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RARE-30. PEDIATRIC GLIOBLASTOMA IN THE POST-TEMOZOLOMIDE ERA: OUTCOMES AND CHARACTERISTICS

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(28.5%) had died, with median OS of 168.5 months. Although PPTIDs have a known potential for local recurrence and craniospinal dissemination (quoted as 22% and 10%, respectively in WHO 2016), our data show a more dismal experience with 71% recurrence and 80% dissemination at first recurrence. Lack of standardized therapies results in challenges in individual patient management.

RARE-26. WHOLE GENOME SEQUENCING OF AN OSSEOUS METASTASIS DURING CHECKPOINT-CONTROLLED INTRACRANIAL GLIOBLASTOMA REVEALS NEW INSIGHTS INTO POTENTIAL MECHANISMS OF IMMUNE ESCAPE

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Glioblastoma (GBM) has a devastating prognosis and recent advances in the treatment of a variety of cancer entities, e.g. through checkpoint inhibition, could so far not be translated into improved outcome in newly-diagnosed GBM. Characterizing rare cases of peripheral metastases which succeeded in overcoming immune control, can help to understand the mechanisms of immune escape. Here we describe the first reported case of a detailed genetic and immunological characterization of a peripheral bone metastasis from a GBM which was controlled intracranially by anti-PD1 checkpoint inhibition. We performed whole genome sequencing (WGS) of the primary- and recurrent tumor, as well as the bone metastasis. Genomic data was analyzed for copy number variations and mutational profiles. In addition, immune monitoring with flow cytometric phenotyping and next-generation sequencing of the peripheral T-cell repertoire was used. A 70-year old patient developed multiple osseous metastases in the spine, while his IDHwt GBM recurrence was immunologically controlled with checkpoint inhibition. Biopsy confirmed peripheral GBM metastases. Immunophenotyping reflected the effective activation of the peripheral T-cell response, with, however, simultaneous upregulation of regulatory T-cells during disease progression. WGS sequencing demonstrated a distinct molecular profile of the GBM metastasis, with amplifications in chromosome 3 and 9, as well as genomic loss on chromosomes 4, 10 and 11. The peripheral metastasis was distinguished by mutations in mismatch repair genes, such as MSH4 and MLH1, associated with a hypermutated phenotype. Among the mutated genes we found potential candidates involved in immune escape of circulating tumor cells. This case represents a unique opportunity to analyze potential mechanisms of GBM-mediated immune escape during immune activation with anti-PD1 checkpoint therapy. It highlights the fact, that although an effective, disinhibited immune response can control the cranial GBM disease, hypermutated tumor clones can evade the tumor-specific T-cell response and disseminate to distant organs.

RARE-27. UNUSUAL CASE OF TEENAGER WITH PRIMARY SPINAL GERMINOMA WITH INTRACRANIAL RELAPSE POST-THERAPY

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We present a case of a 14-year-old male who presented with back pain and difficulty walking and was found to have an intradural intramedullary germinoma in the thoracolumbar spine. After debulking, he was treated with four cycles of carboplatin and etoposide and then received local spinal radiotherapy (RT) to the initial area of disease with margin to 30 Gy in 17 fractions. Six months following completion of therapy, he was found to have an intracranial relapse. CLINICAL IMPORTANCE: Our patient is the second ever Hispanic and twelfth pediatric patient reported with primary spinal germinoma. We reviewed 54 total cases published in literature over last 35 years. Twenty-one patients (39%) were treated with surgery followed by local spinal RT (n=12) or CSI (n=9). Twenty-eight patients (52%) were treated with chemotherapy in addition to surgery and radiation. The remaining 5 patients (9%) either had surgery alone or details of their treatment plan were not reported. Six of the 54 patients experienced disease recurrence. None of the patients treated with CSI experienced disease recurrence after CSI. Ninety-six percent of patients were alive at last follow up. CLINICAL OUTCOME: Our patient had his relapsed disease resected and CSI to 23.4 GY in 13 fractions and focal boost to 21.6 Gy in 12 fractions was delivered to all sites of relapsed disease. He is undergoing surveillance of his tumor and there is no disease recurrence 3 months post-CSI. CONCLUSION: Primary spinal germinomas appear chemo responsive and radiosensitive; however, the optimal management to maximize disease control and minimize side effects is not clear. When using local spinal RT, close surveillance with brain and spine imaging seems indicated as relapses anywhere in the central nervous system are possible. Further study is needed to determine the optimum treatment approach to this tumor.

RARE-28. HYPOTHALAMIC GERMINOMA AND NEUROSARCOIDOSIS: A TALE OF TWO PATHOLOGIES

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CASE 1: 30-year-old Caucasian male with a history of hereditary cavernomas, testicular germ cell tumor s/p orchietomy 2017 presented next year with a chief complain of increasing lethargy. MRI Brain showed a new expansile, homogenously enhancing hypothalamic lesion causing obstructive dilatation of the lateral ventricles. MRI of neuraxis was not concerning for leptomeningeal spread. Initial differentials included suprasellar germinoma vs chiasmatic hypothalamic glioma vs metastatic lesion. Biopsies X2 showed gliosis and granulomatous inflammation. Despite radiation treatment for the hypothalamic mass clinical course continued to deteriorate. CSF results showed RBC - 1,200; WBC - 51 with 77% lymphocytes, 3% neutrophils, 20% monocytes. FDG-PET did not reveal evidence of metastatic disease. He was treated presumptively for neurosarcooidosis with high-dose corticosteroids and azathioprine and later transitioned to methotrexate and infliximab. Follow up MRI scans showed a reduction in the hypothalamic mass. CASE 2: A 23-year-old African American male treated for ADEM in 2010 presented to clinic with behavioral problems in 2017. Initial presentation included lethargy with imaging showing an incidental hypothalamic mass. Initial differentials included germinoma vs infundibular hypophysitis vs granulomatous process. He was treated with immunotherapy (corticosteroids and IVIG) with partial resolution of the growth. He was later diagnosed with suprasellar germinoma on biopsy subsequently treated with 2 cycles chemotherapy and proton beam radiotherapy in 2012. In 2017, to exclude tumor recurrence an LP showed elevated ACE however remainder of the clinical picture was not suggestive of neurosarcooidosis. DISCUSSION: Multiple case series have been described wherein hypothalamic germinoma mimics isolated neurosarcooidosis and vice-versa. Because of similar clinical picture and radiographic findings, the diagnosis is challenging. ACE is a nonspecific test for neurosarcooidosis, and it can be positive in the setting of germinoma as well. Hence specific molecular markers may be helpful in the diagnosis.

RARE-29. AZD8055 ENHANCES IN VIVO EFFICACY OF AFATINIB IN CHORDOMAS

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INTRODUCTION: Chordomas are rare, locally aggressive bone tumors that arise in cranial base, mobile spine, and sacrum. Currently, there are no FDA-approved therapies for chordoma patients, thus there is a high unmet need to develop effective treatments. In this study, we aim to evaluate the anti-tumor efficacy of small molecule inhibitors that target crucial oncogenic pathways in chordoma, as single agents or in combination, to identify novel therapies with the greatest translation potential. METHODS: A panel of small molecule compounds that had exhibited *in vitro* efficacy against human chordoma cell lines or target known chordoma drivers was screened *in vivo* against patient-derived xenograft (PDX) models of chordoma, and their efficacy was further evaluated using chordoma cell lines and xenograft models. RESULTS: The *in vivo* activity of compounds identified in a NIH Chemical Genomics Center screen utilizing chordoma cell lines, together with inhibitors of c-MET and PDGFR, were evaluated in PDX models of chordoma that were previously described or recently established for this study. Inhibitors of EGFR (BIBX1382, erlotinib and afatinib), c-MET (crizotinib) or mTOR (AZD8055) significantly inhibited tumor growth *in vivo* but did not induce tumor regression. Co-inhibition of EGFR and c-MET using erlotinib and crizotinib synergistically reduced cell viability in chordoma cell lines but did not result in enhanced *in vivo* activity. Co-inhibition of EGFR and mTOR pathways using afatinib and AZD8055 synergistically reduced cell viability in chordoma cell lines. Importantly, co-inhibition of EGFR and mTOR also synergistically suppressed tumor growth *in vivo*, showing improved disease control. CONCLUSION: Single inhibition of EGFR, c-MET or mTOR suppresses chordoma growth both *in vitro* and *in vivo*. Co-inhibition of EGFR and mTOR synergistically inhibits chordoma growth in a range of preclinical models. The insights gained from our study provide a novel combination therapeutic strategy for patients with chordoma.

RARE-30. PEDIATRIC GLIOBLASTOMA IN THE POST-TEMOZOLOMIDE ERA: OUTCOMES AND CHARACTERISTICS

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INTRODUCTION: Glioblastoma (GBM) is the most common brain tumor, however, is a rare occurrence in children and is poorly characterized. We evaluated the characteristics and outcomes of pediatric GBM (pGBM). **METHODS:** Retrospective analysis of pediatric (age < 18) patients diagnosed with GBM undergoing first glioblastoma resection at our brain tumor center (2005-2016). **RESULTS:** From 1457 GBM patients, we identified twenty-four (1.65%) pGBMs (Median Age=9 years, Females=45.8%). Median overall survival (OS) was 32.1 months, while the median progression-free survival was 11.5 months. The commonest symptoms at presentation were headaches (54.2%, n=13) and motor symptoms (50%, n=12). Mean tumor diameter was 4.5 cm and 25% of the cohort underwent gross total resection (GTR) of their tumor. Univariate analysis revealed median OS significantly associated with tumor extent of resection (GTR=56.4 months; STR/Biopsy=13.7 months, p=0.001), age at surgery (>10 years=43.9 months, < 10 years= 17.2 months, p=0.01), tumor size (> 4cm= 9.1 months, < 4cm=56.9 months, p=0.01), motor symptoms at presentation (present=14.9 months, absent=41.04 months, p=0.02) and infratentorial tumors (infratentorial=17.4 vs supratentorial=53.4 months, p=0.02). Multivariate analysis revealed GTR (HR 0.2[95% CI 0.07–0.72]; p=0.03), Age >10 years (HR 0.6[95% CI 0.02–0.64]; p=0.002), tumor >4 cm (HR 2.89[95% CI 1.88–4.11]; p=0.001) and EGFR amplification (HR 3.48[95% CI 0.82–17.4]; p=0.005) to be independent predictors of OS. Comparing patients under and over 10 years, we found that older patients had smaller tumors at presentation (4.9 vs 3.6 cms, p=0.03), greater rates of preoperative temozolomide (n=1, 7.7% vs n=6, 54.5%) and bevacizumab (n=1, 7.7% vs n=4, 36.4%) treatment, and lower rates of EGFR amplification (66.7% vs 11.1%) that could explain survival disparities between groups. **CONCLUSION:** Motor symptoms, larger tumors at presentation and tumor EGFR amplification may be indicative of poorer outcomes in pGBM. However, maximal tumor resection, aggressive chemoradiation and tumor presentation at age >10 years may confer better prognosis in these patients.

RARE-31. TREATMENT OUTCOME OF CHILDREN WITH PLEOMORPHIC XANTHOASTROCYTOMA: RETROSPECTIVE ANALYSIS – A SINGLE INSTITUTION EXPERIENCE
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BACKGROUND: Pleomorphic xanthoastrocytoma (PXA) and anaplastic pleomorphic xanthoastrocytoma (APXA) are two types of rare astrocytomas in pediatrics. There is limited literature reporting their outcomes. **METHODS:** A retrospective analysis of pediatric patients with diagnosis of PXA and APXA treated at Nicklaus Children’s Hospital was conducted using descriptive measures. **RESULTS:** A chart review of patients with brain tumors from 2001 to 2019 revealed that 13 patients (median age 6 years, range 2–17 years) were diagnosed with non-metastatic PXA (n=12) and APXA (n=1). Six patients (46%) were male. Clinical presentation included seizures (n=8), headaches (n=2) cranial nerve palsies (n=2). Diagnostic imaging showed tumor in the temporal lobe (n=5), parietal lobe (n=2), temporoparietal lobe (n=2), frontal lobe (n=1), occipital lobe (n=1), others (n=2). BRAF V600E mutation were identified in three of five analyzed tumors including PXA (n=4) and APXA (n=1). Surgical intervention consisted of gross total resection (n=8) and near/subtotal resection (n=5). Ten patients (76%) required a second surgery (median 2; range 1–4) due to local recurrence. The median time to recurrence was 3 years (range 6 months - 7 years). Three patients (23%) had malignant transformation of PXA, which occurred three to eight years from the initial surgery; one of them also had extensive spinal metastasis. Focal radiation was given to six patients (46%) due to multiple recurrence (n=2), malignant transformation (n=3), APXA (n=1). At a median follow up of 8 years (range 3 to 20 years), eight patients remain alive, three patients had lost to follow up, two patients died from progressive disease. Long-term sequelae varied as follows; seizures (n=5), motor weakness (n=4), cranial nerve palsies (n=2), and learning disability (n=1). **CONCLUSION:** PXA is associated with high local recurrence rate and uncommonly malignant transformation to APXA in pediatrics, which requires close follow-up due to unpredictable biological behavior of these tumors.

RARE-32. POLYMORPHOUS LOW-GRADE NEUROEPITHELIAL TUMOR OF THE YOUNG (PLNTY): GENETIC ANALYSIS CONFIRMS FREQUENT MAPK PATHWAY ACTIVATION

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Polymorphous low-grade neuroepithelial tumor of the young (PLNTY) is a recently described epileptogenic tumor characterized by oligodendrogloma-

like components, aberrant CD34 expression, and genetic MAPK pathway activation through alterations such as BRAF V600E mutation, and FGFR2-KIAA1598/CTNNA3 and FGFR3-TACC3 fusions. We report the molecular profiling of PLNTY in 9 patients, 7 female: 2 male, median age at diagnosis of 16 years (range, 5–34). All tumors were supratentorial with diagnostic morphological features of PLNTY including oligodendrogloma-like areas and strong diffuse CD34 immunostaining. Four (of 9; 44%) tumors were positive for BRAF V600E immunostain, indicating the presence of a BRAF V600E mutation. The 6 cases evaluated for IDH status were negative by IDH1-R132H immunostain (n=5; 3 BRAF V600E-negative and 2 BRAF V600E-positive) or by NGS (n=1; BRAF V600E-negative). Oncoscan chromosomal microarray performed in 5 BRAF V600E-negative tumors showed recurrent copy number changes including gain of whole chromosomes 5, 7, 8, 9, 12, 18, 19, 20, 21 and X, and loss of chromosomes 1, 2, 10q, 13, 22 and Xq. The 10q losses (n=2) were highly suggestive of an FGFR2-KIAA1598 and of a potentially novel FGFR2 underlying fusion event in one case each. Custom targeted neuro-oncology DNA and RNA NGS panel performed in 2 cases revealed a fusion similar to fusions previously reported in pilocytic astrocytoma: one with a KIAA1549-BRAF (exon 15-exon 9) fusion associated with a 7q34 ~785 kilobase deletion rather than the characteristic ~2 megabase duplication seen in pilocytic astrocytoma, and another with a QKI-NTRK2 (exon 6-exon 15) fusion associated with a 9q21 ~191 kilobase duplication disrupting NTRK2. The KIAA1549-BRAF fusion-positive case also had a TP53 mutation with loss of whole chromosome 17, suggesting TP53 complete inactivation. This study confirms that PLNTY is a low-grade neuroepithelial tumor with frequent MAPK pathway activation and expands the spectrum of MAPK activating alterations observed in PLNTY.

RARE-33. LEPTOMENINGEAL DISEASE IN PATIENTS WITH MIDLINE GLIOMAS HARBORING HISTONE H3 K27M MUTATIONS
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INTRODUCTION: The 2016 WHO classification describes a specific subtype of midline gliomas harboring histone 3 (H3) K27M mutations which compromise 15–40% of gliomas in children and young adults. Since we began to perform molecular profiling at Memorial Sloan Kettering Cancer Center (MSKCC) we have observed an increased prevalence of leptomeningeal disease (LMD) in this population. However, the true incidence and the clinical behavior of this group has not been well-defined. **METHODS:** This is a retrospective study of patients with H3K27M/I diffuse midline gliomas at MSKCC from 01/2012 to 01/2019. Mutations were identified through next-generation sequencing (NGS). **RESULTS:** We identified 24 patients. Median age was 21 (6–70) and 13 were male. Thirteen tumors were in the thalamus, 6 in the brainstem, 4 in the spinal cord, and 1 in the pineal region. H3K27M mutations were detected by NGS from tumor tissue in 21 patients, from cerebral spinal fluid (CSF) circulating tumor DNA (ctDNA) in 2 and from tissue and CSF ctDNA in one. LMD was diagnosed in 17/24 (71%) patients radiographically. Of these, 8 underwent LP: CSF cytology was positive in 2/8 and CSF ctDNA was detected in 3/3. All patients received RT and one or more lines of chemotherapy. At analysis, thirteen patients remain alive. Median time to last follow up for all patients was 14.2 months. Median time from diagnosis to LMD was 13.2 months (0–45.1), with median OS of 6.5 months (0.3–27) after diagnosis of LMD. **CONCLUSION:** Our study showed that more than two-thirds of the patients with H3 K27M diffuse midline developed LMD. Neuroaxis imaging should be performed in conjunction with CSF studies to diagnose LMD. Besides, CSF ctDNA represents an important tool to identify molecular profile of tumors when biopsy is not feasible or limited for the analysis.

RARE-34. TUMOR IMMUNITY AND EXTRACRANIAL METASTASES, AND MECHANISM OF PD-L1 EXPRESSION IN INTRACRANIAL SOLITARY FIBROUS TUMOR/HEMANGIOPERICYTOMA

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Intracranial solitary fibrous tumor (SFT) /hemangiopericytoma (HPC) are rare, however, these tumors are often associated with aggressive clinical course with recurrence and/or extracranial metastasis. PD-1, PD-L1 play important roles as immune-checkpoint mediators within tumor micro-environment, and the antibodies to these molecules are now approved for the treatment of various kinds of cancers. Some mechanisms of activation of PD-L1 are reported, including cytokines or chemokines from immune cells in tumor microenvironment, and genetic mutations such as translocation, or amplification. We have investigated the expression of PD-1, PD-L1, and tumor infiltrating lymphocytes (TIL) in 16 cases of SFT/HPC by immunohistochemistry. Kaplan-Meier method and log-rank/Wilcoxon tests were used to analyze the relationship between their expression with overall survival (OS), progression free survival (PFS), metastasis free survival (MFS),