Title

PATH-38. ROSETTE-FORMING GLIONEURONAL TUMOR IS DEFINED BY FGFR1 ACTIVATING ALTERATIONS WITH FREQUENT ACCOMPANYING PI3K AND MAPK PATHWAY MUTATIONS

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alterations were analyzed in relation to the patients' tumor locations, demographics, and outcomes. We used multiple binary logistic regressions to assess whether demographics and tumor location were predictive of the above alterations We also assessed the relationship between molecular alterations and outcomes when controlling for treatment and demographic variables. Among demographic variables, age predicted alterations in IDH1, EGFR, TERT, TP53, and PTEN. Frontal lobe tumors were more likely to be IDH1-mutated, irrespective of patient age. Sex and race did not predict the incidence of the molecular alterations of interest. Analysis of outcomes revealed that, when controlling for treatment and demographic variables, TERT promoter mutations, TP53 nonsense mutations, and EGFR A289V were predictive of a decreased progression-free survival, while CDKN2A deletion, PTEN missense mutations, and EGFR A289V were predictive of decreased overall survival. Our experience highlights the importance of incorporating routine NGS in the management of patients with glioblastoma. More studies are required to evaluate the predictive and/or prognostic values of different molecular alterations.

PATH-36. MACHINE LEARNING TO DETECT GLIOMAS IN URINE-BASED LIQUID BIOPSY

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BACKGROUND: Diffuse gliomas are the most common primary malignant brain tumors, whose overall prognosis is quite dismal. Tumor-cell-secreted extracellular vesicles (EVs) participate in physiological and pathological processes and have potential applications to diagnostics of malignant tumors including diffuse gliomas. Because urine is less invasive to collect, development of early diagnosis based on urine EVs is eagerly awaited. In this study, we captured urine EVs of patients with gliomas efficiently with the nanowire device and compared expression profile of microRNAs (miRNAs) within urine EVs with that of healthy donors to identify diagnostic accuracy by a machine learning algorithm. METHODS: 62 patients with diffuse gliomas, including 27 glioblastoma and 35 lower grade gliomas, and 100 healthy donors were analyzed, along with orthotopic transplant mouse model. Urinary EVs were obtained with the nanowire device which could collect EVs more efficiently than the conventional ultracentrifugation method (Yasui et.al., Science Adv.2017). Machine learning methods were performed to select the miRNAs which could distinguish patients with gliomas from healthy control. RESULTS: More than 2400 miRNAs were obtained from all urine samples. We identified miRNA panels that provided high diagnostic accuracy of diffuse gliomas (92.5%). There were 440 miRNAs whose expression increased by more than 1.5 fold ($p< 0.05$) as compared to healthy donor samples (glioma-upregulated miRNAs), whereas the expression of 87 miRNAs decreased to less than 2/3-fold ($p< 0.05$) (glioma-downregulated miRNAs). Mouse miRNAs which were homologous to glioma-upregulated and -downregulated miRNAs showed significantly high and low level expressions, respectively, in glioma mouse models as compared to normal control mice, confirming the reliability of urine miRNA-based diagnosis. Furthermore, some of these glioma-upregulated miRNAs has been reported to be involved in tumor progression. CONCLUSIONS: miRNAs obtained from urine could be biomarkers for detection of gliomas by machine learning and some of these could be associated with tumor progression.

PATH-37. PROGNOSTIC ROLE OF TERT PROMOTER MUTATIONS IMPROVES THE STRATIFICATION OF IDH-MUTATED LOWER GRADE GLIOMA

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TERT promoter mutation is associated with 1p/19q codeletion and favorable prognosis in *IDH*-mutated gliomas. Prognostic and diagnostic significance of *TERT* promoter mutation is well-recognized in *IDH*-wildtype glioblastomas, but not in *IDH*-mutated gliomas. We investigated prognostic efficacy of *TERT* mutation in a cohort of 560 Japanese *IDH*-mutated adult gliomas. The molecular status of *IDH*, *TERT* and 1p/19q and patient clinical data including Karnofsky performance status (KPS) were collected in all cases. *TERT* mutations and 1p/19q codeletions were found in 303 and 285 cases, respectively. The patient cohort was divided into four groups by a combination of the 1p/19q and *TERT* status. The characteristics of 1p/19q intact-*TERT* mutated group (Astro-TERT group, n=24) were compared with those of 1p/19q intact-*TERT* wild (Astro-group, n=251) or 1p/19q codeleted-*TERT* mutated (Oligo-group, n=279) cases. Astro-TERT group with any grade showed intermediate overall survival between the Oligo-group and Astro-group although the survival differences were not statistically significant (median overall survival (OS) not reached (NR) versus NR, and 106 months, respectively. $p >0.05$). We further conducted subgroup analysis by adjusting KPS and WHO grade as Cox regression analysis for survival indicated the unfavorable survival impact of KPS < 90 and WHO grade IV. In the subgroup with favorable KPS (90–100) and grade II-III (n=438), The OS of Astro-TERT group (median NR) was significantly longer survival than that of Astro-group (median 120.2 months, $p=0.032$), and was comparable with that of the Oligo-group (median NR, $p >0.05$). On the other hand, OS of none of the molecular groups significantly differ in poorer KPS subgroups ($p >0.05$). In grade IV tumors, the OS of the Astro-TERT group (NR) was comparable with that of Astro-group (29 months, $p=0.19$) rather than Oligo-group (NR, $p=0.051$). Thus, *TERT* promoter status provides a valuable prognostic information for *IDH*-mutated grade II-III gliomas in the current molecular diagnostic system.

PATH-38. ROSETTE-FORMING GLIONEURONAL TUMOR IS DEFINED BY FGFR1 ACTIVATING ALTERATIONS WITH FREQUENT ACCOMPANYING PI3K AND MAPK PATHWAY MUTATIONS

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BACKGROUND: Rosette-forming glioneuronal tumor (RGNT) is an uncommon CNS tumor originally described in the fourth ventricle characterized by a low-grade glial neoplasm admixed with a rosette-forming neurocytic component. METHODS: We reviewed clinicopathologic features of 42 patients with RGNT. Targeted next-generation sequencing was performed, and genome-wide methylation profiling is underway. RESULTS: The 20 male and 22 female patients had a mean age of 25 years (range 3–47) at time of diagnosis. Tumors were located within or adjacent to the lateral ventricle (n=16), fourth ventricle (15), third ventricle (9), and spinal cord (2). All 31 tumors assessed to date contained *FGFR1* activating alterations, either in-frame gene fusion, kinase domain tandem duplication, or hotspot missense mutation in the kinase domain (p.N546 or p.K656). While 7 of these 31 tumors harbored *FGFR1* alterations as the solitary pathogenic event, 24 contained additional pathogenic alterations within PI3-kinase or MAP kinase pathway genes: 5 with additional *PIK3CA* and *NF1* mutations, 4 with *PIK3CA* mutation, 3 with *PIK3R1* mutation (one of which also contained focal *RAF1* amplification), 5 with *PTPN11* mutation (one with additional *PIK3R1* mutation), and 2 with *NF1* deletion. The other 5 cases demonstrated anaplastic features including hypercellularity and increased mitotic activity. Among these anaplastic cases, 3 harbored inactivating *ATRX* mutations and two harbored *CDKN2A* homozygous deletion, in addition to the *FGFR1* alterations plus other PI3-kinase and MAP kinase gene mutations seen in those RGNT without anaplasia. CONCLUSION: Independent of ventricular location, RGNT is defined by *FGFR1* activating mutations or rearrangements, which are frequently accompanied by mutations involving *PIK3CA*, *PIK3R1*, *PTPN11*, *NF1*, and *KRAS*. Whereas pilocytic astrocytoma and ganglioglioma are characterized by solitary activating MAP kinase pathway alterations (e.g. *BRAF* fusion or mutation), RGNT are genetically more complex with dual PI3K-Akt-mTOR and Ras-Raf-MAPK pathway activation. Rare anaplastic examples may show additional *ATRX* and/or *CDKN2A* inactivation.

PATH-39. DNA MISMATCH REPAIR ENZYME IMMUNOHISTOCHEMISTRY IS A RAPID, EFFECTIVE SCREENING TEST FOR HYPERMUTATED GLIOMAS

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BACKGROUND: While gliomas with hypermutated DNA are resistant to alkylating agents like temozolomide, they may be especially responsive to immunotherapy, since they express abundant neoantigens on their cell surfaces. Screening for hypermutated gliomas is currently being done through next-generation sequencing (NGS) panels that cover large portions of tumor DNA, although this is costly and access to such testing is not universal. Since hypermutated gliomas typically contain inactivating mutations in one of the main DNA mismatch repair (MMR) proteins, and cancers with an MMR mutation usually show loss of normal MMR protein, we sought to determine the feasibility of rapidly screening for hypermutated gliomas with an MMR immunohistochemistry (IHC) panel that is already in widespread use for colorectal adenocarcinomas. METHODS: Tumor mutation burden (TMB) was determined via NGS for 101 gliomas, including 64 GBMs, 24 grade II-III astrocytomas, 9 grade II-III oligodendrogliomas, and 4 grade I gliomas. IHC for MSH2, MSH6, MLH1, and PMS2 was performed and analyzed on all gliomas while blinded to mutation profile and TMB. RESULTS: Seven of 101 gliomas (7%) showed loss of an MMR protein by IHC. All 7 had matching MMR gene mutations and were hypermutated (100%), defined as TMB >20 per megabase of DNA. Of the remaining 94 with intact MMR IHC, only one was hypermutated. That case had an inactivating splice region mutation in another gene involved in DNA repair, *ATM*, although ATM is not part of the IHC panel originally developed for colorectal cancer. Overall sensitivity and specificity of the current MMR IHC panel for hypermutated gliomas was therefore 88% and 100%, respectively. CONCLUSION: The colorectal MMR IHC panel, available in virtually all clinical IHC labs, is also a good screening test for hypermutated gliomas. Expansion of the panel to include even more DNA repair proteins, like ATM, would enhance its utility.

PATH-40. PROFILING PLEOMORPHIC XANTHROASTROCYTOMA WITH DNA METHYLATION AND EXPLORING THE TUMOR IMMUNE CELL-TYPE COMPOSITION WITH METHYLATION-BASED DECONVOLUTION

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INTRODUCTION: Pleomorphic xanthoastrocytoma (PXA) is a rare type of brain tumor that commonly affects children and young adults. PXAs are typically characterized by tumor lymphocytic infiltration, but the significance of the tumor immune microenvironment has not yet been well-defined. In this study, we correlated DNA methylation profiling of PXAs with clinical outcome and explored the tumor microenvironment by analyzing inflammatory cell populations. METHODS: We retrospectively analyzed 30 tumor samples, of which 21 tumor samples from 18 subjects had a diagnosis of PXA both by DNA methylation and by histology. MethylCIBERSORT was used to deconvolute PXA inflammatory cell populations and compare them with inflammatory cell populations in previously published cohorts of IDH wildtype glioblastoma and ganglioglioma samples. RESULTS: Median age at diagnosis was 16 years (range 7–32). 3-year and 5-year overall survival (OS) was 73% and 71% respectively. CDKN2A/B deletion was noted in 15 out of 18 subjects (83%). 10 out of the 12 subjects (83%) that had testing for BRAFV600E showed the mutation. CDKN2A/B deletion and Trisomy 7 did not show any significant association with overall survival ($p = 0.39$ and $p = 0.69$). Decreased survival was observed in subjects with tumors lacking the BRAFV600E mutation ($p = 0.03$). PXAs were observed to have significantly increased CD8 T-cell epigenetic signatures compared to gangliogliomas ($p = 0.0019$) and significantly increased CD8 T-cell and CD19 B-cell signatures compared to IDH wildtype glioblastomas ($p = 0.0011$ and $p = 0.0011$). CONCLUSION: This research suggests that PXAs have a distinct methylation profile that correlates with clinical outcome. PXAs show significant upregulation of CD8 T-cell epigenetic signatures compared to gangliogliomas and significant upregulation of CD8 T-cell and CD19 B-cell epigenetic signatures compared to IDH wildtype glioblastomas. This distinct characterization of immune cell-types in PXAs could have an impact on future development of immunotherapy.

PATH-41. LONGITUDINAL MATCHED MUTATIONAL ANALYSIS IN RECURRENT AND MULTIFOCAL GLIOMAS

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Re-resection of recurrent gliomas and multifocal gliomas are relatively uncommon resulting in limited understanding of the molecular profile of gliomas in those settings. Here we present a comprehensive mutational analysis via next generation sequencing (NGS) of 20 gliomas from 9 patients treated at our institution: one recurrent oligodendroglioma, one secondary glioblastoma (GBM), five locally recurrent primary GBMs, and two multifocal recurrent primary GBMs. Tumor mutational burden (TMB) range was 1.8–60.6 mutations/megabase (mt/Mb). Elevated TMB was seen in the initial (49.2 mt/Mb) and recurrent (60.6 mt/Mb) secondary GBM samples and in the distal recurrent GBM sample (50.9 mt/Mb) of one of the two patients with multifocal recurrent disease, suggesting a temozolomide-induced hypermutated state. Interestingly, the elevated TMB in the patient of multifocal recurrence occurred 5 years after completing 12 cycles of TMZ and was seen in the distal but not local focus of disease recurrence where TMB remained at 1.8 mt/Mb. The patient with multifocal (right frontal and right temporal) GBM at diagnosis developed recurrence in the temporal location only. NGS of the 2 resected tumors revealed 4 common somatic mutations, 3 mutations unique to the right frontal lesion and 8 mutations unique to the right temporal lesion. Additionally, our oligodendroglioma who was heavily treated in the six years prior to his last recurrence retained 4/6 of the initial somatic mutations and acquired 5 new ones upon the last recurrence. This analysis further highlights glioma spatiotemporal heterogeneity and the linear and divergent evolution upon disease recurrence and in the multifocal pre-treatment and recurrent settings. We also show that extensive oncogenic alterations can occur upon glioma recurrence, which is a major therapeutic barrier in managing recurrent disease, a barrier that can render the initial genomic profile of the disease, the basis of molecularly targeted therapy in the majority of cases, less meaningful.

PATH-42. IDH-MUTANT LOWER-GRADE ASTROCYTOMAS CAN BE STRATIFIED FOR RISK BY CDKN2A, CDK4 AND PDGFRA COPY NUMBER ALTERATIONS

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In the 2016 WHO classification of tumors of the CNS, isocitrate dehydrogenase (IDH) mutation is a main classifier for lower-grade astrocytomas and IDH mutated astrocytomas is now regarded as a single group with good prognosis. However, the molecular and clinical heterogeneity among