Posterior fossa ependymoma group PFA

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Ependymoma is the third most common pediatric primary brain tumor, with its most aggressive subtype being posterior fossa group A (PFA).

Posterior fossa group A ependymomas (EPN_PFA) are characterized by a loss of H3 K27 trimethylation due to either EZHIP overexpression or H3 p.K27M mutation, similar to H3 K27-altered diffuse midline gliomas (DMG), but in reverse proportions.

Group A patients are younger, have laterally located tumors with a balanced genome, and are much more likely to exhibit recurrence, metastases at recurrence, and death compared with Posterior fossa ependymoma group PFB patients. Identification and optimization of immunohistochemical (IHC) markers for PF ependymoma subgroups allowed validation of findings on a third independent cohort, using a human ependymoma tissue microarray, and provides a tool for prospective prognostication and stratification of PF ependymoma patients [1)].

Baroni et al. identified an ultra-high-risk PF-EPN-A ependymoma subgroup, which can be reliably ascertained using cytogenetic markers in routine clinical use. A change in treatment paradigm is urgently needed for this particular subset of PF-EPN-A where novel therapies should be prioritized for upfront therapy [2)].

Diagnosis

H3K27me3 (me3) loss by immunohistochemistry (IHC) is a surrogate marker for PFA wherein its loss is attributed to overexpression of Cxorf67/EZH2 inhibitory protein (EZHIP), C17orf96, and ATRX loss. Nambirajan et al. aimed to subgroup posterior fossa ependymomas using me3 IHC and study correlations of the molecular subgroups with other histone-related proteins, 1q gain, Tenascin C, and outcome. IHC for me3, acetyl-H3K27, H3K27M, ATRX, EZH2, EZHIP, C17orf96, Tenascin C, and

fluorescence in-situ hybridization for chromosome 1q25 locus were performed on an ambispective posterior fossa ependymomas cohort (2003-2019). H3K27M-mutant gliomas were included for comparison. Among 69 patients, PFA (me3 loss) constituted 64%. EZHIP overexpression and 1q gain were exclusive to PFA seen in 72% and 19%, respectively. Tenascin C was more frequently positive in PFA (p = 0.02). H3K27M expression and ATRX loss were noted in one case of PFA-EPN each. All H3K27M-mutant gliomas (n = 8) and PFA-EPN (n = 1) were EZHIP negative. C17orf96 and acetyl-H3K27 expression did not correlate with me3 loss. H3K27me3 is a robust surrogate for PF-EPN molecular subgrouping. EZHIP overexpression was exclusive to PFA EPNs and was characteristically absent in Diffuse midline glioma H3 K27M-mutants and the rare PFA harboring H3K27M mutations representing mutually exclusive pathways leading to me3 loss [3].

NF2 and ZFTA

NF2 and ZFTA evaluation in the diagnostic algorithm of pediatric posterior fossa ependymoma with H3K27ME3 retained expression [4]

Differential diagnosis

A contrast rate of less than 50%, based on the magnetic resonance images, was characteristic in the PF-EPN-A group. Comparatively, cystic component and absence of calcification were more characteristic in the PF-EPN-B group [5].

Outcome

Ependymoma (EPN) posterior fossa group A (PFA) has the highest rate of recurrence and the worst prognosis of all EPN molecular groups. At relapse, it is typically incurable even with re-resection and re-irradiation. The biology of recurrent PFA remains largely unknown, however, the increasing use of surgery at first recurrence has now provided access to clinical samples to facilitate a better understanding of this.

Methods: In this large longitudinal international multicenter study, we examined matched samples of primary and recurrent disease from PFA patients to investigate the biology of recurrence.

Results: DNA methylome derived copy number variants (CNVs) revealed large scale chromosome gains and losses at recurrence. CNV changes were dominated by chromosome 1q gain and/or 6q loss, both previously identified as high-risk factors in PFA, which were present in 23% at presentation but increased to 61% at 1 st recurrence. Multivariate survival analyses of this cohort showed that cases with 1q gain or 6q loss at 1 st recurrence were significantly more likely to recur again. Predisposition to 1q+/6q- CNV changes at recurrence correlated with hypomethylation of heterochromatin-associated DNA at presentation. Cellular and molecular analyses revealed that 1q+/6q- PFA had significantly higher proportions of proliferative neuroepithelial undifferentiated progenitors and decreased differentiated neoplastic subpopulations.

This study provides clinically and preclinically-actionable insights into the biology of PFA recurrence.

The hypomethylation predisposition signature in PFA is a potential risk-classifier for trial stratification. We show that the cellular heterogeneity of PFAs evolves largely because of the genetic evolution of neoplastic cells [6].

The overall mortality rate for recurrent infratentorial ependymomas was found to be 49.1%, with a pooled mean survival of 30.2 months in the included sample population. More than 80% of recurrent infratentorial ependymomas were of the PFA molecular subtype, and both PFA tumors and those with 1q gain demonstrated a worse prognosis after recurrence [7]

Ramaswamy and Taylor found that the strongest predictor of poor outcome in patients with posterior fossa ependymoma across the entire age spectrum was the molecular subgroup PFA, which was reported in the paper entitled “Therapeutic impact of cytoreductive surgery and irradiation of posterior fossa ependymoma in the molecular era: a retrospective multicohort analysis” in the Journal of Clinical Oncology. Patients with incompletely resected PFA tumors had a very poor outcome despite receiving adjuvant radiation therapy, whereas a substantial proportion of patients with PFB tumors can be cured with surgery alone [8].

A total of 72 Posterior fossa ependymomas cases were identified, 89% of which were PFA. The 10-year progression-free survival rate for all patients with PFA was poor at 37.1% (95% confidence interval, 25.9%-53.1%). Analysis of consecutive 10-year epochs revealed significant improvements in progression-free survival and/or overall survival over time. This pertains to the increase in the rate of gross (macroscopic) total resection from 35% to 77% and the use of upfront radiotherapy increasing from 65% to 96% over the observed period and confirmed in a multivariable model. Using a mixed linear model, analysis of longitudinal neuropsychological outcomes restricted to patients with PFA who were treated with focal irradiation demonstrated significant continuous declines in the full-scale intelligence quotient over time with upfront conformal radiotherapy, even when correcting for hydrocephalus, number of surgeries, and age at diagnosis (-1.33 ± 0.42 points/year; P = .0042) [9].

Treatment

Effective treatment is limited to surgical resection and focal radiotherapy.

Results provide solid preclinical evidence for the use of CN133 as a new therapeutic agent against PF-EPN-A tumors [10].

Within Posterior fossa type A Ependymoma, chromosome 1q gain is a marker of poor prognosis.

After accounting for treatment, 6q loss remained the most significant independent predictor of survival in PF-EPN-A but is not in Posterior fossa type B Ependymoma. Distant relapses were more common in 1q gain irrespective of 6q loss. RNA-sequencing comparing 6q loss to 6q balanced PF-EPN-A suggests that 6q loss forms a biologically distinct group [11].

Pachtler et al., used DNA methylation profiling to look for further molecular heterogeneity among 675 PFA ependymomas. Two major subgroups, PFA-1 and PFA-2, and nine minor subtypes were

discovered. Transcriptome profiling suggested a distinct histogenesis for PFA-1 and PFA-2, but their clinical parameters were similar. In contrast, PFA subtypes differed with respect to age at diagnosis, gender ratio, outcome, and frequencies of genetic alterations. One subtype, PFA-1c, was enriched for 1q gain and had a relatively poor outcome, while patients with PFA-2c ependymomas showed an overall survival at 5 years of > 90%. Unlike other ependymomas, PFA-2c tumors express high levels of OTX2, a potential biomarker for this ependymoma subtype with a good prognosis. We also discovered recurrent mutations among PFA ependymomas. H3 K27M mutations were present in 4.2%, occurring only in PFA-1 tumors, and missense mutations in an uncharacterized gene, CXorf67, were found in 9.4% of PFA ependymomas, but not in other groups. We detected high levels of wildtype or mutant CXorf67 expression in all PFA subtypes except PFA-1f, which is enriched for H3 K27M mutations. PFA ependymomas are characterized by lack of H3 K27 trimethylation (H3 K27-me3), and we tested the hypothesis that CXorf67 binds to PRC2 and can modulate levels of H3 K27-me3. Immunoprecipitation/mass spectrometry detected EZH2, SUZ12, and EED, core components of the PRC2 complex, bound to CXorf67 in the Daoy cell line, which shows high levels of CXorf67 and no expression of H3 K27-me3. Enforced reduction of CXorf67 in Daoy cells restored H3 K27-me3 levels, while enforced expression of CXorf67 in HEK293T and neural stem cells reduced H3 K27-me3 levels. Our data suggest that heterogeneity among PFA ependymomas could have clinicopathologic utility and that CXorf67 may have a functional role in these tumors [12].

Case reports

A 9-year-old girl with PFA ependymoma characterized by a lack of trimethylation of histone H3 at lysine 27 and elevated chromosome X open reading frame 67 expressions. Despite multiple surgeries and radiotherapies, the patient had a rapid recurrence and developed osseous and pulmonary metastases, which may be attributed to the homozygous deletion of cyclin-dependent kinase (CDK) inhibitor 2A/B and CDK12 mutation. Importantly, the CDK12 mutation observed in the patient may be indicative of the need for further work-up to consider chemotherapy rather than administering poly (adenosine diphosphate-ribose) polymerase inhibitors. Taken together, this is the first report of pediatric PFA ependymoma with extraneural metastases, wherein we clarified the diagnostic procedures of this newly identified PFA ependymoma and provided new cues to study the invasiveness of this disease and treatment selection for such patients [13].

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