these cases for PBT versus intensity-modulated radiation therapy, characterized the cyst evolution during treatment in 3 dimensions, and define an optimized protocol for treatment planning and intra-treatment monitoring.

RARE-07. THE LANDSCAPE OF GENOMIC ALTERATIONS IN ADAMANTINOMATOUS CRANIOPHARYNGIOMAS

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INTRODUCTION: Adamantinomatous craniopharyngiomas (ACPs) are characterized by activating mutations in the *CTNNB1* gene. Here we perform a comprehensive genomic analysis of 23 ACPs to define the landscape of genomic alterations in this disease. METHODS: We performed whole-genome sequencing of 24 ACPs and their matched normal tissues. We used Mutect 2.0 to detect mutations and indels in these samples and MutSig2CV to identify significant mutations. Copy numbers were called using the GATK4 pipeline and GISTIC 2.0 was applied to identify significant alterations. Finally, SvABA was applied to identify genome-wide structural variants and rearrangements. RESULTS: 18/24 (75%) of the sequenced ACPs harbored activating mutations in exon 3 of CTNNB1 gene with an average variant allele fraction (VAF) of 0.4±0.1. These mutations have previously been shown to activate the WNT signaling pathway in these tumors. No other significantly recurrent mutations were detected in our samples. The ACPs were quiet with regard to copy number alterations and no recurrent amplifications or deletions were detected. 528 structural variations and rearrangements were detected in total in all 24 samples with an average of 22 variants per sample. Gene-Set Enrichment Analysis (GSEA) of the RNAseq data revealed upregulation of WNT/B-catenin (FDR q-value <0.25) in the CTNNB1 mutant samples compared to CTNNB1 WT samples. CONCLUSION: Our study identified previously described activating CTNNB1 mutations in the majority of ACPs. In addition, we identified several rearrangements and structural variations in these tumors that could play an important role in the pathogenesis of the disease.

RARE-08. CYST FLUID CYTOKINES MAY PROMOTE EPITHELIAL-TO-MESENCHYMAL TRANSITION IN PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA

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BACKGROUND: Despite poor clinical outcomes, no targeted therapies have been established for the treatment of Adamantinomatous Craniopharyngioma (ACP). The only known genetic aberration is a mutation in *CTNNB1* that results in the nuclear accumulation of beta-catenin. Nuclear beta-catenin is an established inducer of Epithelial-to-Mesenchymal Transition (EMT). ACP cyst fluid is enriched with pro-inflammatory and SASP cytokines, many of which are also directly implicated in EMT. We sought to investigate the role of EMT in ACP pathology. METHODS: Normal human epithelial cells were cultured and treated with ACP cyst fluid (10%) for 1, 2, 4 and 8 days. Cell morphology was monitored by live cell brightfield microscopy. The expression of EMT associated genes, ZEB1, ZEB2, SNAI-1, SLUG, TWIST, E-Cadherin, Beta-Catenin and Vimentin was determined by RT-qPCR. RESULTS: ACP cyst fluid treated epithelial cells were markedly transformed into long, spindle-shaped cells. ACP cyst fluid treatment resulted in the progressive up-regulation of ZEB2 over 8 days (**RQ=12.0; P<0.01**), the progressive up-regulation of SNAI-1 over 4 days (**RQ=5.1; P<0.05**) and up-regulation of Vimentin (**RQ=2.2; p<0.01**), identified only on Day 8. CONCLUSION: ACP cyst fluid can induce EMT-like changes in normal human epithelial cells. In conjunction with the frequency of beta-catenin mutation in ACP, it is possible that EMT plays a crucial role in the pathology of ACP. Understanding ACP pathology in the context of the EMT paradigm may aid the development of new targeted therapeutics.

RARE-09. PRESERVATION OF ENDOCRINE FUNCTION AFTER OMMAYA RESERVOIR INSERTION IN CHILDREN WITH CYSTIC CRANIOPHARYNGIOMA

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INTRODUCTION: Children with craniopharyngiomas (CP) can be subjected to significant morbidities caused by radical surgery and/or radiation with severe long-term consequences. Ommaya reservoir Insertion (ORI) into cystic CP represents a minimally invasive procedure that aims to preserve endocrine, hypothalamic and neurocognitive function. The purpose of this study was to determine the relevance of upfront ORI (+/- intracystic treatment) for preservation of endocrine function. METHODS: A retrospective chart review of children with CP treated at the Hospital for Sick Children between 01/01/2000 and 15/01/2020 was undertaken. Endocrine function was reviewed at the time of initial ORI or surgical resection and throughout the course of follow-up. Event free survival (EFS) was defined as the time to additional surgical resection or irradiation. RESULTS: Fifty-five patients with sufficient endocrine follow-up data were included. The median age of diagnosis was 8.3 years (range 2.1–18.0 years), 31 were males. ORI was performed as upfront treatment in 30 patients, gross total or partial resection in 24 patients and radiation in 1 patient, respectively. Endocrine function remained stable after ORI with a median EFS of 19.2 (0 – 105.3) months while the majority of patients who underwent surgical resection had documented worsened endocrine function postoperatively (median of 0; range 0 – 29.4 months) ($p < 0.001$). The event most commonly related to secondary endocrine deterioration was initial or delayed surgical resection. CONCLUSIONS: Endocrine function was preserved in patients with upfront ORI (+/- intracystic treatment). Further studies will elucidate the implications of ORI with respect to ophthalmological, vascular and neurocognitive long-term outcome.

RARE-10. ADAMANTINOMATOUS CRANIOPHARYNGIOMA RESIDES OUTSIDE THE BLOOD BRAIN BARRIER

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BACKGROUND: Adamantinomatous craniopharyngioma (ACP) is a devastating skull-base tumor believed to derive from epithelial remnants of the primordial craniopharyngeal duct (Rathke's pouch), which gives rise to the anterior pituitary gland. Genetically engineered mouse models of ACP demonstrate that perturbation of the fetal anterior pituitary can generate tumors analogous to ACP. Clinical and preclinical data indicate that IL-6 blockade may contribute to ACP tumor control, with the most common agent being the humanized monoclonal antibody, tocilizumab. This agent demonstrated poor blood-brain barrier (BBB) penetration in primates. We present findings from two children enrolled on a phase 0 clinical trial (NCT03970226) of a single dose of preoperative intravenous tocilizumab prior to resection of newly diagnosed ACP. METHODS: Blood samples were obtained at multiple timepoints. Serum was isolated via ficoll separation. Tumor tissue and cyst fluid were obtained 4–6 hours following the single IV dose of tocilizumab. Tissue was snap-frozen. Tumor was homogenized in RIPA buffer. Free tocilizumab in serum, cyst fluid, and tumor tissue was measured using enzyme-linked immunosorbent assay (ELISA) against a standard curve. RESULTS: Both patients in this trial demonstrated clinically relevant levels of tocilizumab (≥ 4μg/mL) in serum, cyst fluid, and tumor tissue, compared to undetectable levels in control samples. CONCLUSION: ACP resides outside BBB protection. In addition to demonstrating the feasibility of systemic delivery of tocilizumab, these findings indicate that other large molecules, including those known to have poor BBB penetration, may be systemically delivered as part of an antitumor regimen in the treatment of ACP.

RARE-11. QUANTITATIVE MR IMAGING FEATURES ASSOCIATED WITH UNIQUE TRANSCRIPTIONAL CHARACTERISTICS IN PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA: A POTENTIAL GUIDE FOR THERAPY

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METHODS: Through the Advancing Treatment for Pediatric Craniopharyngioma (ATPC) consortium we accumulated preoperative MRIs and tumor RNA for 50 unique ACP patients. MRIs were assessed quantitatively for 28 different features and analyzed using Multiple Factor Analysis (MFA) and optimal clustering was determined via maximization of Bayesian Information Criterion (BIC). Following bulk RNAseq, differential expression and pathway enrichment were performed using standard methodologies (i.e., DESeq2 and GSEA). RESULTS: MRI features were well represented in the first 3 dimensions of MFA (variance explained=67.32%); specifically tumor/cyst size, ventricular size, and cyst fluid diffusivity. Using this three-way axis, we identified 3 patient subgroups. Transcriptional differences between these subgroups indicated one group was enriched for DNA damage response and MYC related pathways, one group enriched for SHH, and one group enriched for WNT/β-catenin and EMT-related pathways. CONCLUSION: This preliminary work suggests that there may be unique gene expression variants within ACP, which may be identified preoperatively using easily quantifiable MRI parameters. These radiogenomic signatures could provide prognostic information and/or guidance in the selection of antitumor therapies for children with ACP.

RARE-12. VASCULOPATHY IN PEDIATRIC CRANIOPHARYNGIOMA PATIENTS TREATED WITH SURGERY AND RADIOTHERAPY

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PURPOSE: As much as 40% of pediatric brain tumor patients will experience varied levels of Vasculopathy (VS), however few predictive factors have been described. Here we describe the type and timing of VS and explore the relationship between treatment modality and the timing, location, and distribution of VS. METHODS: 94 pediatric Craniopharyngioma patients underwent surgery and proton radiotherapy. Pre- and post-treatment imaging, cumulative physical and biological proton dose maps, clinical characteristics, and measures of dyslipidemia were evaluated. MR and MRAs were evaluated for pre- and post-radiotherapy VS (type, workup, location, and severity). VS events were segmented and described according to their normal brain region, and vascular territory. RESULTS: 47 patients were found to have 154 confirmed VS of varying severity with a median time to event of 3.41 years 95% CI 3.08–3.88. 22% (N=21) of patients had ≥1 pre-existing instances of VS and 26.6% (N=25) had a dyslipidemia at diagnosis. Forty-six (48.9%) patients had evidence of VS post-RT with 9.5% (N=9) being clinically significant. Aspirin was recommended in 10.6% (N=10) patients. Only 4 (4.2%) patients required revascularization. Clinical characteristics were not predictive of VS. An increased frequency of VS were observed along the operative corridor and high-dose radiotherapy field. CONCLUSIONS: VS often precedes radiotherapy necessitating appropriate baseline imaging. Surgery type and extent are interrelated to the risk for radiotherapy-induced VS. While the spatial radiotherapy dose distribution approximated most vascular injury events, it was not all-inclusive. Spatial modeling of biological and physical dose may offer insights into therapy related vascular injury.

RARE-13. INFLAMMATORY MYOFIBROBLASTIC TUMOR MIMICKING DESMOPLASTIC INFANTILE GANGLIOGLIOMA (DIG) OF THE TEMPORAL LOBE

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Inflammatory myofibroblastic tumor (IMT) is a mesenchymal neoplasm composed of fascicles of myofibroblastic spindle cells in a background of prominent inflammatory infiltrate. It is categorized as 'intermediate, rarely metastasizing' in the World Health Organization classification of tumors of soft tissue and bone. We present a novel case of concurrent brain and lung tumor with diagnosis of TFG-ROS1-rearranged IMT in a 14 year old female patient, in which targeted next-generation sequencing became a powerful tool for detection of genomic alterations in both lung and brain tumors. At age 9, the patient's lung mass was incidentally found and investigated for various infectious diseases with negative result. At age 14, she presented with seizure and was noted to have a stable size lung mass and a left temporal lobe tumor. The left temporal lobe tumor showed a desmoplastic spindle cell neoplasm involving the meninges and cerebral cortex and Desmoplastic Infantile Ganglioglioma (DIG) was considered one of differentials. Subsequently, her right lung mass was resected and showed a similar spindle cell neoplasm with a background of dense fibrosis and chronic inflammation, consistent with Inflammatory Myofibroblastic Tumor. Molecular microdissection revealed that both tumors shares TFG-ROS1 fusion which is associated with (t(3;6) (q12;q22)), thus it is strongly suggestive that two tumors arose from the same origin. No predisposition syndrome was identified.

RARE-14. DEVELOPMENT OF ANAPLASTIC ASTROCYTOMA AS A THIRD MALIGNANCY IN A PEDIATRIC PATIENT WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD): A CASE REPORT AND EVALUATION OF TUMOR GENOMICS IDENTIFYING BIALLELIC *MSH6* MUTATIONS

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Congenital mismatch repair deficiency (CMMRD) is a pediatric cancer predisposition syndrome secondary to biallelic mutations in mismatch repair genes including *MLH1, MSH2, MSH6*, and *PMS2*. Due to the resulting lack of repair mechanisms, these patients develop a high intracellular mutational burden and have a high risk of development of multiple malignancies at a young age. Similar to patients with Lynch Syndrome (monoallelic mutations in MMR genes), these patients are at risk for development of central nervous system (CNS) tumors including high grade gliomas. Forty-eight percent of patients with CMMRD are diagnosed with a CNS malignancy. In this interesting case, a patient developed three metachronous malignancies prior to the age of 13, including Burkitt lymphoma, T-Cell lymphoma and anaplastic astrocytoma. Genomic analysis revealed a high mutational burden in his initial tumors, with multiple oncogenic mutations, as well as a previously unreported germline compound heterozygous *MSH6* E744fs*12 and R248fs*8 alteration. He received a gross total resection of the tumor which in previous studies has been shown to have the highest impact on survival. Surgery was followed by radiation and ongoing treatment with an immune checkpoint inhibitor with stable disease at 6 months. The purpose of this case report is to describe the interesting presentation of CMMRD and discuss the previously unreported biallelic *MSH6* mutations.

RARE-15. EARLY PSEUDOPROGRESSION POST-RADIATION IN PAEDIATRIC HIGH-GRADE GLIOMA PATIENTS WITH CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY: TWO CASE REPORTS FROM A SINGLE CENTRE

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BACKGROUND: Constitutional Mismatch Repair Deficiency (CMMRD) is a cancer predisposition syndrome caused by biallelic mutations in the mismatch repair pathway, and high-grade glioma (HGG) constitute the most prevalent brain tumours. Pseudoprogression alludes to radiological changes that mimic tumour progression, but are in fact due to other causes such as therapy related inflammation. It can occur as early as three months post treatment. To our knowledge, its characteristics in CMMRD patients has not been reported. METHODS: We retrospectively identified seven patients with CMMRD and history of HGG at The Royal Children's Hospital, Melbourne from 2005 to 2019. Our objective was to review the characteristics of pseudoprogression in this cohort. RESULTS: Out of the seven patients, two with constitutional loss of PMS2 demonstrated evidence of pseudoprogression. Patient 1 presented at 16 years old with a cerebellar anaplastic astrocytoma. She developed clinical and radiological progression within two weeks of starting radiotherapy, persisting up to four months after completion. However, six months post radiation she improved without intervention and the tumour remains stable five years post therapy. Patient 2 presented at 17 years old with a midbrain anaplastic astrocytoma, and showed signs of progression four weeks after completion of radiotherapy. She was then treated with Bevacizumab, an anti-VEGFA antibody with remarkable response. She subsequently received Nivolumab, a checkpoint inhibitor with ongoing stable disease for four