma into three grades that include 15 subtypes with distinct morphological patterns that do not always cleanly segregate within each grade. Recent molecular studies suggest copy number alterations and methylation profiles provide even more accurate prognostic information. However, a detailed AI-based comprehensive landscape of meningiomas has not yet been generated. It is also unknown whether specific AI-extracted features might predict specific molecular profiles.

Methods: To begin investigating these associations, we scanned 2385 slides from 395 meningioma patients at 40□ objective magnification. An AI model was used to analyze high power fields from these whole-slide images (WSIs), generating a high-dimensional embedding for each field. AI foundational models have been trained using thousands of slides from various tissue types, providing a powerful tool for this analysis. However, meningiomas are underrepresented in these models. We explored how well these models can identify morphologic patterns of meningiomas using visualization techniques. For this study we labeled 5782 patches from 21 patient WSIs that include sheeting, collagen, mucoid matrices, whorls, mineralized and non-mineralized psammoma bodies, eosinophilic secretions, microcystic vacuoles, and macrophage clusters. Two AI foundational models were used: one trained on 100 million patches from 100,000 WSIs and another on 200 million patches from 350,000 WSIs and immunohistochemistry slides.

Results: Both models showed clear segregation between labeled morphological patterns. Furthermore, clustering was morphology-driven rather than patient-dependent, as image patches from different patients were observed within the same morphological cluster.

Conclusions: By reliably identifying and quantifying these patterns, we can begin to understand how these morphological features relate to specific high-risk molecular alterations like copy number alterations and genomic methylation patterns.

197

Development of Neuropathology-Specific Entrustable Professional Activities (EPAs)

R Multz [1], K Conway [2], J Ahrendsen [1], R Castellani [1], P Jamshidi [1]; [1] Northwestern University, Feinberg School of Medicine, [2] University of Michigan

Background: Entrustable professional activities (EPAs) have emerged as a methodology for assessing trainee development and readiness for independent practice. In our institution, we have recently developed and implemented EPA forms in surgical pathology for grossing, intraoperative consultation, and sign out (PMID: 39512707). These forms allowed faculty to provide feedback to trainees in real-time (PMID: 38025045). With that background, we sought to expand the use of these forms to our neuropathology service.

Methods: We modeled our EPAs for neuropathology after those of the Royal College of Physicians and Surgeons of Canada. We then modified our existing EPA forms for intraoperative consultations and sign out to reflect the unique aspects of neuropathology training. For the intraoperative consultation form, the trainee is expected to identify pertinent clinical information (i.e. imaging results, hormone abnormalities, etc.) and gross findings, appropriate preparation of the tissue (smear, touch preparation, frozen section), and appropriately triage the remaining tissue for ancillary studies. The sign out form was modified to be applicable to all our clinical services (neurosurgical, neuromuscular, autopsy, and forensic consultations). This included an area to assess the trainee's ability to synthesize relevant molecular, cytogenetic, and DNA methylation data to form a final integrated diagnosis for neurosurgical cases. We also created a unique form to evaluate gross examination of the brain and spinal cord from autopsy cases. These assess the ability of trainees to appropriately orient and section the tissue and to integrate the brain cutting findings with the preliminary autopsy findings.

Results: While implementation of these forms would initially be limited to neuropathology fellows, we intend to expand its use to residents who are on their neuropathology or autopsy rotations.

Conclusions: Our ultimate goal would be for broad implementation within neuropathology fellowship programs to better gauge trainee competence and confidence prior to independent practice.

198

Applying machine learning to assist in the quantitative assessment of brain arteriolosclerosis through automation

J Lou [1], P Chang [2], K Nava [3], C Chantaduly [2], H Wang [3], W Yong [2], V Patel [3], A Chaudhari [4], E Monuki [2], E Head [2], H Vinters [5], S Magaki [5], D Harvey [3], C Chuah [4], C DeCarli [3], C Williams [6], M Keiser [7], B Dugger [3]; [1] UCI Department of Pathology and Laboratory Medicine, [2] University of California, Irvine, School of Medicine, [3] University of California, Davis, School of Medicine, [4] University of California, Davis, [5] University of California, Los Angeles, David Geffen School of Medicine,, [6] University of California, Los Angeles, David Geffen School of Medicine, [7] University of California, San Francisco

Background: Objective quantification of brain arteriolosclerosis remains an area of ongoing refinement in neuropathology, with current methods primarily utilizing semi-quantitative scales completed through manual histological examination. These approaches offer modest inter-rater reliability and do not provide precise quantitative metrics.

Methods: To address these limitations, we present a prototype machine learning (ML)-based algorithm – Arteriolosclerosis Segmentation (ArtS) followed by Vascular Morphometry (VasM) – designed to assist in the morphometric analysis of arteriolosclerotic vessels on whole slide images (WSIs). We digitized hematoxylin and eosin-stained glass slides from human brain frontal or occipital lobe gray and/or white matter of 13 participants (total 42 WSIs) from three brain banks (UCD, UCI, and UCLA). ArtS comprises three ML models for blood vessel detection, arteriolosclerosis classification, and segmentation of arteriolosclerotic vessel walls and lumens.

Results: For blood vessel detection, ArtS demonstrated respectable performance characteristics as a screening tool with area under the receiver operating characteristic curve (AUC-ROC) values of 0.79 and 0.77, Dice scores of 0.56 and 0.74, and Hausdorff distances of 2.53 and 2.15 for internal hold-out and external testing, respectively. Arteriolosclerosis classification achieved robust however not yet clinical grade accuracies of 0.94 (mean, 3-fold cross-validation), 0.86 (internal hold-out), and 0.77 (external), alongside AUC-ROC values of 0.69 (mean, 3-fold cross-validation), 0.87 (internal hold-out), and 0.83 (external). For arteriolosclerotic vessel segmentation, ArtS yielded excellent Dice scores of 0.68, 0.73, and 0.71; Hausdorff distances of 7.63, 6.93, and 7.80; and AUC-ROC values of 0.90, 0.92, and 0.87 for 3-fold cross-validation, internal hold-out, and external testing, respectively. VasM successfully derived sclerotic indices, vessel wall thicknesses, and vessel wall to lumen area ratios from ArtS-segmented vessels, producing results comparable to expert assessment.

Conclusions: This integrated approach shows promise as an assistive tool to enhance current neuropathological evaluation of brain arteriolosclerosis, offering potential for improved inter-rater reliability and quantification.

199

Nonspecific localized amyloid deposition in a patient with hereditary peripheral neuropathy mimicking ATTR amyloidosis

M Milani [1], C Chen [2], Y Koksel [2], A Venteicher [2], G Fitzpatrick [2]; [1] University of Minnesota, [2] University of Minnesota Medical School

Background: Primary solitary, localized amyloidosis of the spine without systemic involvement or plasma cell dyscrasia is rare. Amyloidosis is typically diagnosed via mass spectrometry due to its high sensitivity and specificity. Mass spectrometry is the gold standard for confirming amyloid subtypes.

Methods: We report a case of a 62-year-old female with a history of serum-negative rheumatoid arthritis with hand pain, cervical spondylosis, symmetrical distal peripheral neuropathy, subjective report of incomplete voiding, and a family history of similar peripheral neuropathy. She was previously evaluated by EMG and diagnosed with hereditary peripheral neuropathy, though did not undergo additional genetic testing or workup. She presented with several months of left-sided neck pain radiating to her head and post-auricular area, unsteady gait, dysphagia. Magnetic resonance imaging revealed an enhancing retro-odontoid soft tissue mass at the craniocervical junction, displacing the cervicomedullary junction, alongside multilevel cervical foraminal stenosis.

Results: She underwent excision of the lesion, and Congo red staining of the resected mass confirmed amyloid deposition within fibrocartilaginous tissue. The patient's family history of polyneuropathy and symptomatic overlap with AATR amyloidosis raised concern for hereditary ATTR amyloidosis. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) confirmed the presence of amyloid, but did not identify specific amyloid protein, including transthyretin type, suggesting a localized degenerative process rather than hereditary amyloidosis. Follow-up fat pad biopsy was negative. The patient's symptoms related to her cervical spine lesion improved postoperatively, though she continued to experience neuropathy in her lower legs.

Conclusions: This case highlights the importance of amyloid protein typing, particularly when identified in patients with clinical features overlapping with systemic amyloidosis or plasma cell neoplasms. In this patient, hereditary peripheral neuropathy, hand pain similar to carpal tunnel syndrome, and incomplete voiding serving as evidence of possible autonomic dysfunction, raised concern for systemic amyloidosis, after amyloid deposition was identified in her surgical specimen.

200

The role of histopathology and molecular analysis in the grading and management of spinal meningiomas-an institutional experience

A Koziol [1], Q Wu [2]; [1] UConn School of Medicine, [2] Uconn Health

Background: The grading system for meningiomas is crucial as it guides treatment plans and helps predict prognostic factors like recurrence. All meningiomas, including spinal, are histologically graded using the WHO 2021 CNS tumor classification criteria. Recently, the development of DNA methylation profiling in cancer patients has been promising. However, the role of methylation profiles is not well studied in spinal meningiomas, highlighting the need for more research. This study seeks to determine how the histological grade assigned to spinal meningiomas compares to grading provided by DNA methylation profiling, and how the two can be utilized in the prognosis and treatment of spinal meningioma

Methods: Eight primary spinal meningioma cases were collected for this study. Genomic profiling was completed at the Jackson Laboratory for Genomic Medicine utilizing ActionSeq 2.0 pipeline and JAX SOMASEQ. DNA methylation profiling was also done utilizing the Zymo EZ Methylation Gold kit, Illumina FFPE Restore kit, and Zymo DNA Clean and Concentrator kit for bisulfite conversion. Histopathological slides from tumor biopsies were analyzed. Relevant clinical information and tumor imaging was obtained by retrospective chart review.

Results: All 8 spinal meningiomas in this study were graded as WHO Grade I, intradural extramedullary lesions, located in the thoracic spine region. DNA methylation profiling classified 6 samples as benign and 2 as intermediate. All 8 patients were treated by surgical removal of the tumor. Three to four years of clinical follow-up and imaging demonstrated no tumor recurrence or residual symptoms.

Conclusions: Our data demonstrates a diverse genomic and epigenetic landscape of thoracic spinal meningiomas despite a seemingly homogenous clinical presentation and WHO grade 1 histopathology. Understanding and identifying the molecular underpinnings can lead to a more precise and clinically significant classification of spinal meningiomas, which can further contribute to the development of targeted and improved therapeutic strategies.