

and magnetic resonance imaging (MRI) showed a large well-circumscribed mass in his left cerebellum with ventricular dilatation. He referred to our hospital, and an additional MRI revealed diffuse and weak enhancement of gadolinium and low ADC values in mass. Immediately, he underwent total removal of the tumor and ventricular drainage, and his consciousness recovered soon after surgery. The tumor presented high BCOR expression by IHC, but target PCR did not identify exon 15 ITD of *BCOR*. As the previously-reported clinical and imaging features of CNS HGNET-*BCOR* resembled our case, we clinically diagnosed it as a similar phenotype of CNS HGNET-*BCOR* without exon 15 ITD. He received 60 Gy of extended-local irradiation with concomitant temozolomide and discharged without any neurological deficits. Since *BCOR* alterations, including ITD, gene fusions, and mutations, play an oncogenic role in several cancers, the present case might harbor another gene aberration of *BCOR*.

PATH-04. AN ENHANCED AI-DRIVEN PLATFORM FOR PRECISION MOLECULAR BRAIN TUMOR DIAGNOSTICS

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Tumors of the CNS represent one of the most complex groups of human cancer, with a vast number of different entities occurring across a spectrum of ages and anatomic locations. This heterogeneity makes accurate diagnosis challenging, with the current gold standard relying on multiple subjective elements. We recently proposed a classification algorithm based on tumor DNA methylation profiling as an objective way to assign samples to over 80 distinct molecular classes. Here we present a substantial update to our machine learning-based algorithm, with more than 170 molecular classes now being represented amongst the 5,915 samples in our reference cohort. These new classes include further subclassification of known groups such as medulloblastoma and ependymoma, as well as multiple new molecular entities described here for the first time. A further improvement is the introduction of a more rationally layered output, making use of 'families' of closely-related molecular classes to improve the compatibility with the current WHO classification of CNS tumors. This approach is designed to increase the clinical relevance of the primary output, while also retaining the full information content from the random forest-driven classification. Benchmarking our new algorithm by cross-validation and on an independent validation cohort indicates a retention of the excellent accuracy of diagnosis (error-rate < 4%), with a significant improvement in the proportion of confidently classifiable tumors compared with our previous tool. We believe that this approach, freely accessible through an online web portal, has the potential to enhance diagnostic precision and thereby support clinical care for brain tumor patients.

PATH-05. A CASE OF PILOCYTIC ASTROCYTOMA HARBORING THE FGFR1 GENE MUTATION WITH A PREDOMINANT OLIGODENDROGLIOMA-LIKE COMPONENT

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Pilocytic astrocytomas rarely present with oligodendroglioma-like morphological features, which gives rise to a diagnostic challenge. In this report we present a case of pilocytic astrocytoma harboring the FGFR1 mutation, accompanied with a predominant oligodendroglioma-like component, thus initially diagnosed as oligodendroglioma. A 14-year-old female presented with syncope and simple partial seizure involving her right upper limb. Contrast-enhanced MRI revealed an enhancing lesion with substantial cystic portion and perifocal edema in the left parietal lobe. Open surgery was performed and a gross total resection of the tumor was achieved. On initial histopathological diagnosis, tumor cells with monotonous round nuclei and perinuclear halo predominated with branching capillaries, which were strongly suggestive for oligodendroglioma. Immunohistochemically, IDH1 R132H was negative, and Ki-67 index was around 5%. The patient was thus initially diagnosed as oligodendroglioma, WHO grade II, based on the 2007

WHO classification criteria. However, histopathological re-review revealed a minor astrocytic component with Rosenthal fibers and rare eosinophilic granular bodies, thus the diagnosis was changed as pilocytic astrocytoma. FGFR1 K654E mutation was confirmed by Sanger sequencing. Although she postoperatively developed mild sensory disturbance in her right hands, finger agnosia, and left-right disorientation, her symptoms had gradually improved, and she was discharged on day 17 with a Karnofsky performance status (KPS) of 90 and no cognitive decline. Without any adjuvant therapies, she has remained recurrence-free for 85 months. While the diagnosis of pilocytic astrocytoma with predominant oligodendroglioma-like component can be challenging, analysis of IDH1 and FGFR1 mutations can be beneficial in certain cases.

PATH-06. IMAGE-BASED MACHINE LEARNING CLASSIFIER FOR PEDIATRIC POSTERIOR FOSSA TUMOR HISTOPATHOLOGY

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BACKGROUND: Pediatric posterior fossa (PF) tumors can include astrocytomas, ependymomas, and medulloblastomas, all of which demonstrate unique histopathology. Whole slide image analyses can be time consuming and difficult. Therefore, we used machine learning to create a screenshot-based histopathology image classifier that can distinguish between types of pediatric PF tumors. **METHODS:** We took 179 histopathology slides from Stanford University, dated from 2008–2019: 87 astrocytomas, 42 ependymomas, and 50 medulloblastomas, per pathology report. Each slide was viewed under a microscope at 20x. Then, a screenshot was taken of the region of interest representative of principal slide pathology, confirmed by a trained neuropathologist. These screenshots were used to train Resnet-18 models pre-trained on the ImageNet dataset and modified to predict three classes. Various models with different hyperparameters were trained using a random hyperparameter search method. Trained models were evaluated using 5-fold cross-validation, assigning 20% of the dataset for validation with each evaluation. Qualitative analysis of model performance was assessed by creating Class Activation Map (CAM) representations of image predictions. **RESULTS:** The top performing Resnet-18 model achieved a cross-validation F1 of 0.967 on categorizing screenshots of tumor pathology into three types. Qualitative analysis using CAMs indicated the model was able to identify salient distinguishing features of each tumor type. **CONCLUSIONS:** We present a PF lesion classifier capable of distinguishing between astrocytomas, ependymomas, and medulloblastomas based on a histopathology screenshot. Given its ease of use, this tool has potential as an educational tool in an academic setting.

PATH-07. QUALITY ASSURANCE IN CEREBROSPINAL FLUID CYTOLOGY ASSESSMENT FOR MEDULLOBLASTOMA STAGING LEADS TO POTENTIAL IMPROVED RISK-GROUP ASSESSMENT IN THE PROSPECTIVE MULTICENTER TRIAL HIT-2000

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BACKGROUND: Cerebrospinal fluid (CSF) dissemination of medulloblastoma (M1 stage) is a high-risk prognostic factor. However, because diagnostic criteria for M1 staging are missing we specified process-related and cytomorphological parameters influencing the predictive value of the CSF status. **PATIENTS AND METHODS:** CSF samples and cytology reports from 405 medulloblastoma patients of the prospective multicenter trial HIT-2000 were reviewed and related to 5-year progression free survival (5y-PFS). **RESULTS:** Tumor cells were detected in 237/1073 CSF cytopspins. M1-patients and M2/3 patients with radiologically detected metastases showed a worse 5y-PFS than M0 patients (54% and 52% vs. 76%; p=0.01 and p<0.001). Lumbar sampling was more sensitive than ventricular sam-

pling. M0 diagnosed specimens containing >50% lytic cells and/or less than 10 nucleated cells showed a decreased 5y-PFS (61%). Further investigation of cytological parameters revealed a poor outcome for cases harboring > 3 tumor cell clusters and individual tumor cells (5y-PFS 33%) vs. cases with ≥ 2 individual tumor cells but no clusters (5y-PFS 61%). In bi-variable Cox-regression, ≥ 2 vs. 0 or 1 tumor cells were associated with a Hazard Ratio (HR) of 0.52 (95%-Confidence Interval (CI): 0.12, 2.30; $p=0.39$), whereas > 3 vs. no tumor cell clusters were associated with a HR of 8.94 (95%-CI: 1.66, 48.22; $p=0.01$). CONCLUSIONS: CSF staging in medulloblastoma should comprise lumbar specimens with <50% lytic cells and a minimum of 10 nucleated cells. The predictive value of CSF cytology in M1 cases may predominantly depend on tumor cell clusters. The latter finding needs to be confirmed in prospective trials.

PATH-08. THE IMPORTANCE OF RE-DIAGNOSIS OF TUMORS PREVIOUSLY CLASSIFIED AS CENTRAL NERVOUS SYSTEM PRIMITIVE NEUROECTODERMAL TUMORS

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BACKGROUND: The recent molecular analyses have revealed that central nervous system primitive neuroectodermal tumors (CNS PNETs) those having clusters of small round tumor cells are genetically different tumors. However, the concepts of CNS PNET are complicated, and it is difficult to diagnose them appropriately in clinical field. To overcome this difficulty, we reviewed previous studies associated with CNS PNETs, and carried out several approaches, those are relatively easy access to use in clinics, for our 8 samples of embryonal brain tumors diagnosed CNS PNETs in our institution, initially. **METHODS:** We used in combination with immunohistochemistry (IHC), Sanger sequence, Pyrosequencing, polymerase chain reaction (PCR), real time PCR and copy number analysis referring recent reports. **RESULTS:** In terms of the diagnosis three out of 8 cases were changed based on the results in this study from previous diagnoses. **CONCLUSION:** In this review, it seemed that either the histopathological evaluation or molecular analyses would be not enough to make accurate diagnosis of CNS embryonal brain tumors, and it is essential to combine both of them including recent comprehensive analysis methods.

PATH-09. SJMB12 CLINICAL TRIAL: DISCREPANCY BETWEEN LOCAL AND CENTRAL PATHOLOGY IN ASSESSING ANAPLASTIC MEDULLOBLASTOMA – REPORT FROM A SINGLE SITE EXPERIENCE

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INTRODUCTION: SJMB12 is a phase 2 clinical trial led by the St. Jude Children's Research Hospital (St. Jude) that enrolls patients with medulloblastoma based on their biological subgroup. The large cell/anaplastic (LCA) histologic variant has been identified as an important independent risk factor associated with poor outcome. However, the histologic criteria for LCA is subjective, making the distinction between anaplastic and non-anaplastic medulloblastoma difficult in some cases. **METHODS:** Pathological central review was performed at St. Jude. For all patients enrolled in the study to date, concordance was assessed between the initial and central review diagnosis and histologic variant calls made at the Royal Children's Hospital Melbourne (RCH) and at St. Jude, respectively. **RESULTS:** Since the SJMB12 clinical trial opened locally in 2014, 34 patients were enrolled, and 31 were eligible for this retrospective study. A total of 12 (39%) cases with discordance were identified. The most frequent disagreement was between the designation of LCA (10 cases, 32%). In five cases the tumour was not designated as LCA variant locally. In five cases the initial designation of LCA was refuted centrally. Overall, this led to a change of treatment stratum for four patients (13%). **CONCLUSION:** A high discordance rate exists between neuropathologists in the designation of LCA variant. Differences in interpretation of the subjective histologic criteria and inconsistencies in the material submitted for central review contributed to the discordance. Incorporation of more objective histologic criteria and implementation of unbiased diagnostic tools may improve the generalisability of future risk stratification.

PATH-10. PROGNOSTIC RELEVANT IMMUNOPHENOTYPES OF PEDIATRIC HIGH-GRADE NON-BRAINSTEM GLIOMAS

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Pediatric diffuse astrocytomas comprise a wide range of malignancies with variable prognosis. The 4th grading system used now not always cor-

rectly characterizes the biological behavior of these tumors. We collected 24 pediatric supratentorial non-brainstem high grade glioma cases. Patient age ranged from 1 to 18 years old (median 11y). Main tumor locations were as follows: parietal lobe 8 cases; temporal lobe, 10 cases; frontal lobe, 3 cases; occipital lobe 3 cases. Eight of them were totally removed. All patients were treated with standard CT and RT. The main objective was to assess the prognostic impact of histopathological and molecular criteria on progression-free(PFS) and overall survival (OS) of high grade gliomas. The following criteria were analyzed: IDH1 R132H, BRAF V600E expression, ALT-phenotype, CDKN2A deletion, 1p/19q co-deletion, glial and neuronal markers expression. **RESULTS:** IDH1R132H mutation was identified in 3 cases. 4 cases carried BRAFV600E mutation with CDKN2A deletion and displayed PXA phenotype. 5 cases showed undifferentiated glial morphology and ALT-phenotype. Also there was a group of tumors without any of the above mentioned genetic changes. Interestingly 3 of them were post radiation tumors. Statistical analysis showed that low OS correlated with ALT-phenotype($p=0.015$), absence of neuronal markers expression and absence of molecular changes ($p=0.03$). Mutation of IDH1R132H was a favorable prognostic factor as in the adult population. PFS was affected only by the presence of neuronal expression ($p=0.015$). Employing immunohistochemical analysis with surrogate molecular markers in complex with FISH can provide additional prognostic information in case of pediatric high grade gliomas.

PATH-11. PROSPECTIVE (EPI-)GENETIC CLASSIFICATION OF > 1,000 PEDIATRIC CNS TUMORS—THE MNP 2.0 STUDY

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The large variety of CNS tumor entities affecting children and adolescents, some of which are exceedingly rare, results in very diverging patient outcomes and renders accurate diagnosis challenging. To assess the diagnostic utility of routine DNA methylation-based CNS tumor classification and gene panel sequencing, the *Molecular Neuropathology 2.0* study prospectively integrated these (epi-)genetic analyses with reference neuropathological diagnostics as an international trial for newly-diagnosed pediatric patients. In a four-year period, 1,215 patients with sufficient tissue were enrolled from 65 centers, receiving a reference neuropathological diagnosis according to the WHO classification in >97%. Using 10 FFPE sections as input, DNA methylation analysis was successfully performed in 95% of cases, of which 78% with sufficient tumor cell content were assigned to a distinct epigenetic tumor class. The remaining 22% did not match any of 82 represented classes, indicating novel rare tumor entities. Targeted gene panel sequencing of >130 genes performed for 96% of patients with matched blood samples detected diagnostically, prognostically, or therapeutically relevant somatic alterations in 48%. Germline DNA sequencing data indicated potential predisposition syndromes in ~10% of patients. Discrepant results by neuropathological and epigenetic classification (29%) were enriched in histological high-grade gliomas and implicated clinical relevance in 5% of all cases. Clinical follow-up suggests improved survival for some patients with high-grade glioma histology and lower-grade molecular profiles. Routine (epi-)genetic profiling at the time of primary diagnosis adds a valuable layer of information to neuropathological diagnostics and will improve clinical management of CNS tumors.

PATH-13. PLEOMORPHIC XANTHOASTROCYTOMA INTEGRATED GENOMIC CHARACTERIZATION - WHAT HAVE WE LEARNED?

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