

Clinicopathologic analysis of multifocal myxopapillary ependymoma: Report of 4 cases and literature review

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Research Article

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Abstract

Objective

Myxopapillary ependymoma (MPE) stands as a rare variant of ependymoma, primarily found within the spinal cord and cauda equina regions. This article aims to delve into the clinical and pathological characteristics of multifocal myxopapillary ependymoma (MPE), shedding light on its prognosis and advocating for increased awareness among clinical practitioners regarding this tumor type.

Methods

We conducted a retrospective analysis of clinical data, pathological morphology, immunohistochemical characteristics and next-generation sequencing (NGS) concerning four patients diagnosed with multifocal MPE. Additionally, relevant literature pertaining to this topic was thoroughly reviewed.

Results

The study encompassed two male and two female patients, aged between 20 and 57 years, with an average age of 34.6 years. Tumors were situated within the spinal canal, spanning from the eleventh thoracic vertebra to the second sacral vertebra. Common clinical presentations included lower back pain or soreness. Histologically, the tumors exhibited similar features characterized by papillary structures comprised of radiating cuboidal or elongated epithelioid glial tumor cells, encircling fibrovascular cores exhibiting transparent stromal changes. The interstitium showcased a mucinous appearance. Immunohistochemical analysis revealed expression of GFAP in all cases, while S-100 and CD56 were expressed in three cases. The Ki-67 index ranged from 1% to 5% across the four cases. NGS confirmed *TERT* C250T mutation in two case.

Conclusions

Multifocal myxopapillary ependymoma emerges as a rare variant of spinal cord tumor, with only 15 reported cases in the existing literature. Currently classified as grade 2 by the World Health Organization (WHO), most instances can be effectively managed through complete surgical resection, yielding favorable prognoses. However, compared to single-focus MPE, multifocal MPE exhibits a heightened propensity for recurrence and intraspinal dissemination.

INTRODUCTION

Myxopapillary ependymoma (MPE) is a rare subtype of ependymal tumor primarily found in the filum terminale and cauda equina. It was initially defined in 1932 and has since undergone further characterization [1]. These tumors typically exhibit microcystic vesicles, myxoid structures, and

connective tissue, without accompanying developmental abnormalities. Instances of systemic dissemination are uncommon, although they can spread throughout the neuroaxis via cerebrospinal fluid dissemination. In the World Health Organization (WHO) classification of 2006, MPE was categorized as grade 1; however, in the 2021 classification, it was upgraded to grade 2 [2, 3]. Multifocal occurrences of MPE are rare, with only 15 documented cases in the literature. This study presents four new cases of multifocal MPE, providing an analysis of their clinical characteristics, pathological morphology, immunophenotype, and a review of pertinent literature to enhance understanding of this condition.

METHODS

The cases of MPE were collected between January 2012 and December 2023 from Wenzhou People's Hospital, Ningbo University Yinzhou People's Hospital, and Ningbo Clinical Pathological Diagnosis Center. Adhering to the criteria outlined in the 2021 WHO classification of central nervous system tumors [3], a total of four cases of multifocal MPE were identified and reviewed. Comprehensive clinical data, encompassing gender, age, tumor location, clinical symptoms and signs, imaging findings, and treatment details, were compiled from the patients.

For immunohistochemical staining, typical paraffin blocks were meticulously chosen. Primary antibodies utilized included GFAP, Olig2, EMA, D2-40, S-100, CD56, SSTR2a, CKpan, and Ki-67. The EnVision two-step method with DAB chromogen was employed for immunohistochemical staining, with reagents procured from Fuzhou Mainchem Biotechnology Development Co., Ltd. Positive immunohistochemical staining results were defined by the presence of brown or yellow particles in $\geq 10\%$ of tumor cells within the staining area. Specifically, GFAP, CKpan, CD56, and SSTR2a exhibited cytoplasmic staining, S-100 displayed cytoplasmic and nuclear staining, EMA and D2-40 demonstrated perinuclear dot-like staining, while Olig2 and Ki-67 manifested nuclear staining. Next-generation sequencing (NGS) was performed on an Illumina high-throughput sequencing platform to detect gene fusions and other alterations. Additionally, fluorescence in situ hybridization (FISH) of the *MYCN* (2p24) loci was conducted on formalin-fixed paraffin-embedded tissue to confirm the presence of *MYCN* amplification.

RESULTS

Clinical data

In this series, there were two men and two women, ranging in age from 20 to 57 years, with an average age of 34.6 years. Three patients presented with lower back pain or soreness, while one patient experienced bilateral leg pain. The tumors were located within the spinal canal, spanning from the 11th thoracic vertebra to the 2nd sacral vertebra, with two lesions observed in each case. The maximum tumor diameter ranged from 0.8 to 5.0 cm, with an average of 2.9 cm.

On imaging, the tumors appeared sausage-shaped or elongated, often encasing the cauda equina nerves. Magnetic resonance imaging (MRI) revealed isointense signals on T1-weighted imaging (Fig. 1)

and high signals on T2-weighted imaging. The high signal on T1-weighted imaging was associated with mucin and hemorrhage, while the high signal on T2-weighted imaging was attributed to papillary projections of tumor cells and abundant mucinous matrix. Significant enhancement of the tumors was observed after contrast administration (Fig. 2). Additional patient details are provided in Table 1.

Table 1
Clinicopathologic data of multifocal myxopapillary ependymoma

Case	Sex/age	Location	Number of lesions	Presentation	Radiation	Followup (months)	Outcome
1 ^[4]	M/39	2	L2-L3, L5-S1	Bilateral buttock pain, intermittent claudication	yes	42	no
2 ^[5]	M/28	2	L3-L4, L5-S2	Severe low back pain	yes	12	no
3 ^[6]	M/30	3	C2-C3, T2-T4-T5, T12-L1	Paresthesia, gait instability, ataxia, and lower back pain	yes	120	no
4 ^[6]	M/32	multiple	C7, T2, T4, T5, T8, T10, T11, L1, L3, L5, S1, S2	Low back pain, mild right lower limb paresthesia	no	12	no
5 ^[7]	M/63	3	T2, T12-L2, S1-S3	Low back pain	yes	6	no
6 ^[8]	M/26	2	Lumbar, Conus medullaris	Low back pain and bilateral lower limb pain	-	-	-
7 ^[9]	M/48	multiple	Cervical, Thoracic, Lumbar	Severe back pain	-	-	-
8 ^[10]	M/32	2	L2-L3, L5-S1	Bilateral buttock pain and claudication	no	12	no
9 ^[11]	M/32	3	L1-L2, L3, S1	Urinary incontinence	-	6	no
10 ^[12]	M/43	3	L3, Thoracic, Sacral	-	no	36	no
11 ^[12]	F/20	2	T11-L1, Sacral	-	no	24	no
12 ^[12]	F/18	3	L1-L2, Thoracic,	-	no	6	no
-: not available							

Case	Sex/age	Location	Number of lesions	Presentation	Radiation	Followup (months)	Outcome
			Sacral				
13 ^[12]	M/48	2	L3-L4, L4-S1	-	yes	42	yes
14 ^[13]	M/33	3	L1-L2, L3, S1	Sudden urinary retention	no	-	-
15 ^[14]	M/34	2	L1-L3, S1-S2	low back pain	yes	-	-
16 case1	M/35	2	T12, L1	Low back and hip pain, Left lower limb weakness	no	35	no
17 case2	F/27	2	L4, S2	low back pain	no	24	no
18 case3	F/20	2	T11-T12, L1-L2	bilateral lower limb pain	no	30	no
19 case4	M/57	2	T11-T12, L2	low back pain	no	60	yes
-: not available							

Pathological findings

Upon gross examination, the tumors exhibited solid, friable masses with a gray-white or gray-red color and soft consistency. Histologically, all four cases shared similar features, characterized predominantly by papillary structures (Fig. 3A). Glial tumor cells with cuboidal or elongated epithelioid morphology arranged in a radiating pattern, surrounded by clear fibrovascular cores. The stroma displayed a mucinous appearance often accompanied by degenerative changes. Alkaline mucinous substances were observed around blood vessels and microcysts. Some cases demonstrated fascicular growth and spindle-shaped cells. Mitotic figures were sparse, and there was no evidence of endothelial cell proliferation or necrosis. Immunohistochemical staining revealed that all four MPE cases expressed GFAP (Fig. 3B), while three cases expressed S-100 (Fig. 3C) and CD56, with a Ki-67 index ranging from 1–5% (Fig. 3D). Other immune markers showed negative results. *TERT* promoter mutations (C250T) were detected in two cases through NGS. FISH analysis did not detect amplification of *MYCN*.

Treatment and prognosis

Surgical resection was performed on all four patients, with follow-up ranging from 24 to 60 months. Three patients showed no recurrence or metastasis during this period. However, one case experienced relapse after 24 months, underwent repeat surgery, received standardized radiotherapy, and is currently under observation.

Literature review

A comprehensive literature search on PubMed yielded 19 cases of multifocal myxopapillary ependymoma, including our own. Clinical and pathological data such as gender, age, tumor location, clinical presentation, histopathological diagnosis, and clinical outcomes were compiled for each patient. Detailed information on these cases, including our own, is presented in Table 1 [4–15].

DISCUSSION

Ependymoma, a primary tumor of the central nervous system, was initially categorized into four subtypes: subependymoma, myxopapillary ependymoma (MPE), classic ependymoma, and anaplastic ependymoma. MPE presents distinct histological features compared to other ependymal tumor subtypes. In the 2021 WHO classification of tumors, ependymomas are now classified based on a combination of histopathological features, molecular characteristics, and anatomical location [3]. Notably, papillary tumors, clear cell tumors, tanycytic tumors, and anaplastic ependymomas are no longer recognized as distinct subtypes in this updated classification. While MPEs, previously designated as WHO grade 1, continue to be acknowledged as a separate tumor entity, they have been reclassified from CNS WHO grade 1 to 2 due to their recurrence pattern resembling that of conventional spinal ependymomas.

Multifocal MPE is exceedingly rare, with only 19 documented cases in the literature, including those outlined in this study. This manifestation predominantly affects males (15 cases) compared to females (4 cases), with ages ranging from 18 to 63 years and an average age of 35 years. Tumors are most frequently found in the lumbar and sacral spine, followed by the thoracic and cervical spine. Among the patients, 11 had two lesions, 6 had three lesions, and 2 had multiple lesions. These tumors exhibit slow growth and are associated with a protracted clinical course. The duration of symptoms before diagnosis ranged from 1 month to 6 years. Common clinical presentations in MPE patients include lower back pain, weakness, sensory alterations, and lower extremity pain. Depending on the lesion's location and its compression on nerve roots or the spinal cord, symptoms such as urinary, bowel, or sexual dysfunction may manifest.

Histologically, MPEs typically lack perivascular pseudorosettes and true ependymal rosettes, which are specific features of ependymomas. MPEs are characterized by papillary structures surrounded by cuboidal to spindle-shaped glial cells [15]. A prominent feature of MPEs is the presence of a mucinous matrix, often accompanied by glassy changes in vessel walls. While calcification, necrosis, and cyst formation can occur, mitotic figures are usually rare. Some tumors may exhibit more compact fascicular

structures and occasionally show perivascular pseudocystic clusters and mucin-rich microcysts. Variable and giant cell variations have been described in some cases of MPEs [16].

Immunohistochemically, tumor cells from MPEs often show positive staining for GFAP, S-100, CD56, and CDX2, while staining for Olig2 and EMA tends to be negative. The Ki-67 proliferation index is generally less than 5%. MPEs typically have a unique DNA methylation profile [2]; however, a small subset of typical ependymomas may cluster with MPEs in terms of DNA methylation. Few genetic alterations have been reported in MPEs, although individual cases have reported recurrent gains of chromosome 16 and loss of chromosome 10 [17, 18]. *TERT* promoter mutations (C250T) were detected in these two cases.

The primary treatment for MPE is complete surgical resection, which serves as the cornerstone approach aimed at minimizing tumor recurrence and metastasis [20]. Surgical intervention was conducted in all 19 cases of multifocal MPE, with 6 patients subsequently receiving postoperative radiation therapy. Notably, two patients experienced postoperative recurrence but ultimately survived. However, subtotal resection is linked to a higher tumor recurrence rate, with an average of 30% recurrence within 3.5 years. Notably, there exists a correlation between tumor recurrence and the rupture of the tumor capsule, posing a 45% risk after subtotal resection and 15% after total resection. In instances where the tumor capsule is breached, irrespective of the resection extent, adjuvant radiation therapy is recommended to mitigate the risk of recurrence or metastasis [21].

The use of adjuvant radiation therapy in MPE treatment remains contentious. While some researchers advocate for its use, particularly in cases of subtotal resection, others argue that its efficacy in reducing postoperative recurrence is inconclusive. Consequently, for patients who undergo complete resection without capsule invasion and exhibit no dissemination signs in postoperative cerebrospinal fluid analysis, adjuvant radiation therapy is not advised [22]. Given the recurrence and metastasis risks associated with multifocal MPE, judicious consideration of appropriate adjuvant radiation therapy post-surgery is warranted.

Declarations

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ningbo Clinical Pathology Diagnosis Center. The present study was carried out in accordance with the Declaration of Helsinki. Written informed consent to participate in this study was provided by the participant himself/herself. Written informed consent for the publication of potentially identifiable data in this article was also obtained from the participant.

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AUTHOR CONTRIBUTIONS

SQ: collecting the data and drafting the manuscript. CP: data analysis and statistical analysis. RG: critical revisions of the manuscript. All authors participated in the article and approved the final version.

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Figures

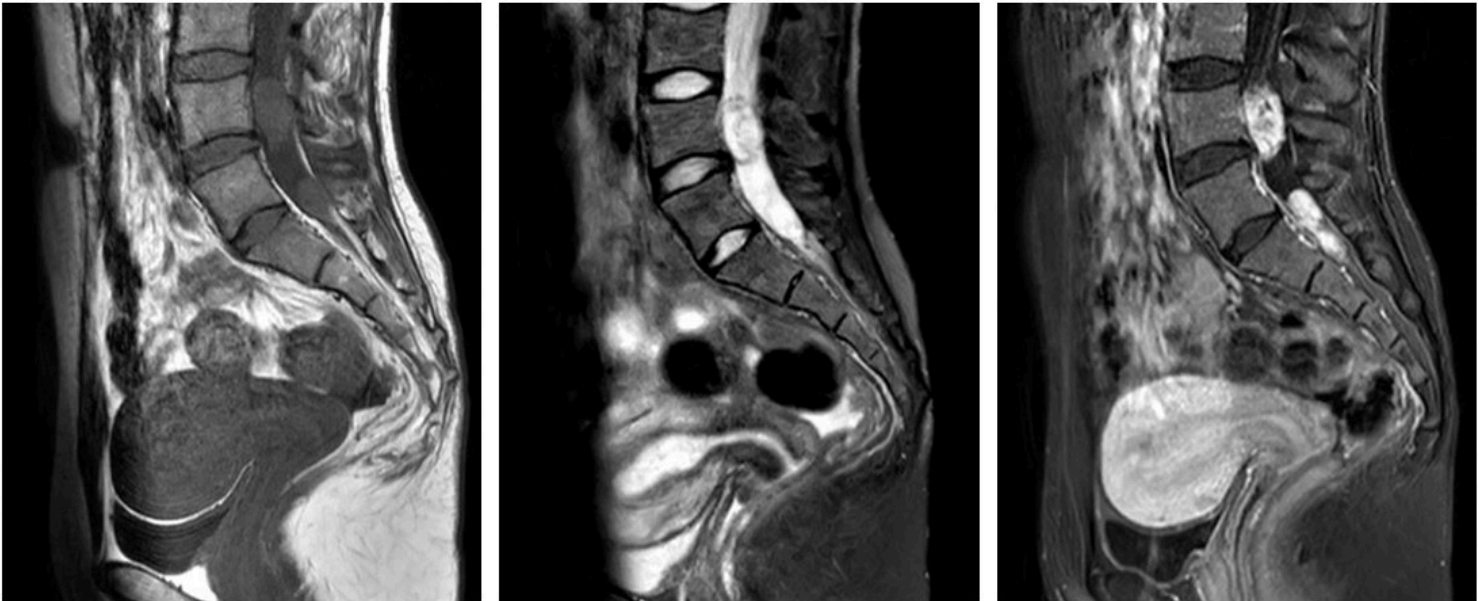


Figure 1

Sagittal MR imaging of the patient 2 before surgery. A. T1W, B. T2W, C. Fat-suppressed T1W



Figure 2

Sagittal MR imaging of the patient 3 before surgery. A. T1W, B. T2W, C. T1W with contrast

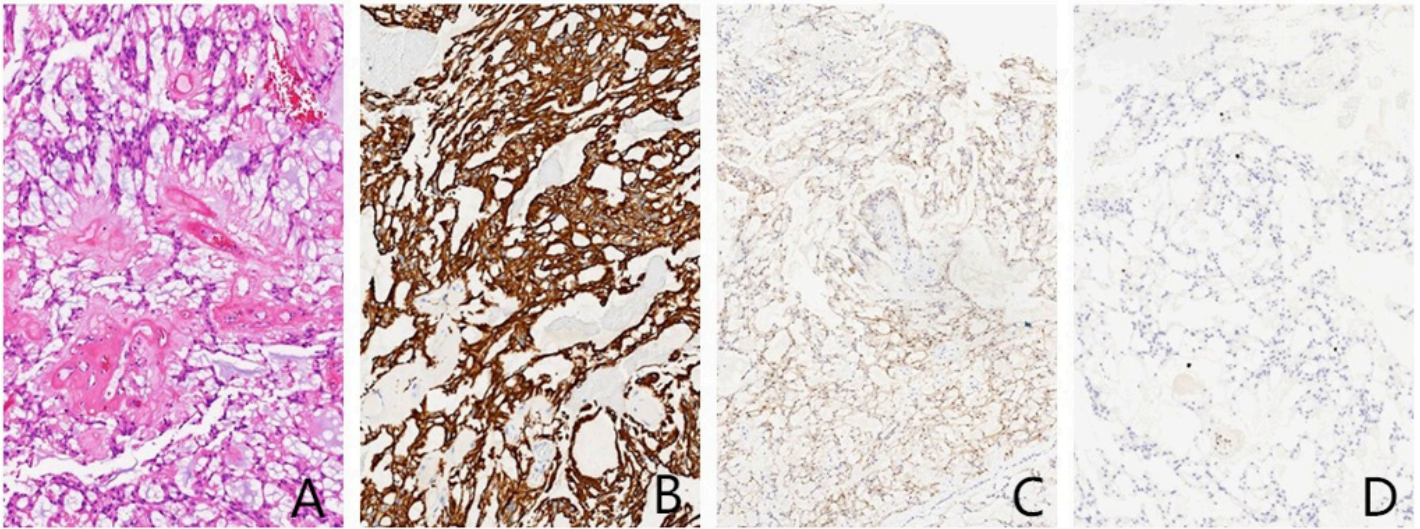


Figure 3

Histopathologic and immunohistochemical features of myxopapillary ependymoma ($\times 100$). A. MPE is characterized by papillary-like structures surrounded by cuboidal to spindle-shaped glial cells around blood vessels. B. Tumor cells show positive expression of GFAP. C. Tumor cells show positive expression of S-100. D. The Ki67 index of tumor cells is low. H&E staining: A. Immunohistochemical staining: B, C, D.