EPEN-25. EXCEPTIONAL CLINICAL AND IMAGING RESPONSE TO TRK-INHIBITION IN A PATIENT WITH SUPRATENTORIAL EPENDYMOMA HARBORING NTRK2 GENE FUSION

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BACKGROUND: Patients with metastatic pediatric ependymoma have limited therapeutic options and poor outcomes. Approximately ¾ of supratentorial ependymomas are driven by *C11ORF95-RELA* fusions, and the remaining by a heterogeneous group of fusion events. We present a six year-old male diagnosed with supratentorial ependymoma with leptomeningeal carcinomatosis harboring an *NTRK2*-fusion. Local and distant multifocal, intracranial and intraspinal tumor recurrence occurred seven months following gross total resection of the primary lesion and proton beam craniospinal irradiation. METHODS: DNA and RNA from FFPE tumor were used for targeted sequencing using an 81-gene fusion panel and 124-gene mutation panel. Separately, capture transcriptome sequencing, exome sequencing, and copy number array were performed as part of the Texas KidsCanSeq study, an NHGRI/NCI-funded Clinical Sequencing Evidence-Generating Research (CSER) consortium project. All sequencing was carried out in CLIA-certified laboratories. RESULTS: An in-frame fusion between 5' exons 1–3 of *KANK1* and 3' exons 16–21 of *NTRK2*, predicted to retain the kinase domain, was identified. At tumor recurrence, therapy was initiated with Larotrectinib, an FDA-approved pan-TRK inhibitor. Clinical improvement in cognitive speed, motor strength, and coordination was observed at two weeks with significant tumor response on MRI at two and four months. CONCLUSION: TRK gene fusions have not previously been reported in ependymoma. Further tumor characterization by methylation profiling is underway and will be of diagnostic interest given the apparent discordance between tumor histology and molecular findings. This case highlights the potential impact of clinical genomic analysis for children with CNS tumors.

EPEN-26. NON-CANONICAL NF-ΚB SIGNALING DRIVES MESENCHYMAL EPENDYMAL CELL SUBPOPULATION IN PFA EPENDYMOMA

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NF-κB signaling is a hallmark of PFA1 ependymoma. Loss of LDOC1, through epigenetic silencing, leads to constitutively active NF-κB signaling and chronic IL-6 secretion. In this study, we investigate the loss of LDOC1 within the PFA tumor clusters. Using our PFA scRNAseq database, in which there are 5 clusters within the tumor cell compartment: mesenchymal (MEC), ciliated (CEC), transportive (TEC), and undifferentiated (UEC). LDOC1 expression was significantly reduced and had an inverse correlation with genes defining the unfavorable MEC subpopulation, predominate in PFA1. This is consistent with our findings that MEC was defined by an NF-κB2 signaling profile. In contrast, LDOC1 expression was higher and positively correlated with genes defining the favorable CEC subpopulation, mostly seen in PFA2. RELA expression, which we studied as a target of LDOC1, was not localized to MEC and was wide-spread throughout the PFA compartment. RELB, part of non-conical NF-κB signaling, was expressed only the MEC subpopulation correlating with IL-6 gene expression found only in this subpopulation. In MAF-811, a PFA cell line with more CEC-like gene phenotype, RELB co-immunoprecipates with the active form of NF-κB2 in both the nucleus and cytoplasm. IL-6 gene expression is almost completely lost when NF-κB2 is knock-down using shRNA. Additionally, loss of LDOC1 leads to over 3 fold increase in NF-κB2 expression. Combined with our previous work, this would suggest that NF-κB2 drives IL-6 expression by binding with RELB in MEC subpopulation and targeting loss of LDOC1 may shift the MEC subpopulation toward the more favorable CEC subpopulation.

EPEN-27. *CDKN2A* DELETION IN SUPRATENTORIAL EPENDYMOMA WITH *RELA* ALTERATION INDICATES A DISMAL PROGNOSIS – A RETROSPECTIVE ANALYSIS OF THE HIT EPENDYMOMA TRIAL COHORT

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INTRODUCTION: Since supratentorial *RELA*-fusion positive ependymomas are considered a biologically distinct disease, we aimed to identify histological and genetic predictors of outcome in a defined cohort of pediatric patients. MATERIALS AND METHODS: We analyzed 54 *RELA* ependymomas in pediatric patients treated according to HIT2000-E protocols. All cases underwent central neuropathological review. Genome-wide copy number alterations were assessed by molecular inversion probe or SNP array. *RELA* alterations were detected by RT-PCR, sequencing and assessment of nuclear p65-RelA protein. Copy number alteration of the *CDKN2A (cyclin dependent kinase inhibitor 2A)* locus and concordant p16 protein expression were analyzed. RESULTS: Fifty-two tumors were classified as WHO-grade III (96.3%) with high mitotic activity in 39 cases (72.2%), vascular proliferation in 47 (87.0%), necrosis in 43 (79.6%) and clear cell morphology in 19 (35.2%). All tumors harbored *RELA* alterations. Homo- or heterozygous *CDKN2A* deletions were detected in 9 (16.7%) and 14 (25.9%) cases, respectively. p16 protein expression was lost in all cases with homozygous deletion. Median follow-up was 5.4 years with 5-years EFS and OS of 74.1% and 92.6%. In Kaplan-Meier analysis high mitotic activity was related to shorter EFS (p=0.016) and clear cell morphology to longer OS (p=0.039); *CDKN2A* deletion was associated with shorter OS (homozygous deletion, p=0.009; homo-or heterozygous deletion, p=0.034). No correlation between *CDKN2A* deletion and high mitotic activity was found but with higher age at diagnosis (p=0.001). CONCLUSION: Deletion of *CDKN2A* occurred in 42.6% of supratentorial ependymomas with *RELA* alteration and represented a genetic predictor of worse overall outcome in pediatric patients.

EPEN-28. NOVEL ONCOGENE AMPLIFICATION IN SPINAL EPENDYMOMA INVOLVING THE MYC LOCUS (8Q24)

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BACKGROUND: We report a unique case of spinal ependymoma with classic histology and aggressive clinical behavior which harbored a focal *MYC* (8q24) amplification. CASE REPORT: A-12-year old male presented with a three months history of back pain and acute onset weakness with ataxia. A spine MRI revealed an avidly enhancing intradural, extramedullary mass occupying the dorsal spinal canal from C6 through T2. The tumor demonstrated mild diffusion restriction and was associated with severe cord compression and mild edema. He underwent gross total resection. Pathological diagnosis was classic grade II ependymoma. Eleven months later, he re-presented with acute onset lower extremity paresthesia and left-handed weakness. Spine MRI demonstrated tumor recurrence extending from C2 through T1-T2 with resultant severe cord compression, again demonstrating avid enhancement and restricted diffusion. He underwent subtotal resection of the mass and focal proton beam irradiation. MOLECULAR CHARACTERISTICS: The patient was enrolled on an institutional comprehensive genomic profiling protocol. The tumor's copy number profile was complex, including homozygous loss of 17p and notably, amplification of the *MYC*