Title

PATH-22. COMPREHENSIVE ANALYSIS OF DIVERSE LOW-GRADE NEUROEPITHELIAL TUMORS WITH FGFR1 ALTERATIONS REVEALS A DISTINCT MOLECULAR SIGNATURE OF ROSETTE-FORMING GLIONEURONAL TUMOR

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PATH-18. A MULTI-CENTER CASE SERIES OF ADULT K27M MUTATED DIFFUSE MIDLINE GLIOMAS REVEALING A POPULATION UNIQUE FROM PAEDIATRIC CASES

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BACKGROUND: Histone mutations in the K27M gene were first described in 2014, and incorporated into the WHO CNS tumour classification system in 2016. They are typically associated with diffuse midline gliomas (DMG). Presenting symptoms vary greatly, with some experiencing significant delay in diagnosis. Median survival is only 9-12 months for these patients. Biopsy samples are small, and in some due to location, not performed. Although data is predominately based on the paediatric population, DMGs are seen in both adolescence and adults. In this multi-site retrospective study, we describe 11 adult patients with K27M DMG gliomas across two tertiary Neuro-Oncology services in Sydney, Australia. To the authors' knowledge we present the largest known collection of adult K27M cases in the Asia-Pacific region with correlation of treatment, clinicopathologic and radiologic features with outcomes. METHODS: The glioma databases of Royal North Shore Hospital (RNSH) and Royal Prince Alfred Hospital (RPAH) between January 2009 and March 2020 were interrogated to identify patients. Selection criteria included patients aged ≥ 18 years who presented with a DMG, had undergone biopsy, and had confirmed K27M via next generation sequencing. Clinicopathologic, radiologic and treatment outcomes were extracted for correlation. RESULTS: Eleven patients fitting the selection criteria were identified and reported. The median age at diagnosis was 30 years and 4 were female. Five presented with hydrocephalus, the most common presenting symptoms were headaches and nausea and/or vomiting (n= 4 and n= 2 respectively). The median progression-free survival was 13 months (4-31 months) and the median overall survival was 23 months (4-59 months). CONCLUSION: This case series reports the outcomes of older patients with K27M. The clinical course demonstrated suggests a divergence from paediatric biology. Ongoing studies are required to further characterise the histopathological and clinical differences of these tumours in older patients.

PATH-19. MOLECULAR, HISTOLOGIC AND CLINICAL CHARACTERISTICS OF OLIGODENDROGLIOMAS: A MULTI-INSTITUTIONAL RETROSPECTIVE STUDY

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In the 2016 WHO classification of CNS tumors, oligodendrogliomas are molecularly defined by *IDH1 or IDH2* mutations and 1p/19q co-deletion. Some reports suggest that PI3K pathway alterations may confer increased risk of progression and poor prognosis in oligodendroglioma. However, factors that influence prognosis in molecularly defined oligodendroglioma (mOGD) have not been thoroughly studied. Also, the benefits of adjuvant radiation and temozolomide in mOGDs remain to be determined. 107 mOGDs diagnosed between 2008-2018 at the University of Texas Health Science Center at Houston (n= 39) and MD Anderson Cancer Center (n= 68) were included. A retrospective review of the demographic, clinical, histologic, molecular, and outcomes were performed. Median age at diagnosis was 37 years and 61 (57%) patients were male. There were 64 (60%) WHO Grade 2 and 43 (40%) WHO Grade 3 tumors. Ninety-five (88.8%) tumors were *IDH1*-mutant and 12 (11.2%) were *IDH2*-mutant. Eighty-two (77%) patients were stratified as high-risk: older than 40-years and/or subtotal resection (RTOG 9802). Gross-total resection was achieved in 47 (45%) patients. Treatment strategies included observation (n= 15), temozolomide (n= 11), radiation (n= 13), radiation with temozolomide (n= 62) and other (n= 6). Our results show a benefit of temozolomide vs. observation in progression-free survival (PFS). However, no benefit in PFS or overall survival (OS) was observed when comparing radiation vs. radiation with temozolomide. *PIK3CA* mutations were detected in 15 (14%) cases, and patients with *PIK3CA*-mutant mOGDs showed worse OS (10.7-years vs 15.1-years, p= 0.009). Patients with WHO Grade 3 tumors had shorter PFS but no significant difference in OS was observed compared to grade 2. Our findings suggest that mOGDs harboring *PIK3CA* mutations have worse OS. Except for an advantage in PFS in temozolomide treated patients, adjuvant treatment with radiation or the combination of both, showed no significant advantage in terms of OS.

PATH-20. A CASE REPORT OF NOVEL BCR-ABL1 FUSION IN GLIOBLASTOMA, IDH-WILD TYPE

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In recent years, molecular tests have become essential to diagnose brain tumor. Although numerous molecular studies of glioblastoma have been conducted, pathogenesis of glioblastoma has not been fully identified. Present report is an extraordinary case of glioblastoma, *IDH*-wild type with *BCR-ABL1* fusion. The *BCR-ABL1* fusion is also called 'Philadelphia gene' and have never been found in solid tumors other than hemato-lymphoid malignancies. A 63-year-old man presented with clumsy and inappropriate word symptoms a week ago. Magnetic resonance imaging test revealed a 6.6 x 5.0 cm heterogeneously enhancing mass in the left temporal lobe and the patient underwent tumorectomy. Microscopically, tumor showed increasing cellularity, marked nuclear atypia and brisk mitosis. Microvascular proliferation and necrosis was present that can be diagnosis as glioblastoma. In addition, tumor showed strong GFAP positivity which indicated the glial differentiation. There is no evidence of diagnosis as another tumor including metastatic carcinoma or hemato-lymphoid malignancy. Interestingly, *BCR-ABL1* fusion was detected in next generation sequencing test. The *BCR-ABL1* fusion was a novel finding in glioblastoma, thus additional fluorescence in situ hybridization tests were conducted for confirmation *BCR-ABL1* fusion and the same alteration was found. The patient had no leukemic presentation in the blood test, radiologic test and clinical symptom. Notably, this is the first case report that glioblastoma has the *BCR-ABL1* fusion.

PATH-22. COMPREHENSIVE ANALYSIS OF DIVERSE LOW-GRADE NEUROEPITHELIAL TUMORS WITH FGFR1 ALTERATIONS REVEALS A DISTINCT MOLECULAR SIGNATURE OF ROSETTE-FORMING GLIONEURONAL TUMOR

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The *FGFR1* gene encoding fibroblast growth factor receptor 1 has emerged as a frequently altered oncogene in the pathogenesis of multiple low-grade neuroepithelial tumor (LGNET) subtypes including pilocytic astrocytoma (PA), dysembryoplastic neuroepithelial tumor (DNT), rosette-forming glioneuronal tumor (RGNT), and extraventricular neurocytoma (EVN). These activating *FGFR1* alterations in LGNET can include tandem duplication of the exons encoding the intracellular tyrosine kinase domain, in-frame gene fusions most often with *TACC1* as the partner, or hotspot missense mutations within the tyrosine kinase domain (either p.N546 or p.K656). However, the specificity of these different *FGFR1* events for the various LGNET subtypes and accompanying genetic alterations are not well defined, nor are the histopathologic features of pilocytic astrocytomas with *FGFR1* alterations versus those harboring the more common *BRAF* mutations or fusions. Here we performed comprehensive genomic and epigenomic characterization on a diverse cohort of 30 LGNET with *FGFR1* alterations. We identified that RGNT harbors a distinct epigenetic signature compared to other LGNET with *FGFR1* alterations, and is uniquely characterized by *FGFR1* kinase domain hotspot missense mutations in combination with either *PIK3CA* or *PIK3R1* mutation, often with accompanying *NF1* or *PTPN11* mutation. In contrast, EVN harbors its own distinct epigenetic signature and is characterized by *FGFR1-TACC1* fusion as the solitary pathogenic alteration. Additionally, DNT and PA are characterized by

either kinase domain tandem duplication or hotspot missense mutations, occasionally with accompanying *NF1* or *PTPN11* mutation, but lacking the accompanying *PIK3CA* or *PIK3R1* mutation that characterizes RGNT. The glial component of LGNET with *FGFR1* alterations typically has a predominantly oligodendroglial morphology, and many of the pilocytic astrocytomas with *FGFR1* alterations lack the biphasic pattern, piloid processes, and Rosenthal fibers that characterize pilocytic astrocytomas with *BRAF* mutation or fusion. Together, this analysis refines the classification and histopathologic spectrum of LGNET with *FGFR1* alterations.

PATH-23. GENOMIC LANDSCAPE OF IDH-MUTANT PRIMARY GLIOBLASTOMAS SHOWS DISTINCT CLINICAL AND MOLECULAR FEATURES AND THAT CDKN2A SHOULD BE SUPPLEMENTED WITH MGMTP AND G-CIMP FOR PRECISE PROGNOSTICATION

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There have only been rare studies of *IDH*-mutant *primary* glioblastomas (*IDH*-mutant astrocytoma IV); there were one or two studies on secondary glioblastomas. In a cohort of 70 cases, we conducted clinical analysis, methylation profiling, RNA sequencing, targeted sequencing, and *TERT*p seqeuncing on available FFPE tissues. Median follow-up was 58.2 months (n= 60). *IDH*-mutant primary glioblastomas had longer median OS (30.4 months) and median PFS (25.9 months) than *IDH*-mutant secondary glioblastomas as in the literature or established databases. *MGMT*p methylated cases had better OS (p= 0.001) and it was an independent prognosticator. We previously showed G-CIMP to be an independent prognostic marker for *IDH*-mutant glioblastomas (NOA 2019). Although *CDKN2A* deletion was an independent prognostic marker for poorer OS (p= 0.036) and PFS (p= 0.005), *MGMT*p methylation had a trend of superseding *CDKN2A* deletion (p= 0.055) for prognostication and G-CIMP subgroups could similarly partially supersede *CDKN2A* deletion (p= 0.582). Hence, *CDKN2A* deletion should be supplemented with these two biomarkers for finer prognostication. Targeted sequencing (n= 55) showed that there were more *ATRX* (35/55, 64%), *TP53* (31/55, 56%), *KMT2D* (18/55, 33%), *POLE* (11/55, 20%) and *MSH6* (7/55, 13%) mutations, but fewer *TERT*p (3/69, 4%) and *PTEN* (1/55, 2%) mutations than *IDH*-wildtype glioblastomas as from literature and databases. CNVs revealed by methylomes (n= 53) and mutations (n= 55) showed that there were more *PDGFRA* (amplification: 9/53, 17%, mutation: 10/55, 18%) alterations, but fewer *MET* (amplification: 3/53, 6%, mutation: 4/55, 7%) alterations and hypermutated (6/55, 11%) cases than *IDH*-mutant secondary glioblastomas from literature. GISTIC analysis revealed amplifications of *CCND2*, *CDK4*, *MYC*, and *PDGFRA*, deletions of *CDKN2A*, *RB1*, and chromosome 10q to be significant CNVs (q< 0.05). There were few *EGFR* amplifications (2/53, 4%), which was different from regular glioblastomas. RNA sequencing (n= 42) showed few fusions (4/42, 10%), which was different from *IDH*-mutant secondary glioblastomas.

PATH-24. DETECTION OF POINT MUTATIONS AND GENE FUSIONS FROM CIRCULATING CELL-FREE DNA (CFDNA) OF GLIOBLASTOMA (GBM) PATIENTS

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BACKGROUND: GBM is characterized by intratumoral heterogeneity. Tumor heterogeneity, clonal diversity and mutation acquisition hamper the ability to tailor personalized therapy for GBM. Tumor sampling has limited ability to accurately capture the molecular landscape of the tumor and to disclose acquired molecular aberrations. Mutation analysis of cfDNA is a non-invasive procedure which may overcome these limitations as it may reflect the real composition of the tumor and track the molecular evolution. We sequenced cfDNA of GBM patients and assessed mutation patterns and fusion genes. METHODS: We collected blood and respective tumor samples from 27 GBM patients and blood samples from 14 healthy controls. Tumor DNA, cfDNA and WBC DNA were sequenced using deep sequencing procedures. The data were analyzed for detection of single nucleotide polymorphism (SNPs) and gene-gene fusions. RESULTS: GBM cfDNA concentrations were significantly elevated (median: 23.63 ng/mL; range 12.6–137) compared to healthy controls (median 2.06; range 1.68–7.62) ($p < 0.0001$). We identified unique SNPs in each glioma patient's cfDNA and the corresponding tumor DNA including the top-10 most frequently mutated genes in GBM. For example, mutation of *TP53* was detected in18.75%; *EGFR* in 37.5%; *NF1*-12.5%; *LRP1B*-25% and *IRS4* in 25%. For gene-gene fusion we used the in-house fusion gene database, ChiTaRS 5.0, and identified fusions in cfDNA and tumor DNA. Thus, *KMT2A-FLNA* was the most frequent fusion found in 16.4% of samples. *BCR-ABL1* in 8.82% and *FGFR1-BCR* in 2.94%. Other fusions included *COL1A1-PDGFB* (5.88%), *NIN-PDGFRB* (5.88%), *KIF5B-RET* (5.88%) and also *TPM3-ROS1*(2.94%), *TFG-ALK*(2.94%), *MSN-ALK* (2.94%) and *NPM1-ALK* (2.94%) which may be targeted by brain penetrating drugs that are ROS1 and ALK inhibitors. CONCLUSIONS: Our study suggests that plasma cfDNA analysis may help to uncover real time mutational and gene fusion status of GBM by a non-invasive procedure. It may identify drug targets based on personalized gene-gene fusions.

PATH-25. EXPERIENCE WITH AN RNA FUSION TRANSCRIPT PANEL FOR DETECTION OF POTENTIAL THERAPEUTIC TARGETS IN GLIOMAS

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Next-generation sequencing to identify fusion proteins is increasingly employed across oncology to identify therapeutic targets.[1] The clinical relevance of detecting fusion transcripts is well described in the pediatric glioma population, but similar reports for adult patients are scant.[2] The University of Pennsylvania Health System (UPHS) has implemented routine use of an RNA fusion transcript panel (ArcherDX, Boulder, CO) on resected brain tumors since August 2017. Here we report the results of this analysis for adult patients with gliomas and highlight potentially targetable fusions. Over the period of August 2017 through December 2019, fusion analysis was performed on resected gliomas of over 200 patients. Ninety-seven patients were found to have a detected fusion protein. Eighty-three of the 97 patients (86%) had glioblastoma and 14 (14%) had lower grade gliomas. A total of 26 unique fusions were found. The most common (n=55) was EGFRvIII. *NTRK* fusions were of special interest as FDA-approved agents are available for patients harboring this genetic alteration.[3] We identified 8 patients (8%) with *NTRK* fusions including *ARHGEFF2:NTRK1*, BNA: *NTRK1*, BCR: *NTRK2*, *PDE5A/NTRK2*, *SKAP2/NTRK2*, and STRN: *NTRK2*. Several of these patients went on to receive TRK kinase inhibitors with clinical benefit. Of the 97 patients with a detected fusion, 24 (25%) were found to have a potentially targetable fusion other than EGFRvIII, with inhibitors available in clinical trials or as off-label therapy. These fusions included *BRAF* (n=5; BRAF: *LHFPL3*, *KIAA1549:BRAF*), *FGFR* (n=9; *FGFR3:BRAP*, *FGFR3:RENBP*, *FGFR3:TACC3*), *MET* (n=7; *CAPZA2-MET*, *KLF12:MET*, *PTPRZ1:MET*, *ST7:MET*), and *ROS1* (n=3; DLL: *ROS1*, GOPC: *ROS1*). In sum, routine clinical use of an RNA-based fusion transcript panel for adult patients with glioma may allow for detection of therapeutically targetable alterations in a meaningful proportion of cases. Prospective trials are needed to determine whether targeting specific fusions is beneficial for adult patients with glioma.

PATH-26. INTEGRATED MOLECULAR AND CLINICAL ANALYSIS OF BRAF-MUTATED GLIOMA IN ADULTS

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INTRODUCTION: *BRAF* mutations in glioma have been recognized as a significant driver of disease in pediatric low-grade glioma, but the implications of *BRAF* alterations on disease trajectory and response to treatment are unknown in adult glioma. Here, we characterize a multi-institutional cohort of adults with *BRAF*-altered glioma. METHODS: We identified patients aged ≥ 18 years with glioma containing *BRAF* alteration on sequencing in multi-institutional cohorts (Dana-Farber/Brigham Cancer Center, Johns Hopkins Hospital, GENIE, TCGA). *BRAF* mutations were grouped into three previously-defined classes: I (RAS-independent/dimerization-independent), II (RAS-independent/dimerization-dependent), III (RAS-dependent/dimerization-dependent). RESULTS: We identified 198 adults with *BRAF*-altered glioma (median age 42 years, range 18-85 years), including 17 WHO grade I, 33 grade II, 26 grade III, 114 grade IV, and