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CLINICAL ARTICLE - SPINE

Spinal myxopapillary ependymomas: a retrospective clinical and immunohistochemical study

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Abstract
Background Myxopapillary ependymoma (MPE) is a rare subtype of ependymoma that develops almost exclusively within the spinal cord. Despite its benign biological nature, MPE has a propensity to recur locally or distantly. Although variables influencing the prognosis, such as age, the extent of surgery and radiotherapy, have been widely discussed, no definitive standard has been established. Compared to other spinal tumors, many fewer histological markers have been elucidated to assist the determination of the prognosis.
Methods Twenty-seven patients who underwent resection of MPE were enrolled. We determined their demographic features, imaging characteristics, clinical presentations and outcomes, surgical procedures and histological properties by chart review, telephone contact, reviewing of surgical notes, pre-/postoperative imaging and immunohistological staining.
Results GTR (gross total resection) was achieved in 18 patients (66.7 %) and STR (subtotal resection) in 9 (33.3 %). Although GTR rendered a better disease control rate, the difference was not significant. Pediatric patients suffered from a greater risk of recurrence as well as a shorter period to disease relapse. In the majority of cases, we observed the overexpression of platelet-derived growth factor receptor α (PDGFRα), matrix metalloproteinase-2 (MMP2) and matrix metalloproteinase-14 (MMP14). Epidermal growth factor receptor (EGFR) was observed in the tumors of 7 of 23 nonrecurrent patients, but not in any recurrent tumors.
Conclusions The results of the present study indicate that the extent of resection and age are major factors related to tumor recurrence. Therefore, gross total resection is recommended whenever possible unless following neurological dysfunction is predictable. Moreover, pediatric patients need considerable attention after surgery, particularly in the early stages. PDGFRα, MMP2 and MMP14 may be new diagnostic and therapeutic targets and EGFR a potential predictor of improved prognosis for MPE.

Keywords Myxopapillary ependymoma · Gross total resection · Epidermal growth factor receptor

Introduction

Myxopapillary ependymoma (MPE), first defined as a distinct subtype of ependymoma by Kernohan in 1931 [18], is classified as a World Health Organization (WHO) grade I glioma [14]. It locates almost exclusively within the spinal cord, especially the conus medullaris, cauda equine and filum terminale. MPE most commonly affects middle-aged individuals, with no obvious gender preference [19]. This tumor, which afflicts 0.05–0.08 per 100,000 individuals per year, accounts for about 13 % of all types of ependymomas [2]. The microscopic morphology of MPE is characterized by a papillary arrangement of cuboidal or elongated tumor cells

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surrounding a fibrovascular core, which contains both hyalinized blood vessels and a marked abundance of extracellular mucoid matrix. Although MPEs are characterized as histologically benign, slow-growing tumors, some patients demonstrate local recurrence or even distant metastasis [2, 27]. In particular, younger patients are believed to have greater risks of recurrence or metastasis [19, 32]. According to most studies, gross total resection (GTR) is strongly associated with progression-free survival (PFS), while other studies suggest that GTR must be combined with high-dose radiotherapy (RT) in order to increase PFS [23]. The therapeutic use of adjuvant RT is potentially the most controversial factor in the treatment of MPE. Although high-dose RT has been reported to provide benefits to patients treated with subtotal resection (STR) [2] or even GTR [4], a systematic review reported that radiotherapy did not significantly improve tumor control for patients who received either type of surgical resection [13]. Moreover, the side effects, such as poor wound healing, impairment of spinal growth, radiation-induced myelopathy or even neoplasms, still hinder its universal applications, in particular in pediatric patients [5]. Unlike WHO grade II or III ependymomas, there are few retrospective studies, let alone prospective ones, examining MPE patient outcomes to establish the optimal treatment options because of its low incidence. In addition, although several markers were reported to be correlated with tumor recurrence [16, 30], to the best of our knowledge, no definite relationships among these markers have been confirmed to date.

In this study, we conducted an institutional retrospective study of 27 patients diagnosed with MPE from 2004 to 2013. The clinical characteristics were collected and analyzed. An immunohistochemical study was performed on a total of 28 samples, and the expressions of epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor α (PDGFRα), matrix metalloproteinase-2 (MMP2) and matrix metalloproteinase-14 (MMP14) were evaluated in MPE as prognostic markers for recurrence.

Materials and methods

Patients and follow-up

We screened pathological reports in our database from 2004 to 2013. A total of 42 cases were histologically verified as myxopapillary ependymomas from 41 patients who underwent surgical resection. One patient had both primary and secondary tumor resections in our hospital. Among the 42 cases, we were able to evaluate 28; the remaining cases did not include post-treatment follow-up. The slides of these 28 cases were reevaluated using the following diagnostic criteria: the cuboidal to elongated tumor cells arranged radially in a papillary manner around vascularized stromal cores; the myxoid matrix material accumulated between tumor cells and blood vessels, also collected in microcysts. All clinical information and follow-up data were obtained from chart review and telephone contact, including age at diagnosis, gender, symptoms, location of tumors, extent of surgery, treatment after surgery (radio-/chemotherapy), recurrence status and operational complications. All patients received preoperative MRI scanning to confirm the location and morphology of their lesions and postoperative scanning to determine the state of recurrence or tumor residual as well as follow-up scanning at least 12 months after the surgery. The extent of resection was based on careful review of the operative notes and evidence of the presence or absence of residual tumor on postoperative imaging about 3 months after surgery.

Immunohistochemistry (IHC)

Samples were obtained from 28 cases of 27 patients, and IHC was performed on these archived paraffin-embedded specimens. All sections were stained in batch fashion. Following deparaffinization, rehydration, antigen retrieval and endogenous peroxidase blocking, slides were incubated with primary antibodies for EGFR, PDGFRα, MMP2 or MMP14. Antibodies for IHC included rabbit polyclonal anti-EGFR at a 1:200 dilution (Cell Signaling Technology, USA), rabbit monoclonal anti-PDGFRα at a 1:100 dilution (Cell Signaling Technology, USA), rabbit polyclonal anti-MMP2 at a 1:200 dilution (Abcam, UK) and rabbit monoclonal anti-MMP14 at a 1:200 dilution (Abcam, UK). Samples incubated with PBS were used as negative controls. Sections were washed and incubated with corresponding secondary antibodies and then colored by 3,3′-diaminobenzidine (DAB). Interpretation of the IHC results was carried out as previously reported [7, 21, 26, 28]. The immunoreactivity of EGFR was scored as follows: − (0 %), + (<10 %), ++ (10–50 %) and +++ (>50 %). Only tumors with scores of ++ and +++ were considered as positive. For the evaluation of MMP2 and MMP14, the following standard was used: negative (≤5 % positive cells) vs. positive (>5 % positive cells). The scale for PDGFRα staining was scored as − (absence of staining), + (very focal staining) and ++ (25 to 100 % of cells staining), and samples with scores ++ were considered positive. Two senior neuropathologists who were blinded to the diagnosis and status of recurrence evaluated the results.

Statistical analysis

The correlations between certain variables and tumor recurrence were calculated for statistical significance using Fisher's exact test with GraphPad (GraphPad Software, USA) software. A p-value ≤0.05 was considered statistically significant.

Results

Demographic and clinical features

The characteristics of the patients in the study are summarized in Table 1. Of the 27 patients, 14 were female. The age at diagnosis varied from 7 to 57 years, with a median age of 33. Pediatric patients (≤18 years) accounted for 18.5 % of the total number (5 in 27). The patients most commonly presented with symptoms of pain in the back/limbs/buttocks. Motor/sensory dysfunction, dysuria/dysphoria and urinary/fecal incontinence were also observed. In our study, tumor growth was restricted to the spinal cord; 21 (56.8 %) of them were located in the lumbosacral region. All of the 27 patients underwent an MRI scan at least 1 year after primary surgery, and 26 patients were available for telephone contact at the date of follow-up. The mean follow-up period was 49.8 months, ranging from 13 to 122 months. The mean follow-up period in pediatric patients (≤18 years) was 43.2 months, ranging from 17 to 83 months, and 51.3 months in adult patients (>18 years), ranging from 13 to 122 months. MRI findings demonstrated that the MPEs usually were isointense on T1-weighted images and hyperintense on T2-weighted images, with homogeneous or rim enhancement on postcontrast T1-weighted images (Fig. 1).

Outcome of surgery and postoperative treatment

All patients were treated with surgical resection. GTR was achieved in 18 patients (66.7 %); STR was achieved in 9 (33.3 %). Only one patient underwent RT following GTR, and this patient experienced no radio-induced complications or tumor recurrence. The dose of RT was not clear. The MPE recurrence rate was 4 in 27 (14.8 %), with a median time of 26.5 months (range, 17–83 months). Patients who received GTR had a lower recurrence rate (11.1 % vs. 22.2 %), although not statistically different (P=0.41). Two of five pediatric patients suffered from relapse compared with 2 of 22 adults, suggesting that the pediatric patients had a higher risk of recurrence (P=0.045). Moreover, the time from surgery to the first recurrence was much shorter in pediatric patients (11 vs. 59.5 months). All of the four recurrent patients did not respond to salvage treatment. Two patients demonstrated lower limb paralysis. The other two patients were adolescents, and the small recurrent tumors were not resected temporarily to prevent neurological dysfunction. A few surgical complications were observed, including two cases of urinary/fecal incontinence, two of dysuria/dysphoria, one of pain in the left lower limb and one of left lower limb paralysis. As time went by, all the postoperative complications were relieved to some extent or kept steady. The clinical characteristics and surgical outcomes in our study are compared with those in other studies in Table 2.

Table 1 Demographic and clinical features

Variable	Number (%)
Patients	27
Age at diagnose (years)	
Median	32
Range	7–57
Gender	
Female/male	14/13
Symptoms	
Pain in back/buttocks/limbs	22 (81.5 %)
Limbs weakness	9 (33.3 %)
Limbs numbness	10 (37.0 %)
Dysuria/dysphoria or urinary/fecal incontinence	8 (21.6 %)
Gait impairment	5 (18.5 %)
Sexual dysfunction	1 (3.7 %)
Tumor location	
Cervicothoracic	1 (3.7 %)
Thoracolumbar	5 (18.5 %)
Lumbosacral/filum terminale	21 (56.8 %)
Extent of surgery	
GTR	18 (66.7 %)
STR	9 (33.3 %)
Postoperative complication	6 (22.2 %)
Urinary/fecal incontinence	2 (7.4 %)
Dysuria/dysphoria	2 (7.4 %)
Limbs paralysis	1 (3.7 %)
Limbs numbness	1 (3.7 %)
Recurrence	4 (14.8 %)

GTR gross total resection, *STR* subtotal resection

Immunohistochemical findings

EGFR expression was observed, although not frequently, in 7 of 23 patients who did not demonstrate tumor relapse. Samples from patients suffering from relapse, including primary and recurrent tumors, as well as the two recurrent cases in which primary surgeries were performed at different institutions, did not show EGFR expression (Fig. 2). EGFR expression seemed to be an indicator of lower risk of relapse but was not statistically significant (P=0.09). Overexpression of PDGFRα was observed in all 28 cases, and the intensity of every sample was scored as ++. In addition, 28 and 27 of the samples demonstrated overexpression of MMP2 and MMP14, respectively (Fig. 3).

Discussion

Myxopapillary ependymoma is a rare subtype of ependymoma, which occurs most frequently in the 4th decade of life [5].

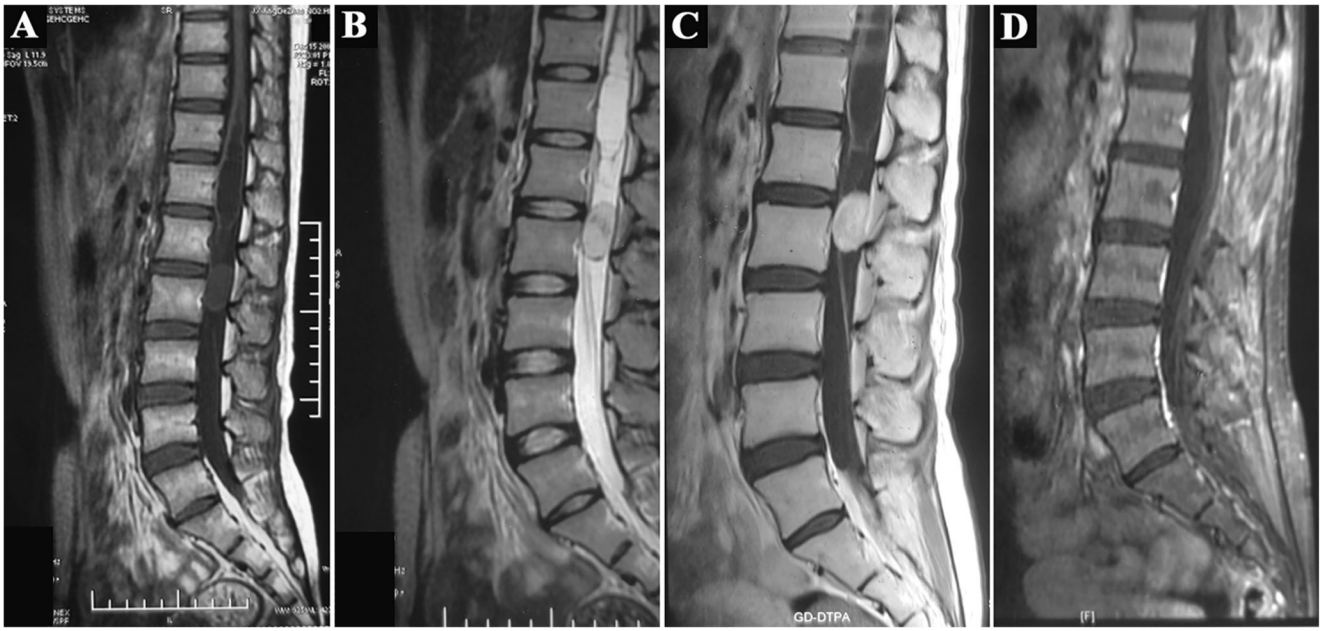

Fig. 1 Sagittal MRI showing an intramedullary mass at the L1–2 level, with syringomyelia at the T10–L1 level. **a** T1-weighted image showing an isointense lesion. **b** T2-weighted image showing a hyperintense lesion. **c** Postcontrast T1-weighted image showing homogeneous enhancement of the lesion. **d** Postoperative image showing disappearance of the L1–2 level lesion and T10–L1 level syringomyelia

Despite the predilection for the spinal cord, in particular within the lumbosacral region, primary MPEs can potentially originate from the brain [9, 29] or even subcutaneous tissue [24]. Although MPEs grow in slow and indolent patterns with benign histological characteristics, these tumors have been reported to disseminate along the craniospinal axis [22] or metastasize distantly [15]. Primary MPEs that originate within the region of the cauda equine rarely metastasize systemically, but those arising in extraspinal locations are not locally restricted [27]. In our study, 4 out of 27 patients experienced recurrence, rendering the recurrence rate lower than previously reported, even if two additional patients who had recurrent tumor resections in our hospital were included. At other institutions, the rate of treatment failure, namely recurrence or dissemination, varied from 17 to 34.7 % [2, 20, 23, 27].

Although GTR has been supported as playing a significant role in the improvement of PFS and overall survival (OS) [19], the rates of GTR from other studies are not optimal, varying from 47 to 60 % [2, 20, 23, 27]. There are two possible explanations for the relatively low GTR rates. First, MPEs have a histological feature of myxoid degeneration. The myxoid matrix that accumulates between the tumor cells and blood vessels renders the GTR challenging. Second, the nerve roots of the cauda equine may be embedded in the neoplastic tissue, so the manipulation of the intertwined tumor and nerve tissue may cause irreversible neurological morbidities. Under such circumstances, aggressive removal may not be the preferred option. In this study, we have reported a GTR rate of 66.7 %, which may explain the low incidence of treatment failure.

The role of adjuvant radiotherapy may be the most controversial among all prognostic indicators for MPE. In 2006, Akyurek et al. [2] observed a significant decrease in the rate of tumor progression with adjuvant RT regardless of the extent of resection. This finding was supported by a study in 2008 analyzing the effect of RT in 85 patients from the Rare Cancer Network. This study demonstrated that the 5-year PFS was improved in patients receiving surgery plus RT (74.8 %)

Table 2 Clinical characteristics and surgical outcomes in myxopapillary ependymomas—a review of the literature

Reference	Number of cases	Time period	Mean age (years)	GTR rate (%)	Mean follow-up (years)	Recurrence rate (%)	Time to recurrence (months)	Median time to recurrence (months)
Sonneland et al. [27]	77	1924–1983	36.4	58.4	N/A	16.9	24–180	N/A
Akyurek et al. [2]	35	1968–2002	35	60	10.7	34	5–378	65
Bagley et al. [6]	52	1982–2003	35.4	N/A	6.1	40	N/A	88
Pica et al. [22]	85	1970–2007	36.9	47	10	28	1.7–120.1	26
Present study	27	2004–2013	33	66.7	4.1	14.8	5–83	26.5

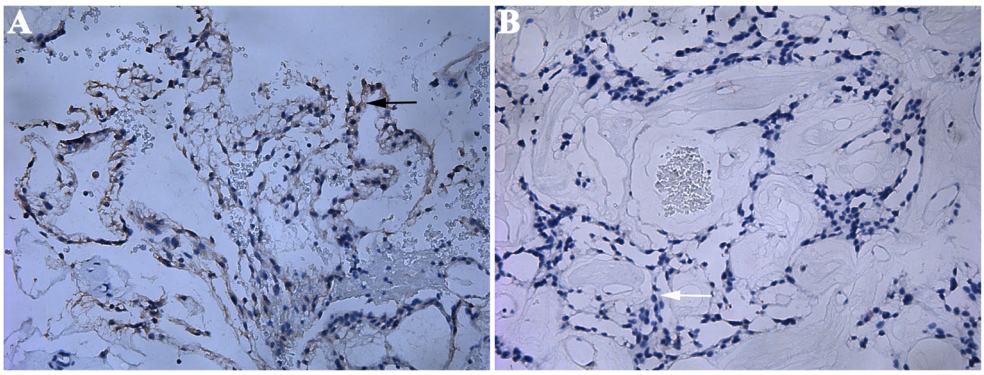

Fig. 2 Immunohistochemistry for EGFR, original magnification 200×. **a** Nonrecurrent myxopapillary ependymoma (MPE) showed positive staining for epidermal growth factor receptor (EGFR) (*black arrow*). **b** Tumors with recurrence showed no staining for EGFR (*white arrow*)

compared to PFS in patients who received surgery alone (50.4 %) [23]. Moreover, research that focused on pediatric MPE patients suggested that STR with adjuvant RT provided an improved prognosis in disease control than GTR alone [4]. Schild et al. [25] reexamined their data concerning the use of adjuvant radiotherapy for treatment of ependymomas, and after screening for MPE subtypes, they found a significant improvement in the 5-year local control rate in patients who were treated with radiation doses higher than 50 Gy than those who received lesser doses. A systematic analysis evaluating 109 MPE patients treated with radiotherapy also demonstrated a dose-response relationship with PFS [19]. However, a meta-analysis conducted by Feldman et al. found that radiotherapy did not result in significant improvements in treatment with GTR alone compared with GTR and RT or in treatment with STR alone compared with STR and RT. In our study only one patient received radiotherapy, so the effect of RT could not be evaluated. However, the effects of GTR on disease control could be examined more directly because the RT variable was excluded. In addition to its ambiguous benefits on tumor control, the side effects of radiotherapy potentially include spinal deformities, decreased cartilage growth and increased rates of postoperative kyphosis or scoliosis [12, 17]. These complications need attention, particularly in pediatric patients. As a result, we suggest that the evaluation of treatment options for MPE patients should include both the necessity for use of RT as well as the potential complications.

Although MPE has a low incidence in younger individuals, pediatric patients are more likely to experience recurrence or metastasis. According to the report from Bagley et al. [6] in 2009, compared to adult patients (>18 years), pediatric patients (<18 years) had a higher risk of local recurrence and dissemination within the neural axis as well as a more aggressive clinical course. Interestingly, Kukreja et al. [19] found that younger patients were potentially more sensitive to adjuvant RT, thus placing radiotherapy in a more important position in the management of pediatric MPEs. The reason for the unique clinical presentation of pediatric MPE is still not clear, but it is thought to be relevant to its predilection for lumbosarcal region where lymphatic spread and dissemination are more frequent [1, 5]. Conversely, it has also been hypothesized that the biological characteristics of the tumors are more important indicators of recurrence than the anatomical location [3]. In our study, we observed a significant difference between younger patients and adults in tumor recurrence, but also discovered that younger patients demonstrated a shortened recurrence time (11 vs. 59.5 months). Therefore, we suggest the follow-up should extend to at least 5 years after the surgery. In addition, radiological follow-up should be performed in the early stages (1 year) following surgery particularly in pediatric patients in order to avoid missing asymptomatic recurrence. Because of the possibility of disseminating tumor cells throughout cerebrospinal fluid (CSF) of the neuraxis, the pre- and postoperative diagnosis to differentiate

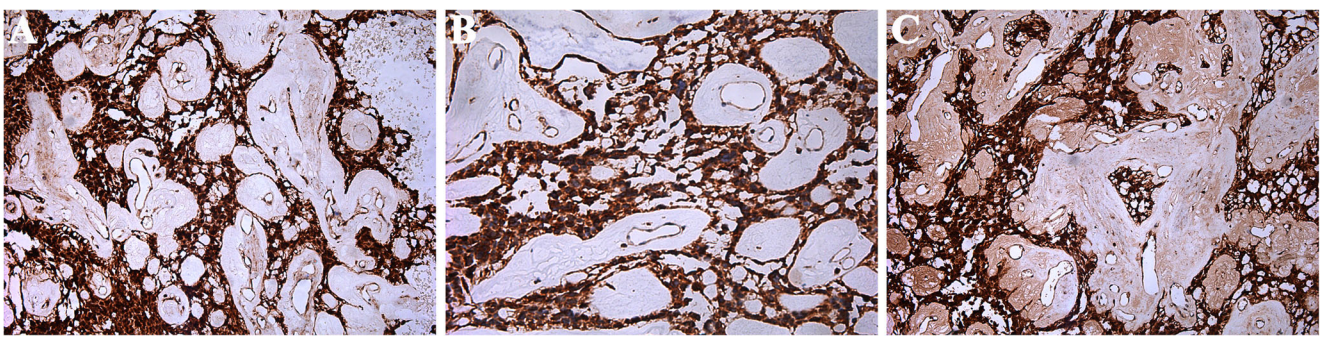

Fig. 3 Immunohistochemistry for MMP-2, MMP-4 and PDGFRα, original magnification 200×. Almost all myxopapillary ependymoma (MPE) samples showed strong positive staining for matrix metalloproteinase-2 (**a**), matrix metalloproteinase-14 (**b**) and platelet-derived growth factor receptor α (**c**) in the immunohistochemical study

MPEs from other tumors is imperative. The mechanism of neuraxis spread is unclear, but one potential possibility is through tumor cell migration within the CSF pathway after capsular rupture [10]. Sonneland et al. [27] reported that in two groups of MPE cases, which both received GTR treatment, patients whose tumors were removed intact exhibited a lower rate of recurrence than those whose tumors were removed piecemeal. For this reason, MPEs should be removed en bloc whenever feasible in order to avoid the potential dissemination. MRI should be the primary diagnostic tool used before surgery because of its ability to determine the extent of the tumor and its relationship to surrounding structures. Through careful analysis of the MRI imaging before surgery, the surgeon may have the best opportunity to remove the mass intact if the tumor is a suspected MPE.

Since MPEs are more likely to recur or disseminate through the neuraxis compared to other benign tumors, the follow-up should be closely monitored. Postoperative differential diagnosis by experienced neuropathologists is indispensable. Because the typical histologic features of MPEs consist of tumor cells surrounding vascularized myxoid stromal cores, MPEs share a similar myxoid matrix with other tumors, such as chondrosarcomas and chordoid meningiomas. In order to differentiate these tumors, Cho et al. [11] performed IHC and found that D2-40, EMA, cytokeratin and GFAP were useful markers to delineate these tumors. In this study, we observed overexpression of MMP2 and MMP14 in MPEs, suggesting that these proteins could be potential new markers for the differential diagnosis.

Although MPE has indolent biological characteristics, even when patients undergo GTR, long-term PFS is not guaranteed. This suggests that some unknown histological features must play a role in the high incidence of MPE recurrence. MIB-1, a marker for cellular proliferation, has low expression in MPEs due to their inherent benign biological profiles. High expression of the EGFR protein has been associated with tumor progression and enhanced tumorigenicity in other types of CNS tumors [8, 28]. Verma et al. [30] performed histological evaluation of MPEs from seven patients and found that EGFR was overexpressed in three out of four relapsed cases at both diagnosis and recurrence, but not in the nonrecurring tumors. This finding suggested that elevated EGFR expression could be a predictive biomarker for recurrence of MPE. However, another study observed no correlation between tumor recurrence and EGFR expression [31]. In contrast to the previous report, we observed that overexpression of EGFR correlated with improved prognosis, although the relationship was not statistically significant, suggesting that MPEs might have a different biological nature than other CNS tumors. In agreement with Barton et al.' work [7], we also observed that PDGFRα expression was strongly positive in all our samples. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are capable of degrading extracellular matrix proteins, which may lead to the promotion of metastasis. Matija el al. [26] found that MMP2 and MMP14 were predictors of poor OS and PFS in pediatric intracranial ependymomas. We also observed the overexpression of both MMP2 and MMP14 in our study, thus presenting potential diagnostic and therapeutic targets for MPEs.

Limitations

First, the low incidence of MPE makes a prospective and randomized study improbable, so our study was limited by its retrospective nature. Second, limited by the communicational conditions, about 1/3 patients in our study were lost to follow-up. These patients were more often seen in the earlier part of our study's time range, and we believe the reason for losing to follow-up was the inconvenience of communication rather than the difference in operational outcome. Third, because neuromonitoring is helpful to preserve neurological functions, it has been put into use in our institution in recent years. However, neuromonitoring was not used in this study, because some recent cases of MPE with neuromonitoring were excluded because of the short follow-up period. Finally, as it has been reported that the median time of tumor recurrence is 26–88 months, the mean follow-up time of 49.8 months in our study probably led to the relatively low recurrence rate. However, the continuous follow-up will be carried out to observe their long-term outcomes. Moreover, in consideration of the small number of patients (n=1) who received radiotherapy in our study, the effect of GTR on prognosis we analyzed was more persuasive because the variable of RT was excluded.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

For this type of study formal consent is not required.

Conflict of Interest None

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