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# Anti-NMDA-Receptor Encephalitis in a Patient with Ovarian Teratoma, Harboring Brain Histology of Varying Developmental Stages

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Results: Clinical appearance consisted of mostly coin-shaped atrophic area without hair growth on the vertex of the scalp with a radiating hair collar. Radiologic impression was lipoma or glioneuronal heterotopia in a few cases but none of the cases showed these elements. Review of histologic features identified meningothelial cells in 5/15 cases which were confirmed by EMA or SSTR2A immunohistochemical stain. Although cases of ACC occurring in association with other congenital abnormalities have been reported, none were found on radiologic or clinical examination in our cohort. In conclusion,

Conclusions: ACC is a rare congenital abnormality, presenting on the vortex of the skull that should be on the differential for skull lesions. The presence of meningothelial tissue suggests a possible etiologic relationship with neural tube defects, a connection that should be explored in future studies.

## Other Topics

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**Hyaline Protoplasmic Astrocytopathy in an Epilepsy Patient with Aberrant Supracallosal Bundles and Hypoplastic Optic Pathway**

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Hyaline protoplasmic astrocytopathy (HPA) is a rare disorder of protein accumulation often described in association with intractable epilepsy, developmental delays, and brain malformations. While various cases demonstrating this unusual neuropathological finding have been reported in the literature, the nature of these inclusions and the genetic and metabolic anomalies that underlie their aggregation in astrocytes remain to be elucidated. Here, we report an autopsy case of HPA occurring in the context of adult-onset intractable seizures, lifelong developmental delay, and mutations in KCNH2 and PRRT2 genes, which was associated with several brain abnormalities including marked optic pathway hypoplasia and aberrant longitudinal tract bundles overlying the anterior corpus callosum. Microscopic examination of cortical tissue revealed abundant PAS-negative eosinophilic cytoplasmic inclusions within astrocytes with an immunohistochemical profile consistent with published HPA cases, appearing as osmiophilic granules within astrocytes without limiting membranes on electron microscopy. Protein mass spectrometry analysis of tissues with and without HPA inclusions revealed an abnormally high expression of proteins with functions related to protein metabolism (UBA2, FBXO2) and synthesis (TARSL2, EEF1E1, etc.). hyaline protoplasmic astrocytic inclusion formation and their putative role in epileptogenic mechanisms in HPA. This is the first documented case of HPA occurring in conjunction with aberrant myelinated longitudinal supracallosal bundles and hypoplastic optic pathways, and characterization of its astrocytic inclusions suggests that HPA, unlike single proteinopathies, involves accumulation of several proteins in the setting of dysregulated synthesis and metabolism within affected cortical astrocytes, reflecting a possible pathophysiological mechanism behind their putative role in epileptogenesis.

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**Detection of gene fusions, cryptic rearrangements, and gene regulatory interactions in brain tumors by whole-genome Hi-C**

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Introduction: Gene rearrangements play a critical role in the development of brain tumors. RNA next-generation sequencing (NGS) panels cover a limited number of genes, are rarely successful in FFPE samples $>$ 5 years old, and cannot detect rearrangements between genes and non-coding regulatory regions. We evaluated whole genome Hi-C NGS for detection of gene fusions and cryptic rearrangements.

Methods: DNA was extracted from FFPE scrolls of 55 glial and non-glial brain tumors and processed using Arima-HiC+ FFPE Sample protocol, consisting of chromatin fragmentation, labeling, and re-ligation, followed by DNA purification and library preparation for paired-end Illumina sequencing with an average of 10X genome coverage (100M PE reads per sample). Data were analyzed using the Arima-SV pipeline using Juicer and HiCUP, SV detection using HiC-Breakfinder, loop calling using Juicer Tools, and integrative data visualization using Juicebox. Overexpression of putative driver genes was confirmed by immunohistochemistry.

Results: Hi-C libraries were prepared and sequenced from FFPE tissues including samples that failed RNA NGS. Hi-C successfully detected gene-gene fusions including actionable EML*4-NTRK3*, *ETV6-NTRK3,* fusions. We detected rearrangements missed by RNA NGS (i.e., complex MYBL1 rearrangement) or between non-coding regions and known cancer genes (i.e. *PD-L1*, PAX5, *NRAS*, *TERT*, *KAT6A*, *GATA6,* and *ARID1B*). Since Hi-C data captures 3D genome structural features such as chromatin loops and topological domains, datasets were of high quality and capable of detecting up to 13,000 chromatin loops per tumor.

Conclusion: Genome-wide Hi-C NGS is successful in detecting gene fusions and cryptic rearrangements between coding and non-coding regions in archival FFPE tissue including degraded samples. Because Hi-C data captures 3D genome structures, these datasets simultaneously inform gene regulatory mechanisms that may play a role in oncogenesis or tumor progression. Whole-genome Hi-C NGS expands our ability to detect actionable and novel drivers, and potentially new therapeutic targets in a single NGS workflow.

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**Anti-NMDA-Receptor Encephalitis in a Patient with Ovarian Teratoma, Harboring Brain Histology of Varying Developmental Stages**

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Anti-NMDA-receptor encephalitis is a subacute, autoimmune disorder thought to be caused by autoantibodies directed against the N-methyl-D-aspartate (NMDA) receptor. Although NMDAR encephalitis is a familiar entity to psychiatrists and neurologists, it is less commonly reported in the pathology literature. Clinical symptoms of anti-NMDAR encephalitis may mimic schizophrenia and psychotic spectrum disorders or substance-induced psychosis. Although initially described in association with ovarian teratomas in women, anti-NMDAR encephalitis has been reported in individuals without paraneoplastic association, as well as in males. Previous literature has suggested NMDA receptor expressing teratoma neurons are densely aggregated and are smaller in size. Ki-67 index can be higher in these neurons and they usually show B-cell lymphocytic infiltration around them. Herein, we report a case of a 29-year-old woman with suicidal ideation and other neuropsychiatric manifestations who was found to have a right ovarian cystic mass by imaging study. Microscopically, the resected ovarian mass is composed of mature skin, fat, cartilage and neural tissues. Nerve, ganglions and multiple brain tissues are present. Interestingly, cerebellum including external granular cell layer (normally only seen in infants), cerebrum-like, choroid plexus and other neural elements are present. There is peripheral lymphoplasmacytic infiltrates around and within the neuroglial matrix. Cerebral spinal fluid tested positive for Anti-NMDAR. The combined clinical, histological, and laboratory findings confirmed the above diagnosis. Its resultant relationship to cystic teratoma warrants awareness of this condition by pathologists. Although slow to respond to treatment, this patient now continues to show improvement with plasmaphoresis. Portions of this abstract have been previously presented at the ASCP meeting in 2021.