Meeting Abstracts

64th Annual Meeting of the Canadian Association of Neuropathologists Association canadienne des neuropathologistes (CANP-ACNP)

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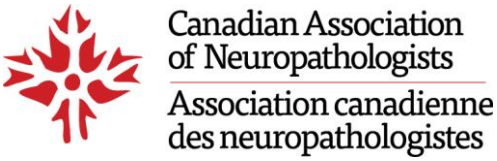
October 3rd–5th, 2024
Toronto, ON



Submitted: 04 December 2024 · Accepted: 05 December 2024 · Published: 29 January 2025

The Canadian Association of Neuropathologist – Association canadienne des neuropathologistes (CANP-ACNP) held their 64th annual meeting at the SickKids – Peter Gilgan Centre for Research and Learning, in Toronto, Ontario, from October 3rd-5th, 2024, under the leadership of Dr. Robert Hammond, President of the CANP-ACNP, Dr. Peter Schutz, Secretary Treasurer of the CANP-ACNP, and with technical support from CANP administrator Colleen Fifield.

The academic program comprised 13 scientific abstracts, 9 unknown cases, the Neuropathology in Practice forum on molecular testing of brain tumours in Canada, and the Presidential symposium on Looking to the Future – Digital Pathology and Spatial Transcriptomics. Digital pathology images from the 9 unknown cases were available for viewing online (www.canp.ca). The unknown case session was moderated by Dr. Andrew Gao.

The Presidential Symposium 2024 on Looking to the Future – Digital Pathology and Spatial Transcriptomics featured the David Robertson Lecture given by Dr. A. Kriegstein on Transcriptomic cytoarchitecture of the brain, and the Jerzy Olszewski Guest Lecture given by Dr. M. Faiz entitled *An integrated single-cell and spatial transcriptomics approach reveals the heterogeneity of the astrocyte response to stroke.* The program was completed by three invited presentations with Dr. Brittany Dugger presenting on *Digital pathology applications in neurodegeneration,* Dr. S. Camelo-Piragua presenting on *Digital pathology applications in neuro-oncology,* and Dr. Matthew Cecchini presenting on *Optimizing Digital Pathology with AI: Strategic Approaches for Modern Clinical Practice.*

The Mary Tom Award for best clinical science presentation by a trainee went to Dr. Christopher Newell (Supervisor Dr. Christopher Dunham), and the Morrison H. Finlayson Award for best basic science presentation by a trainee was won by Dr. Erin Stephenson (Supervisor Dr. Voon Wee Yong).

The following abstracts were presented at the 64th annual meeting of the Canadian Association of Neuropathologists – Association candienne des neuropathologistes (CANP-ACNP) in October 2024.

Abstract 1

Free Neuropathol 6:1:4

Meeting Abstract

Distinctive pattern of cerebral amyloid angiopathy in the cerebellum

David G. Munoz[1,3], Julia Keith[2,3], Sara Mitchell[4], Mario Masellis[4], Alyona Ivanova[5], Sandra Black[4]

[1] *Department of Laboratory Medicine, St. Michael's Hospital, Unity Health Toronto, Toronto, ON, Canada*

[2] *Department of Anatomic Pathology, Sunnybrook Health Sciences Center, Toronto, ON, Canada*

[3] *Department of Laboratory Medicine & Pathobiology, University of Toronto, Toronto, ON, Canada*

[4] *Division of Neurology, Sunnybrook Health Sciences Center, Toronto, ON, Canada*

[5] *Institute of Medical Science, University of Toronto, Toronto, ON, Canada*

We aimed to compare the patterns of cerebral amyloid angiopathy (CAA) in the cerebral and cerebellar cortices.

We studied 24 brains from the pathology departmental archives at Sunnybrook, ages 56–93. Diagnoses included Alzheimer's disease and vascular dementia. Meningeal, parenchymal, and capillary CAA were evaluated in frontal, occipital, and basal temporal cortices, and cerebellum. CAA and plaques were scored 0–3 as per Love 2014. CAA was identified in 21/24 cases. Cerebellum CAA was present in 17/24 cases; it was never present without some CAA in one of the neocortical regions. However, the cerebellar CAA score exceeded the score in any neocortical region in 4 cases, was equal in 9, and less than at least one neocortical region in 7. In the cerebellum meningeal exceeded parenchymal scores in 12 cases, and parenchymal exceeded meningeal in 5 cases. Cerebellar CAA with scores of up to 3 was present in cases without cerebellar plaques; likewise cerebellar plaque scores of 2 were present in a case without cerebellar CAA. There never was capillary CAA in the absence of parenchymal CAA in any region. There was no correlation between meningeal and parenchymal CAA scores in the cerebellum, whereas they were highly correlated in neocortical areas. We conclude that cerebellar CAA is common, often equal or more severe than neocortical CAA. In the cerebellum, unlike in the neocortex, meningeal and parenchymal CAA are not correlated, suggesting that they are responses to largely independent pathophysiological mechanisms.

Abstract 2

Free Neuropathol 6:1:5

Meeting Abstract

Nigral astrocytic tau pathology in PSP

Hidetomo Tanaka[1], Seojin Lee[1], Shelley L. Forrest[1], Gabor G. Kovacs[1]

[1] *Department of Laboratory Medicine and Pathobiology and Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, ON, Canada*

Background: Astrocytic tau pathology is a major feature of primary tauopathies and aging-related tau astrogliopathy (ARTAG). Although tau pathology in the substantia nigra (SN) is usually neuronal, we recently reported cases with prominent nigral tau astrogliopathy (NITAG). Interestingly, despite diverse primary diseases, NITAG exhibited shared distinctive features: abundant tau-positive astrocytes with fewer tau-positive neuronal cytoplasmic inclusions (NCIs) and mild neuronal loss in the SN, and some astrocytic lesions in the other brainstem regions.

Method: We investigated the nigral astrocytic tau pathology in 39 progressive supranuclear palsy (PSP) cases.

Results: Compared to the cases with prominent NITAG, the severity of nigral astroglial tau pathology was not as high and was present in 36 of the 39 PSP cases, with varying amounts. We classified PSP cases into high and low groups based on the number of tau-positive astrocytes in the SN and compared clinicopathological features. Morphologically, nigral tau-positive astrocytes in PSP were distinct from typical tufted astrocytes and resembled those seen in NITAG. Unlike NITAG, both groups exhibited more than moderate neuronal loss and NCIs in the SN, with no significant difference. However, the extent of tau-positive astrocytes in midbrain regions outside the SN was significantly higher in the high-group.

Conclusion: We stratified PSP cases based on the presence and severity of NITAG-type pathology and identified distinct features supporting the notion that PSP might have different pathological subtypes eventually reflect distinct pathogenesis.

Abstract 3

Free Neuropathol 6:1:6

Meeting Abstract

Keratan sulfate is a chemical template for neuroblast migratory pathways and axonal fascicles in human fetal forebrain

Harvey B. Sarnat[1,2], **Weiming Yu**[3]

[1] *Departments of Paediatrics, Pathology (Neuropathology) and Clinical Neurosciences, University of Calgary Cumming School of Medicine, Calgary, Alberta, Canada*

[2] *Alberta Children's Hospital Research Institute (Owerko Centre), Calgary, Alberta, Canada*

[3] *Department of Pathology and Laboratory Medicine, Alberta Children's Hospital, Calgary, Alberta, Canada*

Objectives. Timing of keratan sulfate (KS) during morphogenesis in normally developing human fetal forebrain structures was studied. KS is a proteoglycan secreted in fetal brain by astrocytes and radial glia into extracellular parenchyma as granulofilamentous deposits. It envelops neurons except dendritic spines, repels glutamatergic and facilitates GABAergic axons. The same genes are expressed in both neuroblast migration and axonal growth.

Methods. Twenty normal human fetal brains from 9–41 weeks gestational age were studied at autopsy. KS was examined by immunoreactivity in formalin-fixed paraffin sections, plus other markers including synaptophysin, S-100β protein, vimentin and nestin.

Results. Radial and tangential neuroblast migratory pathways from subventricular zone to cortical plate were marked by KS deposits as early as 9wk GA, shortly after neuroblast migration initiated. During later gestation this reactivity gradually diminished and disappeared by term. Long axonal fascicles of the internal capsule and short fascicles of intrinsic bundles of globus pallidus and corpus striatum also appeared as early as 9–12wk, as fascicular sleeves before axons even entered. Intense KS occurs in astrocytic cytoplasm and extracellular parenchyma at 9wk in globus pallidus, 15wk thalamus, 18wk corpus striatum, 22wk cortical plate, and hippocampus postnatally. Corpus callosum and anterior commissure do not exhibit KS at any age. Optic chiasm shows peripheral reactivity but not around intrinsic subfasciculi. Cross-immunoreactivity with aggrecan may confuse molecular distinctions.

Conclusion. KS forms a putative chemical template (but not a structural scaffold) for many long and short axonal fascicles before axons enter and for neuroblast migratory pathways at initiation of migration.

Abstract 4

Free Neuropathol 6:1:7

Meeting Abstract

Unique neuropathological mechanisms underlying cognitive impairment in schizophrenia

Naomi C. Futhey[1], Elizabeth Gregory[1,3], Belen Arranz[4], Josep Maria Haro[4], Fidel Vila-Rodriguez[3,5], Mark S. Cembrowski[2,5–7], Veronica Hirsch-Reinshagen[8]

[1] *MD/PhD Program, University of British Columbia, Vancouver, Canada*

[2] *Department of Cellular and Physiological Sciences, Life Sciences Institute, University of British Columbia, Vancouver, Canada*

[3] *Non-Invasive Neurostimulation Therapies Laboratory, Department of Psychiatry, University of British Columbia, Vancouver, Canada*

[4] *Sant Joan de Déu, Serveis de Salut Mental, Barcelona, Spain*

[5] *School of Biomedical Engineering, University of British Columbia, Vancouver, Canada*

[6] *Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, Canada*

[7] *Department of Mathematics, University of British Columbia, Vancouver, Canada*

[8] *Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, Canada*

Cognitive impairment is a core tenet of chronic schizophrenia, impacting as many as 98 % of patients. It is not targeted by any currently available therapies, and the underlying neuropathology only occasionally includes neurodegenerative processes such as Alzheimer's Disease. This study seeks to understand the cellular mechanisms for cognitive impairment which may be unique to schizophrenia. Demographic, clinical, and autopsy data were obtained for 55 elderly patients with chronic schizophrenia and post-mortem neuropathological evaluation, with additional neuropsychological testing conducted during life in a subset. Standard evaluation of neurodegenerative conditions and exploratory data analyses including clinical-pathological correlations were performed. Further dimensionality reduction and clustering analysis were conducted using Uniform Manifold Approximation and Projection (UMAP) and k-means clustering to illustrate characteristics of patient subpopulations. On average, patients experienced multiple decades of symptoms, with marked disruption of reality by hallucinations and delusions. Scoring of negative symptoms at this advanced disease stage outweighed that of positive symptoms, although both were present. Significant cognitive impairment was noted across different neuropsychological testing modalities. Only 56 % of patients had sufficiently severe neuropathological changes to explain their cognitive impairment, and distinct subpopulations were highlighted in clustering analysis. Together, this suggests the presence of additional mechanisms underlying cognitive impairment in chronic schizophrenia. Better understanding of the pathophysiology of this impairment may inform our knowledge of schizophrenia as a whole and provide the basis for novel precision medicine applications.

Abstract 5

Free Neuropathol 6:1:8

Meeting Abstract

Recent advances in spatial transcriptomics of the extracellular matrix

Erin L. Stephenson[1], Rajiv W. Jain[2], Samira Ghorbani[2], Rianne P. Gorter[2], Charlotte D'Mello[2], Voon Wee Yong[2]

[1] *Department of Pathology and Laboratory Medicine, University of Calgary, Calgary, AB, Canada*

[2] *Hotchkiss Brain Institute and Department of Clinical Neurosciences, University of Calgary, AB, Canada*

The extracellular matrix (ECM) of the central nervous system (CNS) is an interconnected network of proteins and polysaccharides with critical roles in maintaining brain homeostasis and modulating responses to injury. In neurological diseases, alterations of the ECM can be beneficial or detrimental depending on the constellation of changes. However, there is a lack of data investigating how ECM members change in relation to each other or the relevance of location following injury. The purpose of this research was to investigate how the ECM is altered in multiple sclerosis and glioblastoma, and the spatial heterogeneity of ECM changes. Active and inactive demyelinated lesions from multiple sclerosis were investigated with a combination of spatial mRNA-sequencing, single-nucleus RNA sequencing, and immunohistochemistry. There were widespread changes in the ECM and distinct ECM profiles within inactive cores, lesion rims, and surrounding white matter (Int J Mol Sci 2024; 25(2):1240). Results uncovered multiple novel ECM targets, including the SPARC family, which have the capacity to affect immune cell activation. Brain parenchyma of genetically engineered mice invaded by glioblastoma were separated into tumour core, tumour edge, and infiltrated cortex and analysed using spatial transcriptomics. There were differentially expressed ECM genes that defined tumour regions and unique expression was associated with different tumour molecular drivers. The profound spatial changes of the ECM deserve more scrutiny to appreciate the impact on neuroinflammation, injury, and repair.

Abstract 6

Free Neuropathol 6:1:9

Meeting Abstract

An anatomic transcriptional atlas of focal cortical dysplasia

Ameesha Paliwal[1,2], Kevin Faust[2], Okty A. Borhani[2], Parsa B. Zadeh[2], Phedias Diamandis[1–4]

[1] *Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON M5S 1A8, Canada*

[2] *Princess Margaret Cancer Centre, 101 College Street, Toronto, ON M5G 1L7, Canada*

[3] *Department of Medical Biophysics, University of Toronto, 101 College St, Toronto, ON M5G 1L7, Canada*

[4] *Laboratory Medicine Program, Department of Pathology, University Health Network, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada*

Focal cortical dysplasia (FCD) is a severe neurodevelopmental malformation that manifests in medically refractory epilepsy. FCD presents with classic histological hallmarks, such as cytomegalic dysmorphic neurons, that are presumed to be key anatomical drivers of disease. The relatively low frequency and interspersed patterns of dysmorphic neurons within resected lesions has challenged traditional molecular characterization approaches and consequently, therapeutic options. Therefore, the objective of this study is to systematically identify the key anatomical components of FCD in multiple tissue sections in order to perform molecular sequencing on dysmorphic neuron-enriched samples. To accomplish this, we leveraged unsupervised deep learning approaches to map the conventional pathological features of this disease for spatially-conserved RNA-sequencing. Using this approach, we present the highest resolution molecular catalog of FCD to date. Our analysis has uncovered non-canonical signaling and neurotransmitter pathways in dysmorphic neurons that could serve as new targets for this debilitating disorder. Specifically, we have found aberrant enrichment of an inhibitory glycinergic neurotransmission regulator, glycine transporter 2 (GlyT2). Immunohistochemical staining in eight additional cases of FCD revealed precise enrichment for GlyT2 in dysmorphic neurons. GlyT2 inhibitors have demonstrated efficacy in treating central nervous system disorders by reducing excessive excitatory signaling, making this transporter a compelling therapeutic approach for further research in FCD. Importantly, we have generated a comprehensive resource for discovery in FCD, which reflects the key pathologic features of this disease including cytomegalic dysmorphic neurons, balloon cells, and rarefacted white matter. We anticipate that the research and resource produced here will improve outcomes in FCD.

Abstract 7

Free Neuropathol 6:1:10

Meeting Abstract

Transcriptomic profiling reveals hippocampal white matter inflammation as potential epileptogenic focus in temporal lobe epilepsy

Xuan Wang[1], Rober Abdo[1], Carolyn Twible[1], Chelsey Zhao[1], Qi Zhang[1,2]

[1] *Department of Pathology and Lab Medicine, Western University, London, Ontario, Canada*

[2] *Department of Pathology and Lab Medicine, London Health Sciences Center, London, Ontario, Canada*

Rationale: Hippocampal sclerosis (HS) is the most common pathological finding in surgically resected brain tissue in mesial temporal lobe epilepsy (mTLE). The histopathologic hallmark of HS is pyramidal neuronal loss within the Cornu Ammonis (CA) sectors. Twenty percent of TLE cases have no significant neuronal loss (no-HS, ILAE type 4). About 40 % of no-HS patients achieve seizure freedom post-operatively.

Objectives: We performed spatial transcriptomic profiling of no-HS hippocampi to identify molecular changes associated with post-operative outcomes.

Method: Eight no-HS hippocampi were obtained from the Department of Pathology at LHSC. Five patients had Engel 1a outcome (seizure free, SF); three patients with Engel outcome 2–4 (non-seizure free, NSF). Six samples (3 SF and 3 NSF) were selected based on anatomical integrity and RNA quality. Spatial transcriptomic profiling was performed using 10x Genomics Visium technology. Data analysis was conducted using the Loupe Browser and R/Bioconductor packages to compare gene expression across various hippocampal regions.

Results: Unsupervised data-driven clustering (BayesSpace) correlates well with histology based manual annotation. Two distinct spatial domains (cluster 7 and 8) were identified in hippocampal CA1 region. Differential expression analysis identified upregulated neuroinflammation genes in the seizure free group, predominantly in the hippocampal white matter (e.g. stratum radiatum). Trajectory analysis indicated disease spatial progression starting from hippocampal white matter, progressing to CA sectors, and reaching the dentate gyrus at the end.

Conclusions: Our findings suggest molecular heterogeneity of the human CA1 sector. Patient who had better post-surgical outcomes possess elevated neuroinflammatory signature in the hippocampal white matter.

Abstract 8

Free Neuropathol 6:1:11

Meeting Abstract

Global proteomics reveals bidirectional integrin signaling as a driver of glioblastoma invasion

Rifat S. Sajid[1], Lennart J. van Winden[2], Nakita Gopal[1], Evelyn R. Kamski-Hennekam[2], Okty Abbasi Borhani[2], Ameesha Paliwal[1], Phedias Diamandis[1–4]

[1] *Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada*

[2] *Princess Margaret Cancer Centre, Toronto, Canada*

[3] *Laboratory Medicine Program, University Health Network, Toronto, Canada*

[4] *Department of Medical Biophysics, University of Toronto, Toronto, Canada*

Glioblastoma (GBM) is the most aggressive form of adult brain cancer with a median survival of 15 months despite multimodal treatment. A significant treatment challenge is the ability of tumour cells to infiltrate into surrounding brain tissue. Recent studies have revealed an enrichment of hypoxia-associated signatures in invasive GBM cells and that tumour cells actively migrate away from hypoxic areas to distant brain regions. While these studies have advanced our understanding of GBM invasion, the significant heterogeneity of clinical tissue samples makes it difficult to prioritize migratory signaling pathways for therapeutic targeting. Therefore, we utilized a diverse cohort of patient derived GBM stem cell (GSC) lines and experimental systems to stimulate more controlled invasion models and identify targets to impede tumour infiltration. To investigate these signaling pathways, we leveraged mass spectrometry-based proteomics to profile GSCs cultured under varying oxygen concentrations. This analysis revealed the enrichment of integrin-related signaling pathways in hypoxia. Next, we utilized the GSC and cerebral organoid (GLICO) co-culture model of GBM brain infiltration to investigate hypoxia-independent GBM invasion and discovered the upregulation of proteins involved in both outside-in and inside-out integrin signaling pathways. We then spatially correlated this increased expression in GSCs through spatial transcriptomics. Finally, we functionally evaluated the role of integrin signaling in GBM invasion through pharmacological inhibition in GLICOs, which resulted in significantly reduced GSC infiltration. Therefore, this study highlights the pivotal role of bidirectional integrin signaling as a driver of GBM invasion, and further exploration of key regulators presents a promising therapeutic avenue.

Abstract 9

Free Neuropathol 6:1:12

Meeting Abstract

Integration of molecular and morphometric features improves prognostication of diffuse gliomas

Dimitrios G. Oreopoulos[1,2], Ameesha Paliwal[2], Parsa Babaei-Zadeh[2], Alberto Leon[2], Kevin Faust[2], Phedias Diamandis[2–4]

[1] *Temerty Centre for Artificial Intelligence Research and Education in Medicine, University of Toronto, Toronto, ON, Canada*

[2] *Department of Pathology, Princess Margaret Cancer Centre, 101 College Street, Toronto, ON, M5G 1L7, Canada*

[3] *Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada*

[4] *Department of Medical Biophysics, University of Toronto, Toronto, ON, Canada*

Background: Diffuse gliomas are the most common forms of adult brain cancer, but exhibit substantial heterogeneity in outcomes. While much of the clinical variability has recently been objectively resolved by molecular profiling and subclassification of gliomas into isocitrate dehydrogenase (IDH)-wildtype (Glioblastoma) and IDH-mutant tumors, the later with and without 1p19q chromosomal codeletions (Oligodendroglioma, Astrocytoma respectively), these subgroups still exhibit patient-level differences in progression that challenge precision management and care.

Hypothesis: We hypothesized that integrating Artificial Intelligence-derived tissue features with modern molecular subgrouping may resolve further variation of outcome within established glioma subtypes.

Scientific approach: To explore this hypothesis, we retrieved the clinical cohort of gliomas from The Cancer Genome Atlas and used a publicly available tool we previously developed, PHARAOH, (bioRxiv 2024), to automatically extract and analyze morphometric features of all available cases (TCGA-LGG, n = 722; TCGA-GBM, n = 670). We systematically analyzed 160 different nuclear features and correlated the results with accompanying clinical pathological survival data in 3–5 relevant glioma subcohorts.

Results: This systematic analysis revealed morphometric features that track variations in nuclear staining and cellularity as strong predictors of aggressive disease and poorer outcomes in patients with grade 3 oligodendrogliomas; a notoriously clinical heterogenous glioma subgroup. Importantly, this feature extraction resource is publicly available, allowing these results to be generalized to other cohorts.

Conclusions: Systematic characterization and validation of morphometric features in additional cohorts and clinical practice may support the development of more advanced multimodal biomarkers that can better predict outcome in this aggressive and heterogeneous disease.

Abstract 10

Free Neuropathol 6:1:13

Meeting Abstract

A 13 year review of non-diffuse large B cell lymphomas of the central nervous system at a tertiary hospital: a case series study

Niloofar Sina[1], Chris Heyn[2], Zeina Ghorab[1], Julia Keith[1]

[1] *Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada*

[2] *Diagnostic Imaging, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada*

Background: Non-diffuse large B cell lymphomas (non-DLBCL) of the central nervous system (CNS) are rare. The rarity of such involvement poses a diagnostic challenge for neuropathologists and increases the risk of misclassification, particularly in the absence of a preceding lymphoma diagnosis.

Patients and methods: In this retrospective study we reviewed the clinicopathologic and imaging characteristics of seventeen cases of non-DLBCL of the CNS diagnosed from 2010 to 2022 by neuropathology at our tertiary hospital.

Results: The seventeen cases included eight primary lymphomas and nine secondary lymphomas of the CNS, fifteen neurosurgical cases and two autopsies. The tumours were extra-axial in nine and intra-parenchymal in eight cases, thirteen cases were B cell origin (including nine small mature B cell lymphomas, three large B cell lymphomas and one pleomorphic posttransplant lymphoproliferative disorder) and four cases were T cell origin (including two peripheral T cell lymphoma not otherwise specified, one anaplastic T cell lymphoma ALK negative and one case of disseminated mycosis fungoides). Four distinct radiographic patterns were appreciated on central imaging review.

Conclusion: Our study highlights the heterogeneity of non-DLBCL lymphomas of CNS. This associated with their rarity and variable atypical features increases the risk of misdiagnosis. Reports such as this foster consensus of the diagnostic and management strategies of these rare entities.

Abstract 11

Free Neuropathol 6:1:14

Meeting Abstract

Cost-benefit analysis of fluorescence in situ hybridization testing in the diagnosis of IDH-mutant 1p/19q-codeleted Oligodendrogliomas

Jacob A. Houpt[1], **Robert R. Hammond**[1]

[1] *Department of Pathology and Laboratory Medicine, London Health Sciences Centre, London, ON, Canada*

Fluorescence in situ hybridization (FISH) testing has long served as a diagnostic cornerstone in confirming codeletion of the 1p and 19q chromosome arms in IDH-mutant 1p/19q-codeleted oligodendrogliomas; a test necessary to distinguish the entity from other diffuse adult-type gliomas. However, FISH is both costly and time-consuming relative to other ancillary tests such as next generation sequencing (NGS), requiring expensive fluorescent probes, specialized microscopy suites, and manual evaluation/counting by dedicated medical lab technologists (MLTs). As institutions such as London Health Sciences Centre (LHSC) proceed to validate NGS copy number variation assessment in place of direct FISH testing for the evaluation of 1p/19q-codeletion in gliomas, we reviewed all 1p/19q cytogenetic test results at our institution to better contextualize FISH testing in terms of cost-benefit ratio (CBR). From 2010 to 2024, 700 cytogenetics cases reporting 1p/19q-codeletion were retrieved. Of these, 171 were positive for codeletion of 1p/19q (24.4 %). Repeat testing was requested in 25 cases (3.6 %) due to borderline results and/or increased clinical suspicion, yielding a different diagnosis in at least 3 cases. Conservative estimates of the per case cost of FISH testing (including facility/equipment, reagents, and MLT labour/time) total at least $1400 CAD. While its CBR is comparable to other oncological investigations and can be less expensive than NGS on a per test basis, NGS is often ordered in conjunction to facilitate confirmation of IDH mutations and therefore is poised to save considerable time and cost if all but borderline cases of 1p/19q-codeletion can be elucidated without undertaking cytogenetic evaluation via FISH.

Abstract 12

Free Neuropathol 6:1:15

Meeting Abstract

Infant-type hemispheric glioma is mostly relatively well-demarcated tumor and not diffusely infiltrative

Murad Alturkustani[1]

[1] *Department of Pathology, King Abdulaziz University, Jeddah, Saudi Arabia*

Background: IHG has been identified as a distinct entity with unique methylation patterns and gene fusions, presenting a better prognosis than other pediatric high-grade gliomas. The current WHO classification presents discrepancies regarding the tumor's circumscription, necessitating further investigation.

Methods: The Children's Brain Tumor Network dataset of 1029 samples was accessed, selecting tumors from patients aged 0–4 years, resulting in 191 gliomas, glioneuronal tumors, and ependymomas. Methylation profiles were analyzed using the Heidelberg v12.5 and v12.8 classifiers. Cases were selected based on diagnoses of IHG, desmoplastic infantile astrocytoma / ganglioglioma (DIA/G), or high-grade gliomas with available methylation class. Morphological assessments focused on tumor circumscription, low-grade areas, glial differentiation, and high-grade features.

Results: The final cohort included 12 cases: 4 with an initial diagnosis of DIA/G, and 8 with an initial diagnosis of high-grade astrocytoma (6 diagnosed as IHG). All IHG cases were infantile tumors, while DIA/G cases were in older children. Both IHG and DIA/G were well-circumscribed, whereas the case with diffuse infiltration was classified as diffuse pediatric high-grade glioma. The 4 DIA/G cases were heterogeneous, with only one showing the methylation profile of DIG. One DIA/G case was reclassified as IHG. The remaining six IHG cases were initially diagnosed as high-grade astrocytoma.

Conclusion: IHG is predominantly a well-circumscribed tumor, contrasting with the diffuse infiltration characteristic of other pediatric high-grade gliomas. Recognizing these histological features, along with molecular profiling, is crucial for accurate diagnosis and management.

Abstract 13

Free Neuropathol 6:1:16

Meeting Abstract

Features of central nervous system metastases by neoplasms of gynecological origin

Mimi Zhang[1], Jacob A. Houpt[1], Lee-Cyn Ang[1]

[1] *Department of Pathology and Laboratory Medicine, London Health Sciences Centre, London, ON, Canada*

Central nervous system involvement by metastasis from extra-axial malignancies represent the most common CNS neoplasms in adults, with primary lung, breast, renal, and colorectal carcinomas and cutaneous melanomas representing the majority of such. CNS metastases of gynecological origin are relatively rare – making up no more than 3 % of cases of CNS metastases and occurring in as few as 0.6 % of gynecological cancer patients. All previous cases of CNS metastases at London Health Sciences Centre (LHSC) were screened for keywords related to ovarian, endometrial, and cervical origin. Cases where another possible primary was speculated to be more likely or cases lacking a known or suspected primary gynecological malignancy (based on previous pathology or imaging investigations) were excluded. This yielded 6 and 15 cases of metastases compatible with ovarian and endometrial primaries, respectively. Of the 6 ovarian cases, 3 (50 %) were associated with poorly-differentiated ovarian adenocarcinoma primaries, 2 with high-grade serous ovarian adenocarcinomas, and a single case of mixed clear-cell and serous ovarian adenocarcinoma in which the serous component predominated in the metastasis. Within the 15 cases of uterine primaries, 4 were associated with endometrioid, 1 with serous, 1 with mixed, and 4 with poorly-differentiated adenocarcinomas. The remaining cases included a leiomyosarcoma and 4 carcinosarcomas, the latter of which featured a predominating epithelial component in 2 cases, dual components in a single case, and a rhabdomyosarcoma component in the final case. Relative to other primary malignancies, poorly-differentiated primary carcinomas are over-represented in metastases from gynecological origin (both in ovarian and non-ovarian cases).