**ETMR-02. NOVEL CIC-LEUTX FUSION IN CNS EMBRYONAL TUMOR: A CASE REPORT AND REVIEW OF THE LITERATURE**

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INTRODUCTION: Central nervous system (CNS) embryonal tumor is a group of rare, poorly differentiated neuroepithelial malignant neoplasm predominantly occurs in pediatrics. Herein, we firstly report a CNS embryonal tumor harboring pathogenic CIC-LEUTX fusion. METHODS: Immunohistochemistry (IHC), Fluorescence in Situ Hybridization (FISH) and Next Generation sequencing (NGS). RESULTS: A 2-year-old male was found to have solid and cystic mass in left temporal lobe-basal ganglia and left parietal lobe (maximum diameter=75mm). The pathological diagnosis was CNS embryonal tumor (NEC) after totally resection. The tumor was poorly differentiated embryonal neoplasms of neuroectodermal origin that lacked the specific features and rosettes. IHC showed Syn was strongly/diffusely positive and Ki67 proliferation index was high (50%+), and copy number at the 19q13.42 C19MC locus showed no alterations. NGS showed pathogenic mutations including a brand new CIC-LEUTX fusion, heterozygous germline NBN c.C127T mutation and somatic TSC2 c.G2714A mutation. One month after operation, intracranial tumor recurred (maximum diameter=55mm) and spinal cord implantation metastasis occurred, and then the patient received chemotherapy (CTX+CBP+VCR/DDP+VP-16) and had significant improvement in symptoms and tumor shrinkage (maximum diameter=31mm). Literature review revealed CIC fusion predominantly presented in sarcomas, such as CIC-NUTM1 fusion in rare CNS sarcoma, CIC-LEUTX fusion in epithelioid angiosarcoma and CIC-DUX4 fusion in Ewing-like sarcoma. Hitherto, apart from this case, there were only two cases which had CIC-LEUTX fusion in CNS, including a case of CNS angiosarcoma and a case of anaplastic ganglioglioma. CONCLUSIONS: We firstly found a specific new type in CNS embryonal tumor with distinct molecular-pathological characteristics of CIC-LEUTX fusion.

**ETMR-03. THE ROLE OF FOXR2 IN PEDIATRIC BRAIN CANCER**

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Forkhead Box R2 (FOXR2) is a transcription factor of the Forkhead Box family that has been correlated with tumorigenesis, aberrant cell growth or tumor progression. Expression of *FOXR2* in pediatric brain tumors is, besides in subsets of medullo-, pineo- and glioblastoma, primarily present in CNS neuroblastoma with FOXR2 activation (CNS NB-FOXR2), a novel entity that we in 2016 identified from the former class of primitive neuroectodermal tumors of the central nervous system (CNS-PNET). Analyzing CNS-NB-FOXR2 tumors we found that *FOXR2* mRNA is expressed in an anti-correlative manner compared to the proto-oncogenes *MYC* and *MYCN*. With immunoprecipitation analyses we show that FOXR2 binds to MYC and MYCN and is thereby stabilizing these proteins. These observations on the interaction and the anti-correlative manner suggest that FOXR2 and MYC(N) may drive tumor formation in a molecularly similar fashion. To investigate this further we stably expressed *FOXR2*, *MYCN* and *MYC* and a combination of *FOXR2* with *MYC(N)* in human neural stem cells (hNSC) and injected these in the striatum of NSG mice. We could show that hNSC itself do not from a tumor, whereas the expression of *FOXR2* and/or *MYC(N)* in hNSC results in tumorigenesis. Tumors expressing both, *FOXR2* and *MYC(N)* were growing faster than tumors with *FOXR2* alone. In addition, tumors are currently being analyzed by ChIP-sequencing for FOXR2, MYC, and MYCN, to better understand the mechanisms how FOXR2 drives tumor formation compared to its interaction partners MYC and MYCN.

**ETMR-04. EMBRYONAL TUMOR WITH MULTILAYERED ROSETTES: THE MD ANDERSON CANCER CENTER EXPERIENCE**

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BACKGROUND: Embryonal Tumor with Multilayered Rosettes (ETMR) are rare tumors that are molecularly diagnosed by C19MC amplification. Rarity of this tumor has precluded profiling uniform therapeutic strategy. METHODS: Retrospective review after institutional approval, identified 10 pediatric case of ETMR, treated at MD Anderson Cancer Center during the period of 2005 to 2019. RESULTS: Median age of at diagnosis was 4.6 years. Tumor sites include frontal or parietal lobes (3), spine (3) and posterior fossa involving the brainstem (4). All patients received a combination of chemotherapy and radiation. 4 patients had metastasis at the presentation. 9 patients received focal radiation but only 6 of them received Craniospinal irradiation (CSI). Average dose of radiation was 50 Gy. Surgical resection was performed in all cases except the brainstem tumors. 7 children had recurrence including all the patients with metastasis at diagnosis (median time: 9.4 months), 1 passed away secondary to hemorrhage in brainstem and data was not available for 2 patients. 5/6 patients who received CSI had recurrence. CONCLUSIONS: To-date no well-defined treatment regimens exists for these neoplasms, resulting in poor overall survival. Preclinical drug screen have shown the efficacy of topotecan, actinomycin D, and volasertib as potential new therapeutic candidates, though this has not translated successfully into the clinical arena. Given the limited success with current conventional therapeutic methods, molecular interrogation in addition to histopathological diagnosis are essential upfront, as it could provide clues to targeted therapy. Defining molecularly-based treatment with less toxicities and increased survival are warranted.

**ETMR-05. SINGLE-CELL RNA-SEQ OF ETMR REVEALS CELL PROGRAMS OF DEVELOPMENTAL HIERARCHY AND CELLULAR DIVERSITY IN THE TUMOR MICROENVIRONMENT**

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Embryonal tumors with multilayered rosettes (ETMR) are deadly brain malignancies affecting young children. No standard treatment is available and the median survival is less than 12 months. Molecularly, the disease is characterized by the miRNA C19MC cluster amplification, with the expression of multiples miRNAs related to a stem cell program. The discoveries on the purely molecular mechanisms of the disease did not help to create a bridge for new treatment strategies so far and the cellular diversity of ETMR remains poorly understood. In this study, we used single-cell RNA sequencing of murine and human tumors to describe ETMR cellular heterogeneity. Our findings support that intra-tumoral heterogeneity is mainly characterized by 4 cellular programs defining a developmental hierarchy related to different metabolic states: 1) Early quiescent NSC-like cells supported by fatty-acid oxidation 2) Late NSC and NP-like proliferative cells fueled by glycolytic metabolism; 3) Post-mitotic neuroblast-like cells, relying on oxidative-phosphorylation; 4) NSC-like proliferative cells, with metabolic plasticity and capable of performing the three types of metabolism. Tumor-specific ligand-receptor interaction analysis revealed that ETMR exchange with microglia and vascular mural cells (MC) signals related to extracellular matrix (ECM) organization (*Cxcl12-CxCr4*), stem cell signaling (BMPs-BMP receptors), anti-apoptosis and survival (*Ntf3-Ntrk*), not seen in the control brain. In addition, the vascular MC showed a cancer-associated fibroblast (CAF) phenotype, with potential prognostic implications, as previously demonstrated for other tumors. This study provides new findings to build up a more robust understanding of ETMR biology and opens space for further studies in the field.

**ETMR-06. DISSECTING THE MOLECULAR AND DEVELOPMENTAL BASIS OF PINEOBLASTOMA THROUGH GENOMICS**

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