Pediatric Myxopapillary Ependymomas: Clinico-pathological Evaluation

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Abstract

PURPOSE: Myxopapillary ependymomas (MPE) have an indolent clinical course, corresponding to WHO Grade I designation. 13 pediatric MPEs have been reported in the literature to show "anaplastic features", including elevated proliferative activity ([?]5 mitoses per 10 high-power fields and/or Ki67 labeling index of >10%), necrosis, and microvascular proliferation. No consensus exists regarding the prognostic significance of such features. PROCEDURE: Retrospective clinicopathologic review of pediatric MPEs diagnosed between 1996-2018 at Mayo Clinic. RESULTS: The study included 8 pediatric MPEs (6 male; age range 7.52-16.88 years). 3 had disseminated disease at presentation. All patients underwent surgical resection (7 gross-total; 1 subtotal). 5 cases harbored [?]5 mitoses per 10 high-powered fields (range: 5-9), 3 of which showed necrosis (2 with disseminated disease). Following surgery, 2 patients received radiation; one with widely disseminated disease and another with increased mitotic activity and necrosis; neither has recurred at last follow-up (1.18 and 3.19 years). 2 patients with disseminated disease, elevated mitotic activity, and necrosis had new metastatic disease/progression of non-resected metastatic foci (2.6 and 26.8 months). Both received radiation therapy and have remained progression free (3.01 and 9.34 years). All patients are alive (median follow-up 1.31 years, range: 0.66-11.75 years). CONCLUSION: Our findings suggest that among pediatric MPEs, the concurrent presence of elevated mitotic activity and necrosis may be associated with a more aggressive clinical course, warranting closer surveillance and consideration of adjuvant therapies such as radiation. Attention to the presence of mitotic activity and necrosis may help identify children at higher risk for tumor recurrence/progression.

Background

Myxopapillary ependymomas (MPE) are slow growing glial neoplasms, corresponding to a Grade I designation per the 2016 WHO Classification of CNS Tumors. MPEs typically arise in the conus medullaris, cauda equine, and filum terminale, and account for the majority of intramedullary tumors in this region.[1] MPEs have been noted to arise in other locations, including the cervical or thoracic spinal cord, the fourth and lateral ventricles, brain parenchyma, and less commonly subcutaneously in the sacrococcygeal or presacral regions.[1] Overall, MPEs represent 9-13% of all ependymomas.[1] Although rare, distant metastasis and brain parenchymal metastasis has been reported in both adult and pediatric patients.[2]

MPEs arise in both the adult and pediatric patients, with an average of 36 years of age at presentation.[1] The presenting symptom is often chronic back pain.[1] Although WHO Grade I classification implies an indolent clinical course and good prognosis, it has been documented that pediatric cases may behave more aggressively, with a higher rate of disease recurrence, even after gross total resection. [1-2] Additionally, pediatric patients demonstrate higher rates of treatment failure, and often present with disseminated disease. [1-5] It has been suggested that age is the strongest predictor of recurrence and overall prognosis.[1] Additional adverse predictors of prognosis include surgical treatment alone and subtotal resection. [6]Indication for adjuvant therapy in pediatric patients with disseminated disease at diagnosis remains unclear, although a recent

study evaluating 18 pediatric patients suggested improvement in local control of disease with post-surgical radiation. [7]

Molecularly, MPEs are characterized by polyploidy, with gains in various chromosomes. [1] In particular, copy number alterations in chromosome 7 have been described. [8] Other studies have suggested overexpression in *HOXB13* , *NEFL* , and*PDGFRA* . [9] One study has suggested that MPEs may have a "Warburg" metabolic phenotype, i.e. elevated glycolysis and possible accumulation of lactate, due to increased protein expression of*HIΦ-1a, HK2, ΠΔK1* , and phosphorylation of *PDHE1A* .[10] Studies have demonstrated a distinct DNA methylation profile for MPEs, with chromosomal gains and losses across large regions. [11]

To date, 13 pediatric MPEs have been reported in the literature to show "anaplastic features", including necrosis, microvascular proliferation, an elevated Ki-67 labeling index, and increased mitotic activity ([?]5 mitoses per 10 high-power fields). [12-17]However, there currently are no consensus criteria for classifying MPEs as histologically anaplastic and more importantly, clear treatment guidelines for this sub-group. Here, we present our institutional experience with pediatric MPEs, with detailed evaluation of their clinical and pathological features, and chromosomal microarray analysis, in order to help identify features associated with adverse outcomes among this patient population.

Methods

Following Institutional Review Board approval, the pathology and clinical database was queried for cases of myxopapillary ependymoma (MPE) occurring in patients less than 18 years of age diagnosed or treated at our institution between 1996 and 2018. The electronic medical record was reviewed for pertinent clinical data. The slides for available cases were reviewed, and histologic information was collected from the microscopic descriptions of the internally generated slide reviews of the other cases. Histologically, each case was evaluated for overall cellularity, mitotic activity, necrosis, microvascular proliferation, presence of an identifiable capsule, leptomeningeal involvement, and nerve root involvement. Immunohistochemical studies for H3K27me3 (C36B11 clone; Cell Signaling) and chromosomal microarray analysis were performed on all cases with available tissue (5 of 8 cases).

The OncoScan® FFPE Assay Kit (Thermo Fisher Scientific; Santa Clara, CA) was applied to isolated DNA. The technicalities of the molecular inversion probe (MIP) assay have been previously described.[18] The genome-wide functional resolution of this array is approximately 500 kilobases for non-mosaic deletions and non-mosaic duplications. Deletions larger than 1 megabase, duplications larger than 2 megabases, and copy neutral loss of heterozygosity (cnLOH) larger than 10 megabases are generally reported. As a caveat, the functional resolution of this array varies significantly dependent upon size of the abnormality, probe density in region, percentage of abnormal cells, and quality of the DNA obtained, and mosaic clonal abnormalities, especially those that are represented in a minor fraction of the sample, may not be detected. . All data were analyzed and reported using the February 2009 NCBI human genome build 37.1 (hg19). The genome coordinates described are best estimates and may not represent precise breakpoints, especially for abnormalities detected in a low percentage of cells.

Results

Patient Demographics and Clinical Features

Eight patients (2 female; 6 male) were identified with a median age of 13years (range 7.52-16.88years) at diagnosis. Pain was the presenting symptom in all 8 patients and one patient also had lower extremity weakness. All primary tumors were noted to be intradural and predominantly in the lumbrosacral region of the spine, except one that arose in the lower thoracic spine, involving the filum terminale or adjacent to the tip of the conus medullaris (Fig.1.A-B). Three patients had radiologically identified disseminated disease at presentation (Fig.1.C-D).

Surgical Management

All patients underwent surgical resection of the primary tumor (7 gross total; 1 subtotal). In cases where

the operative report was available (6 of 8), an intact tumor capsule was noted at time of surgery in 5 cases and was removed en bloc in 4 of these cases. In one case there was no clear plane between the tumor and the conus medullaris.

Histologic evaluation

All cases demonstrated features of myxopapillary ependymoma with fibrillary processes arranged around fibrovascular cores with variable amounts of myxoid material (Fig.2.A). One case had focal (10%) features of classic ependymoma. The cases ranged from low to moderate cellularity. 5 cases harbored [?]5 mitoses per 10 high-powered fields (range: 5-9, Fig.2.B), 3 of which also showed necrosis (including two with disseminated disease, Fig.2.C). Microvascular proliferation was identified in one case that had increased mitotic activity and necrosis. An identifiable capsule was present in 4 cases. Leptomeningeal involvement was identified in 4 cases and nerve root involvement was present in 1 case.

Immunohistochemistry

All cases showed retained H3K27me3 expression by immunohistochemical studies (Fig.2.D). The clinicopathologic findings are summarized in Table 1.

Chromosomal Microarray Analysis

All cases showed chromosomal gains across the genome (Figure 3). The chromosomes with gains included 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 15, 16, 17, 18, 19, 20, 21, 22, and X. Additional findings included copy neutral loss of heterozygosity of whole chromosome 8 including*MYC* at 8q24.3 and copy neutral loss of heterozygosity on chromosome 13. Pertinent negatives in this analysis included no relative gain of 1q, no apparent chromothripsis, no alterations of *RELA* or *YAP1* , and no deletion of *NF2* . A summary of patient chromosomal microarray analysis results can be seen in Table 2.

Post-operative Management and Outcomes

Following surgery, 2 patients received proton beam radiation therapy, including one with widely disseminated disease and another with increased mitotic activity and necrosis; neither has recurred at last follow-up (1.18 and 3.19 years). No patient received chemotherapy.

Two patients with disseminated disease, elevated mitotic activity, and necrosis had new metastatic disease/progression of non-resected metastatic foci at 2.6 and 26.8 months. One patient underwent an incomplete surgical resection of the original tumor. Both of these patients received radiation therapy, and have remained progression free since (3.01 and 9.34 years). All patients were alive at last follow-up (median follow-up 1.31 years, range: 0.66-11.75 years).

Discussion

Myxopapillary ependymomas are rare in children. Though MPEs are WHO Grade 1 tumors and are thought to have an indolent course, the natural history of these tumors as well as the management remains unpredictable and unclear in the pediatric population.

Reduced H3K27me3 expression has been described in pediatric posterior fossa "Group A" ependymomas. [19] The retained expression of H3K27me3 in all cases of this series suggests that this is likely not a driver mechanism in the tumorigenesis of myxopapillary ependymomas. The molecular basis of pediatric MPE behavior remains to be determined.

The copy number gains observed in the cases tested in our series indicate chromosomal instability (CIN). CIN is a feature of myxopapillary ependymomas, for which the oncogenic driver is currently unknown. [19] The pattern of copy number gain in these specimens suggests intermediate ploidy, which has been seen in myxopapillary ependymomas, as well as in posterior fossa "Group B" ependymoma, which harbor large genomic aberrations.[20-22] The prognostic significance of these alterations in myxopapillary ependymoma remains to be determined.

There is no clear treatment consensus for the management of pediatric MPEs with anaplastic features. Surgery remains the mainstay of treatment with adjuvant radiation therapy a consideration in some clinical situations. Moreover, the management of pediatric MPEs showing increased mitotic activity and presence of necrosis is even less studied.

A Surveillance, Epidemiology, and End Results (SEER) database study that looked at 122 cases of primary spinal MPE in the pediatric population (ages 21 years and under) showed patients who received gross total resection (GTR, surgery alone) had a 5-year overall survival rate of 100 %, while those who received subtotal resection (STR) plus radiation had a 5-year overall survival of 91 %, suggesting GTR whenever feasible is the best treatment option. This study did not have information on presence/absence of 'anaplastic features'. [6]

A large pediatric MPE study which included 18 patients showed patients with disseminated disease trended towards inferior event free survival (EFS) compared to those with localized disease. Nine patients had disseminated disease. Three of the 18 patients who did not undergo a gross total resection received radiation at diagnosis (of which one patient had disseminated disease). No patient received adjuvant chemotherapy at diagnosis. Though the study had patients with atypical histopathologic features including vascular proliferation, atypia and necrosis, the association of these features with dissemination, management and outcomes was not elucidated in this study. Also, the small number of patients that received adjuvant radiation therapy precluded any further analysis. [7]

To date, there are 13 cases of pediatric myxopapillary ependymomas (MPE) with "anaplastic features" described in the literature.[12-17] Our study adds 5 additional cases with increased mitotic activity, 3 of which also demonstrated necrosis. Among the three patients with both increased mitotic activity and necrosis, two had disseminated disease and had disease recurrence. Our findings are similar to previous studies that demonstrated more aggressive clinical behavior, particularly in pediatric patients, when at least 2 of the following criteria suggesting anaplasia: [?]5 mitoses per 10 HPF, Ki-67 labeling index of >10%, necrosis, and microvascular proliferation were present. [14] Similar to our cohort, with the previous 12 pediatric cases reported, the primary treatment modality was surgical resection. In some patients, radiation therapy was administered either at diagnosis if the patients presented with disseminated disease or at first recurrence. [12-17]

Our findings and available literature suggests that in pediatric patients with MPE, the concurrent presence of elevated mitotic activity and necrosis may be associated with a more aggressive clinical course and may help identify patients at higher risk for recurrence and progression. Although prior to our cohort there were only 13 cases reported in the literature, given that we identified 5 additional patients in our cohort suggests that there may be underreporting or lack of recognition of the clinical importance of these histologic features. Patients with such findings may warrant closer surveillance, as well as consideration of adjuvant therapies such as radiation, especially in the setting of disseminated disease at presentation.

Further studies including more cases of MPE with these features are needed to help create management guidelines in the subset of patients that demonstrate anaplastic features.

Conflicts of Interest Statement

None of the authors have a conflict of interest to report.

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Figure Legend

FIGURE 1: Patient 4. (A) Typical appearance of a myxopapillary ependymoma. Sagittal T2 fat saturated image shows a well-circumscribed, ovoid, intradural lesion of the cauda equina, hyperintense to the adjacent cord, causing near complete spinal canal stenosis. (B) Sagittal, post contrast, T1 fat saturated image shows intense enhancement of the tumor. Patient 6. (C) Myxopapillary ependymoma with subarachnoid dissemination. Sagittal T2 image shows an intradural lesion of the conus and cauda equina with nodular tissue in the thecal cul-de-sac (arrow), representing local dissemination. (D) Sagittal, post contrast, T1

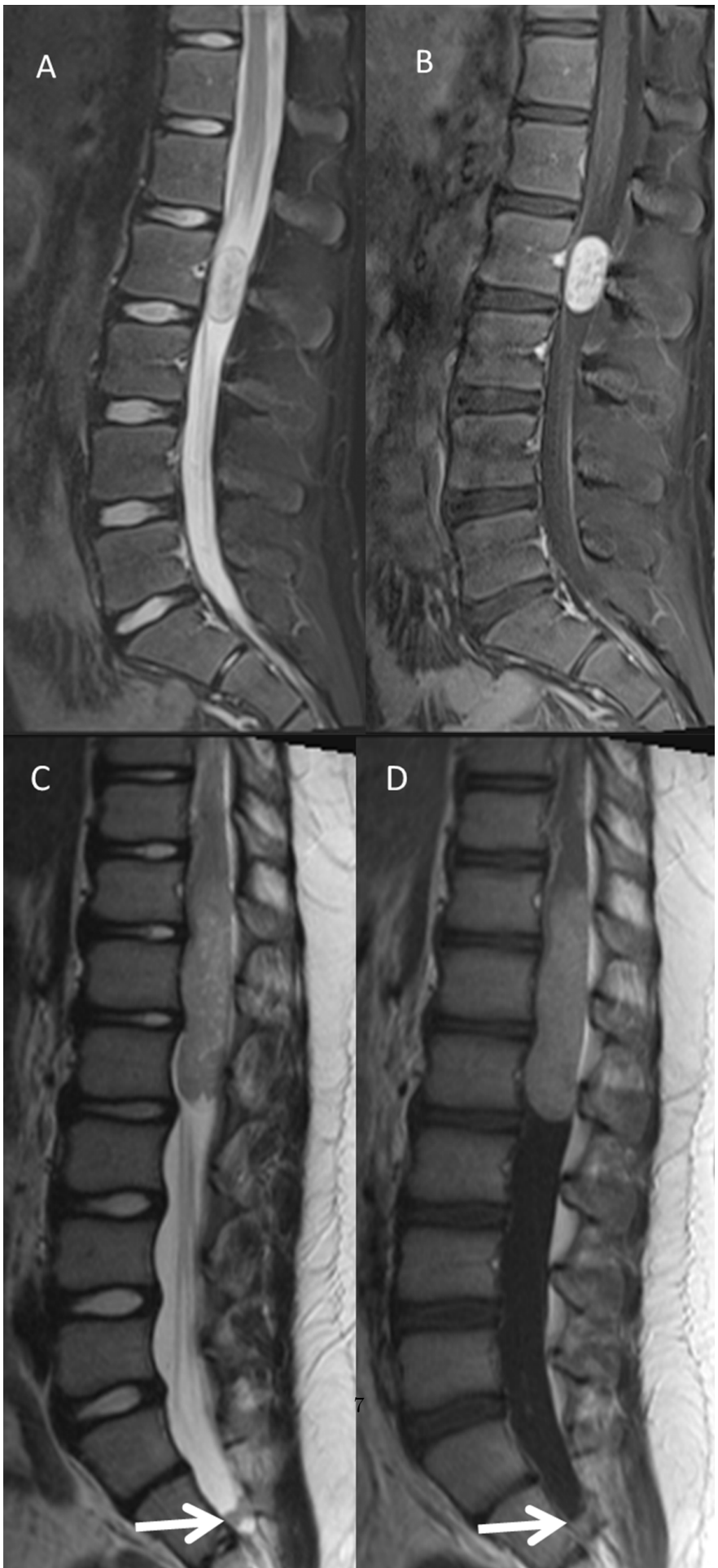
image shows intense enhancement of the tumor, similar in appearance to the dissemination (arrow).

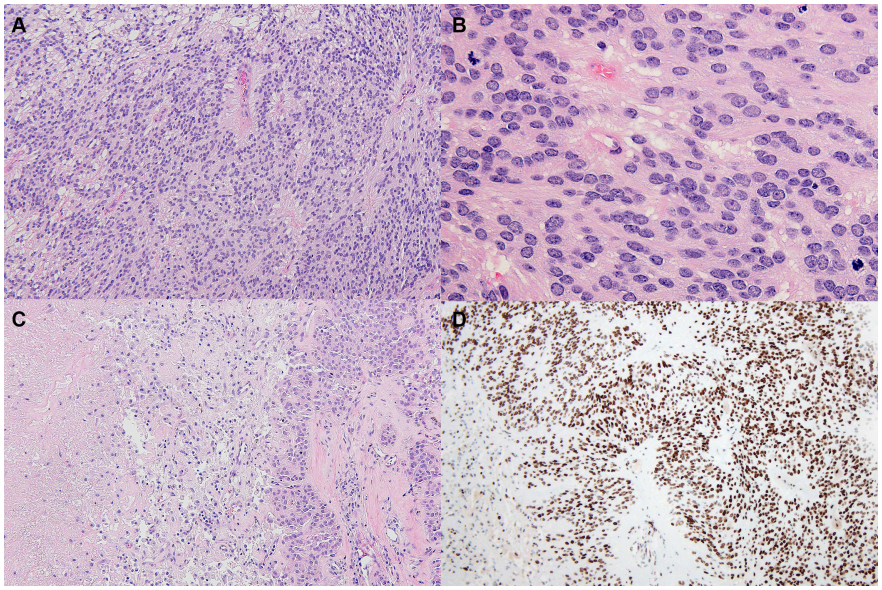
FIGURE 2: Patient 5. (A) H&E, 100x: Myxopapillary ependymoma with fibrillary processes arranged around fibrovascular cores with variable amounts of myxoid material (B) H&E, 400x: Multiple mitotic figures in a single HPF (C) H&E, 100x: Tumor necrosis (D) H3K27me3, 200x: Retained nuclear expression.

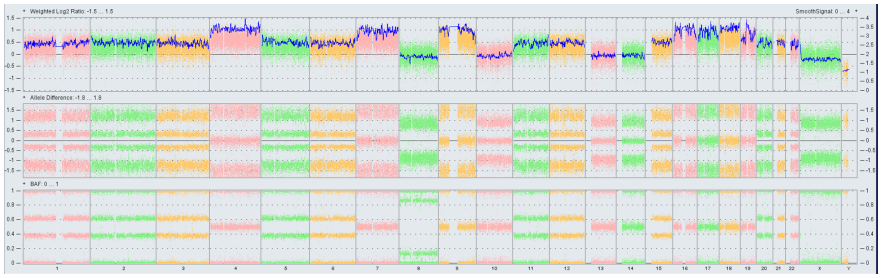
FIGURE 3: Patient 4. Chromosomal microarray demonstrating chromosomal gains across the genome including 1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 15, 16, 17, 18, 19, 20, 21, 22, X. Additionally there is loss of heterozygosity of whole chromosome 8 including MYC at 8q24.3.

TABLE 1: Summary of Clinico-pathologic Features

TABLE 2: Summary of Chromosomal Microarray Analysis







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