



Clinical features and surgical outcomes of primary spinal anaplastic meningioma: a cases series and literature review

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Background: Primary spinal anaplastic meningioma (PSAM) is a very rare entity in the spinal canal. Therefore, the clinical features, treatment strategy, and long-term outcomes remain poorly studied.

Case Description: Clinical data of six patients with PSAM treated at one single institution were retrospectively analyzed and all previously reported cases in the English literature were reviewed. There were three male and three female patients with a median age of 25 years. The duration of symptoms before initial diagnosis ranged from one week to one year. PSAMs occurred at cervical level in four, cervicothoracic in one and thoracolumbar in one. In addition, PSAMs presented isointensity on T1 weighted imaging (WI), hyperintensity on T2WI, and hetero- or homogeneously marked enhancement with contrast. Eight operations were performed in six patients. Simpson II resection was achieved in four (50%), Simpson IV in three (37.5%), Simpson V in one (12.5%). Adjuvant radiotherapy was performed in five patients. With a median survival time of 14 months (4–136 months), three patients had recurrence, two experienced metastases, and four died of respiratory failure.

Conclusions: PSAMs are a rare disease, and there is limited evidence as to the management of these lesions. They may metastasize, recur, and portend a poor prognosis. A close follow-up and further investigation are therefore necessary.

Keywords: Primary spinal anaplastic meningioma (PSAM); World Health Organization (WHO) grade III; malignant meningioma; case series

Submitted Oct 28, 2022. Accepted for publication Mar 30, 2023. Published online Apr 07, 2023.

doi: 10.21037/tcr-22-2505

View this article at: <https://dx.doi.org/10.21037/tcr-22-2505>

Introduction

Meningiomas represent 40.0% of primary central nervous system (CNS) tumors, and 4.2% of meningiomas are located in spinal meninges (1). With a prevalence of 0.33 in 100,000 population, spinal meningiomas are usually benign and slow-growing tumors (2). However, primary spinal anaplastic meningioma (PSAM) is one of the rare malignant subtypes, which were pathologically classified as World

Health Organization (WHO) grade III meningiomas (3-5). Distant metastasis could occur to intracranial meningiomas, and a systematic review concluded that 15.2% happened intraspinally (6). Accompanying metastasis from intracranial meningioma might complicate the clinical course, so we focus on PSAM, which developed and progressed originally within the spinal canal (6).

To the best of our knowledge, only seven articles concerning PSAM were published in English literature

since Solero *et al.* reported the first case (7-13). Incomplete description was common, which increased the difficulty of understanding the disease (10,11). We noticed there were tumor recurrence, metastasis, and interestingly, “malignant transformation” recorded in literature (7-9). The phenomena seemed to be consistent with its WHO grading. We therefore report a case series of 6 patients with histologically confirmed PSAM at one single institution and discuss the clinical features, treatment strategy, and long-term outcomes of this rare entity. Hopefully, this will add to our knowledge of PSAM and provide raw data for further study. We present this article in accordance with the AME Case Series reporting checklist (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2505/rc>).

Case presentation

Methods

From January 2008 to September 2017, six patients were consecutively admitted, surgically treated, and pathologically diagnosed with PSAM at the Department of Neurosurgery, Beijing Tiantan Hospital. All six patients were included based on the following criteria: (I) preoperative magnetic resonance imaging (MRI) demonstrated a lesion in the spinal canal; (II) intraoperative and histological findings confirmed the diagnosis of anaplastic meningioma; and (III)

no other lesions in CNS or other systems were identified during initial diagnosis. We collected clinical data and completed follow-ups in December 2019 with the approval from institutional review board of Beijing Tiantan Hospital (No. KY-2019-076). The median follow-up time was 8.5 (range, 4–136) months. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case series and accompanying images was waived from patient consent according to the Beijing Tiantan Hospital ethics committee/institutional review board.

We routinely performed laminectomy and laminoplasty through posterior midline approach. Simpson grading was applied to define the extent of resection (14). The tumors which increased in size and caused relapsed or new neurological deficits after primary surgery were considered as tumor regrowth or recurrence. MRI with gadolinium contrast was routinely performed before and after surgery. Multimodal intraoperative neurophysiologic monitoring (IONM) was routinely applied to intra- and juxtamedullary tumors at our institution to identify and prevent potentially risky maneuvers (15,16).

Surgical specimens were all fixed in formaldehyde overnight and embedded in paraffin, which were analyzed through microscopic and immunohistochemical techniques and reviewed independently by two experienced neuropathologists. All pathological diagnoses met the criteria of anaplastic meningioma of WHO 2016 classification as below: (I) presence of at least 20 mitoses per 10 high-power fields, and/or (II) presence of overtly malignant morphological aspect resembling that of sarcomas, carcinomas or melanomas (5).

Modified McCormick classification (MMC) were applied to assess neurological function (17,18). This assessment was performed before surgery and during the last follow-up. All six patients or their kin consented to the use of their medical records for research purposes.

A comprehensive literature search was performed to identify articles relevant to PSAM. Keywords and MeSH terms such as “primary spinal anaplastic meningioma”, “spinal cord neoplasms” and “anaplastic meningioma” were incorporated into our search strategy. We used PubMed and the Ovid MEDLINE databases to identify the relevant English articles and found seven articles for inclusion (3,7-11).

Highlight box

Key findings

- Primary spinal anaplastic meningioma (PSAM) is a rare disease. They may metastasize, recur, and portend a poor prognosis.

What is known and what is new?

- Seven PSAMs were reported in literature. Recurrence and metastasis were recorded though the data were usually incomplete.
- Three female and three male patients were diagnosed with PSAM, and the median age of the patients was 25 years old. After treatment, the median survival time was 14 months. Three had recurrence, two experienced metastases, and four died of respiratory failure.

What is the implication, and what should change now?

- PSAM is an extremely rare disease. The efficacy and safety of the treatment require further investigation. A close follow-up might be necessary.

Table 1 Summary of clinical presentations and outcomes of six patients with primary spinal anaplastic meningiomas

Case	Age (years), sex	Duration from onset to diagnosis	Location	Presentations	MRI Findings			Treatment*	Modified McCormick		Metastasis	Follow-up
					T1WI	T2WI	+GA		Pre-op	Follow-up		
1	20, male	1.5 months	C1-2, IM & IDEM	Right side weakness and reduced superficial sensation	Iso	Mixed hyper	Hetero	IV + RT	II	NA	Disseminated to thoracic spinal canal	9 months, rec [†] ; 20 months, dead [†]
2	46, male	4 months	C1-3 (1 st), C1-2 (2 nd), IDEM	Neck pain and head tightness; right upper limb weakness (2 nd)	Mixed iso	Mixed hyper	Hetero	IV + RT (1 st); II (2 nd)	Ib (1 st) II (2 nd)	I (1 st) I (2 nd)	Non (1 st) Non (2 nd)	11 years, rec; 11 years & 4 months, alive
3	19, male	1 year	C6-T1, IDEM	Left scapula pain, hands atrophy & weakness	Iso	Mixed hyper	Hetero	V + IV + RT	II	NA	Brain, femurs and multiple areas	8 months, rec & dead
4	46, female	1 week	C3-4, IDEM	Left upper arm weakness	Iso	Hyper	Homo	II + RT	II	NA	NA	4 months, no rec & dead
5	30, female	6 months	T12-L1, IDEM	Lower back pain and reduced superficial sensation	Iso	Hyper	Homo	II + RT	Ib	I	Non	9 years, no rec & alive
6	13, female	1 month	FM/C1-C2, IDEM	Neck & head pain and left side weakness	Iso	Hyper	Homo	II	II	NA	NA	4 months, no rec & dead

*, extent of resection was recorded according to Simpson (I–V) resection; †, since initial diagnosis. MRI, magnetic resonance imaging; T1WI, T1 weighted imaging; T2WI, T2 weighted imaging; +GA, gadolinium administration; IM, intramedullary; IDEM, intradural and extramedullary; Iso, isointensity; Hyper, hyperintensity; Hetero, heterogeneously; RT, radiotherapy; NA, not available; Rec, recurrence; FM, foramen magnum; Homo, homogeneously.

Demographics and clinical presentations

Six PSAM patients at our center account for approximately 1% of all spinal meningiomas in the same period (Table 1). There were three male and three female patients with a median age of 25 (range, 13–46) years, and the duration of symptoms ranged from one week to one year. PSAMs occurred at cervical level in four patients, cervicothoracic in one, and thoracolumbar in one. Clinical presentations included focal pain, sensory deficits, and limb weakness, similar to that of common spinal tumors. The preoperative assessments showed that four patients were at MMC grade II (Case 1, 3, 4, 6), followed by one at grade Ib (Case 5). Case 2 was respectively classified as grade Ib and

II during two different admissions.

Radiological findings

Six PSAM cases generally demonstrated isointensity on T1WI, hyperintensity on T2WI, and hetero- (Case 1–3) or homogeneously (Case 4–6) marked enhancement with contrast (Figure 1). Two of the lesions were spindle-shaped (Case 2, 3), two were lobular (Case 1, 6) and two were spherical (Case 4, 5). All tumors were located at intradural and extramedullary space, while spinal cord was infiltrated in Case 1. Three PSAMs grew on the ventral side of the spinal cord (Case 2, 3, 6), while three on lateral side (Case 1, 4, 5). Case 1, 4, and 6 presented hyperintensity of the spinal

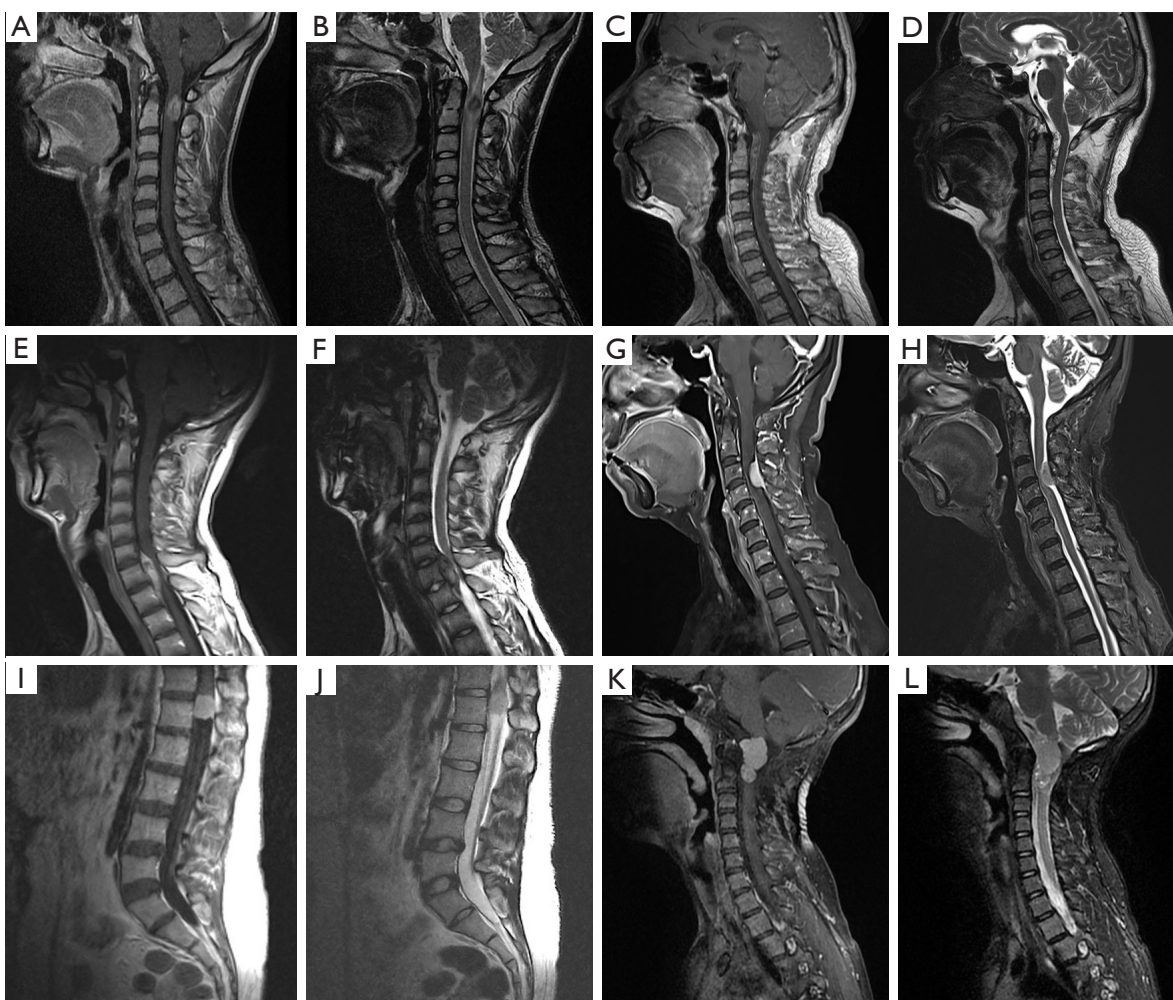


Figure 1 Preoperative sagittal magnetic resonance imaging demonstrated hetero- or homogenous enhancement on T1 weighted imaging with contrast (Case 1–6: A,C,E,G,I,K) and hyperintensity on T2 weighted imaging (Case 1–6: B,D,F,H,J,L).

cord on T2WI to certain extent.

Pathological examination

Histologically, markedly elevated mitosis, abundant cytoplasm, prominent nucleoli and extensive necrosis could be found, which met the criteria of the WHO 2016 classification of anaplastic meningioma (Figure 2). Immunohistochemical analyses were also performed, reporting high Ki-67 indices as well as positive Vimentin and epithelial membrane antigen (EMA) in all cases. Ki-67 indices were 20%, 40%, 30%, 40%, 60%, 30%, respectively (Case 1–6).

Treatment

Eight operations were performed in six patients. Simpson grade II resection was achieved in four (50%, Case 2, 4–6), grade IV in three (37.5%, Case 1–3), grade V in one (12.5%, Case 3). Intraoperatively, we observed tumors with various textures, ranging from elastic to firm, and found irregularly brownish surfaces with well-defined capsules. PSAM in Case 1 had infiltration into spinal cord at the upper side of the tumor. IONM reported no abnormalities in all six patients during surgery. Postoperative courses were uneventful in five patients, and they were therefore discharged at 10th day after surgery. Case 4 was put on ventilator for 15 days and

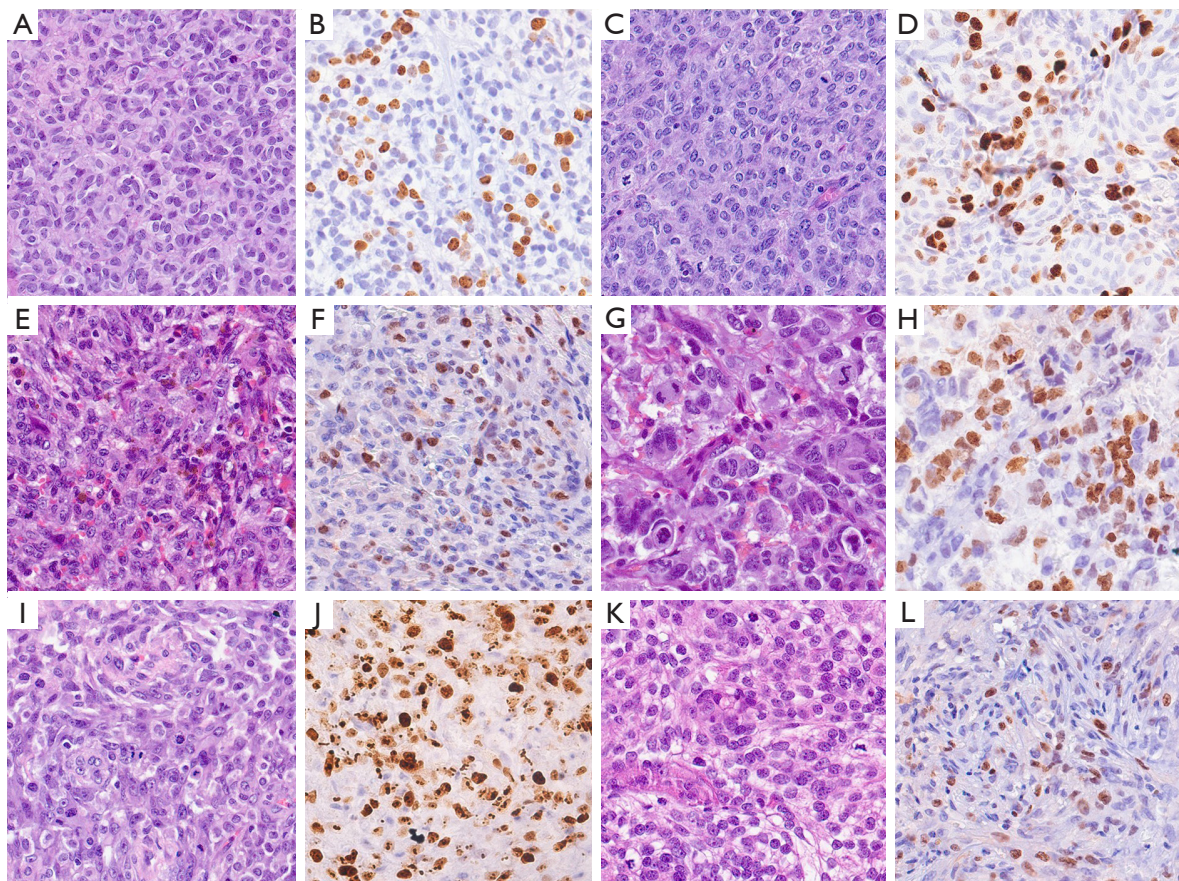


Figure 2 Pathological findings revealed elevated mitotic counts and large epithelioid cells with abundant cytoplasm and prominent nucleoli in six primary spinal anaplastic meningiomas (Case 1–6: A,C,E,G,I,K, hematoxylin-eosin staining, $\times 400$). Ki-67 indices were 20%, 40%, 30%, 40%, 60%, 30%, respectively (Case 1–6: B,D,F,H,J,L, Ki-67 staining, $\times 400$).

transferred to a local hospital. Adjuvant radiotherapy was recommended after surgery. However, one patient refused the treatment (Case 6), and one patient chose to wait and see, because he had radiotherapy 11 years ago (Case 2).

Long-term outcomes

We completed follow-ups in December 2019 and found the median survival time after the initial diagnosis was 14 (range, 4–136) months. Three patients had recurrence (Case 1–3), two experienced metastases (Case 1, 3) and four died (Case 1, 3, 4, 6) at the completion of the last follow-ups. The median time for recurrence was 9 (range, 8–11) months. PSAM in Case 3 metastasized to brain, femur and multiple other sites, while PSAM in Case 1 recurred and disseminated to thoracic canal. All four deceased patients died of respiratory failure with lung infection due to

confinement to bed. Case 2 survived over 11 years since initial diagnosis, and Case 5 survived 9 years without major complications. They both were clinically and radiologically stable without evidence of tumor regrowth and returned to MMC grade I status.

Illustrative cases

Case 2

A 46-year-old man complaint of intermittent neck pain and head tightness for 4 months and claimed it could be relieved by acupuncture. No neurological deficit was found. The MRI scan showed a lesion with mixed isointensity on T1WI, mixed hyperintensity on T2WI, and heterogeneously marked enhancement with contrast at C1-3 level. He underwent subtotal resection of the ventral tumor (Simpson IV resection), and a PSAM was pathologically

Table 2 Summary of previously reported cases of primary spinal anaplastic meningiomas

Authors & years	Cases	Age (years), sex	Location	Presentations	Recurrence*	Metastasis	Treatment	Follow-up
Solero <i>et al.</i> , 1989 (7)	1	NA	T4-5; IDEM	Slight neurologic deficit	9 years	NA	GTR (1 st); STR (2 nd)	10 years, dead*
Nishida <i>et al.</i> , 2016 (8)	1	68, male	C7-T2; IM & IDEM	Back pain and left lower limb paralysis	Non	Mediastinal lymph nodes	STR + RT	NA
Ye <i>et al.</i> , 2016 (10)	2	NA	NA	NA	Within 5 years	NA	NA	Within 5 years, dead
		NA	NA	NA	Non	NA	NA	5 years, alive*
Ito <i>et al.</i> , 2017 (9)	1	60, male	T2-3; intra- & extraspinal	Thoracic pain	Non	Rib, lumbar vertebra, and sacrum	Biopsy	1 year, dead
Hua <i>et al.</i> , 2018 (11)	8	NA	IDEM	NA	NA	NA	NA	NA
Ampie <i>et al.</i> , 2021 (12)	1	50, male	Thoracic, IM & IDEM	NA	NA	NA	STR + RT + Sunitinib	1 month, dead
Krauss <i>et al.</i> , 2021 (13)	1	47, female	NA	Neck/back and extremity pain; sensory deficit	Non	NA	STR + RT	Dead

*, since initial diagnosis. NA, not available; IDEM, intradural and extramedullary; GTR, gross-total resection; STR, subtotal resection; IM, intramedullary; RT, radiotherapy.

confirmed. Postoperatively, the previous symptoms were all relieved and the MRI demonstrated the ventral residue. The patient subsequently underwent adjuvant radiotherapy at a local hospital. Eleven years later, he was again admitted with progressive right upper limb weakness. A muscle strength of grade 4/5 was observed in the whole right upper limb, and no other abnormality was found. MRI demonstrated homogeneously marked enhancement at C1-2 level, which indicated tumor recurrence. The patient achieved gross total resection (Simpson II resection) this time and refused adjuvant radiotherapy. The postoperative course was uneventful, the limb weakness was significantly improved, and postoperative MRI proved no residue. Four months later, no recurrence or metastasis was found.

Case 3

A 19-year-old man presented with progressive left scapula pain for approximately 1 year, and muscle atrophy of both hands was observed. MRI demonstrated heterogeneously marked enhancement at C6-T1. He underwent biopsy initially at another hospital which confirmed a PSAM. We admitted him, performed subtotal resection of the ventral tumor (Simpson IV resection), and confirmed the diagnosis. Radiotherapy was arranged afterwards. He regained

ambulation without cane but soon found a growing mass beneath his laryngeal prominence. Therefore, a positron emission tomography scan was arranged at a local hospital and reported metastases to brain, femurs and multiple areas. Seven months later, he suffered quadriplegia with pain all over the body. Soon, he died of respiratory failure with lung infection.

Discussion

Epidemiology and clinical features

PSAM is extremely understudied due to its rarity (*Table 2*). Spinal meningioma is generally considered to have female predilection and the corresponding male to female ratio ranges from 1:1.5 to 1:14.5 (2,19,20). However, the numbers of male and female patients are even in our small sample. The incidence of meningioma increases over age, and people aged over 65 are most commonly affected (21). Similarly, spinal meningiomas most frequently occur in older patients (22). A systematic review concluded the average age of spinal meningiomas was 62.6 years old after adjusting the sample size of various studies (20). The median age of our patients was 25 (range, 13–46) years, while the median age of

literature cases was 55 (range, 47–68) years (8,9,12,13). Both samples were small and apparently heterogenous, thereby offering no consistent information concerning susceptible age. A case series reported 73% of spinal meningiomas were located in the thoracic region, 16% in cervical, and 4.5% at thoracolumbar junction (23). However, PSAMs seemed to occur more frequently in cervical region (66.7%) followed by cervicothoracic (16.7%) and thoracolumbar areas (16.7%) in our sample. In literature, four PSAMs were all found at thoracic level (7-9,12).

Pain and limb weakness might be the most common initial symptoms, leading to the difficulty of differentiating PSAMs from other spinal tumors. The duration of symptoms varied from 1 week to 6 months, and MMC grading varied from Ib to II. The literature cases revealed similar clinical presentations, though duration of symptoms and MMC grading were hardly recorded (7-13).

The radiological features of PSAM were rarely mentioned in literature. Ito *et al.* and Nishida *et al.* respectively reported a case with homogeneous enhancement and swelling spinal cord (8,9). PSAMs in our study demonstrated a relatively consistent presentation. A study found non-spherical shape as well as the intratumoral heterogeneity on MRI had a significant association with high-grade intracranial meningiomas (WHO II–III) (24). In our sample, PSAMs presented spindle-shaped or lobular in four (66.7%), spherical in two (33.3%) and showed heterogeneity with contrast in three patients. In addition, the spinal cord swelling occurred in three (50%) patients. Ito *et al.* found PSAM could surround the spinal cord, occupy the limited intradural extramedullary space, and cause the swelling of the cord (9). Nishida *et al.* recorded the spindle-shaped PSAM grew on the left side and also caused the swelling (8). Further study on the correlation between the tumor morphology and intratumoral heterogeneity might assist in differential diagnosis of spinal meningiomas of different WHO grading.

Histopathology

The fifth edition of WHO grading of CNS tumors focuses on the integrated diagnosis of histology, immunohistochemistry, and molecular diagnostics (25). For meningiomas, anaplasia still features in WHO grade III tumors (25). Malignant features such as prominent nucleoli, extensive necrosis and markedly elevated mitosis might all explain the aggressive biological behaviors of anaplastic meningiomas (5). However, anaplasia in spinal meningiomas

was rarely reported (7,10-13).

Molecular diagnostics and immunohistochemistry are two critical tools for classification, though we know little about the overlap between them and anaplasia. Li *et al.* pointed that Ki-67 index might serve as an indicator for poor prognosis in meningiomas (26). We routinely performed the Ki-67 staining and found the median index was 35% (range, 20–60%), which indicated highly proliferative growth of PSAM. However, we could not conclude anything confirmative about the index and patient's clinical outcomes. We know the presence of telomerase reverse transcriptase (TERT) promoter mutation or homozygous loss of CDKN2A/B could also define WHO grade III meningioma (25). TERT mutation correlates with higher risk of recurrence and mortality in meningiomas (27). Mirian *et al.* therefore suggested aggressive surveillance of TERT genetic alterations (27). CDKN2A/B homozygous deletion was another factor associated with early recurrence and highly prognostic in meningiomas, whose monitoring was also suggested by Sievers *et al.* (28). Unfortunately, our study was retrospective, and the genetic sequencing was not performed. Therefore, we failed to find any association between the genetic alterations and anaplasia in PSAM.

Interestingly, Ito *et al.* reported the malignant transformation of spinal atypical meningiomas to PSAM (9). Though we did not find similar phenomena, this was recorded in intracranial anaplastic meningiomas, revealing histological heterogeneity as well as malignant progression from low-grade ones. The mechanisms remain poorly understood. However, this might warn us of thorough survey of the tumor pathology.

Treatment and outcomes

National Comprehensive Cancer Network recommend complete surgical resection to symptomatic meningiomas (if feasible) and adjuvant radiotherapy if the meningioma was pathologically defined WHO grade III tumor (29). In addition, systematic therapies might be considered once the tumor was not amenable to surgery or radiation (29). However, PSAM is located at spinal canal, which might affect the treatment of choice, and the clinical outcomes remain unclear. Furthermore, no standard protocol might be established due to the rarity, and thereby case series is a critical reference for future cases.

Surgery is the first consideration for treatment and pathological classification (10,11,13,29,30). Gross total resection should be the best line of treatment whenever

feasible (13,29). However, Simpson grade I resection in spinal canal is usually difficult to achieve due to limited space and we performed Simpson grade II resection in 50% operations. A systematic review investigated 13 studies regarding spinal meningiomas and found there was no significance between Simpson grade I and II with respect to tumor recurrence (30). In addition, higher Simpson grade of resection could significantly increase recurrence over time (30,31). Therefore, a more comprehensive treatment option should be trialed.

The role of adjuvant radiotherapy in treating PSAM is rather unclear. Five patients in our sample applied radiotherapy, and the outcomes were different. Due to lack of study in PSAM, we could only reference the trial or experience from intracranial anaplastic meningiomas. A study based on National Cancer Database observed a survival benefit for performing both gross total resection and radiotherapy (32). However, another retrospective cohort study of intracranial anaplastic meningioma suggested though conventional adjuvant radiotherapy helped local tumor control, its effects on overall survival remained controversial (33). The initial results of phase II RTOG 0539 trial revealed that the 3-year local control and overall survival rate of the patients with high-risk meningioma (including new anaplastic meningiomas) treated with intensity-modulated radiotherapy was 68.9% and 78.6%, respectively (34). The authors believed the results favored postoperative intensity-modulated radiotherapy.

No standard chemotherapy concerning anaplastic meningioma treatment has been established yet (29). However, multiple drugs have been on certain experimental therapy or early-stage clinical trials (35,36). Among them, bevacizumab, an anti-angiogenic drug, was found to have induced partial response in an experimental therapy of a patient with intracranial anaplastic meningioma (35). In addition, Sunitinib was proven active in treating recurrent malignant meningiomas despite its toxicity in a phase II trial.

In our sample, PSAMs had poor outcomes overall with a median survival time of 14 months after initial diagnosis. Recurrence occurred to three patients, and the recurrence-free survival time ranged from eight months to eleven years. Among the three, two were severely affected by multiple metastases and thus refused further treatment. The two patients died consequently. Two other patients without recurrence both died at 4-month after initial diagnosis. The respiratory failure induced by lung infection was the

mortality cause. El-Hajj *et al.* concluded that the recurrence rate of spinal meningiomas was 6%, and the higher WHO grade, higher Simpson grade, ventral location, and male sex were all correlated with higher recurrence (30). By contrast, the recurrence rate of PSAM reached 50% in our sample and 33.3% (2/6) in literature, which was consistent with El-Hajj's finding. Interestingly, all our male patients experienced recurrence while females did not. In both our sample and literature, metastasis was another dismal event. Nishida *et al.* reported that their patient experienced metastasis to mediastinal lymph nodes, while Ito *et al.* recorded PSAM metastasis to rib, lumbar vertebra, and sacrum (8,9). The former patient's survival status was not available, and the latter died one year after initial diagnosis.

In literature, the survival time was heterogenous, ranging from 1 month to 10 years (7-13). Despite the unfavorable prognosis, two patients of ours respectively survived about eleven years and nine years without major complications and achieved favorable recovery. Though Case 2 had recurrence 11 years after Simpson IV resection followed by radiotherapy, he witnessed no regrowth 4 months after another Simpson II resection. We could not conclude anything confirmative about the survival, because there was no significance regarding gender, extent of resection, or even Ki-67 indices (40% for Case 2; 60% for Case 5). However, both of them presented with MMC grade Ib at initial diagnosis, and no metastasis happened to either of them. Some bold speculations might be that the timing of intervention and certain tumor statuses somehow spared the patients. Though the two survivors were alive and classified as MMC grade I after some years' follow-up, regular checks will still be needed.

Limitations

There are a few limitations about our retrospective study. Firstly, there might be recall bias, because the last follow-up was done through telephone if the patient was deceased. Secondly, we did not perform genetic analysis, which hardly explained the potential relationship on molecular levels. Thirdly, we could only apply the best treatment plan at the time. Lastly, due to the limited sample size, we could not conclude anything confirmative.

Conclusions

PSAMs are a rare disease, and there is limited evidence as

to the management of these lesions. They may metastasize, recur, and portend a poor prognosis. A close follow-up and further investigation are therefore necessary.

Acknowledgments

We would like to thank all the patients who trusted us and all the physicians and staff who helped in this study.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2505/rc>

Peer Review File: Available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2505/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://tcr.amegroups.com/article/view/10.21037/tcr-22-2505/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by institutional ethics committee of Beijing Tiantan Hospital (No. KY-2019-076). All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case series and accompanying images was waived from patient consent according to the Beijing Tiantan Hospital ethics committee/institutional review board.

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Cite this article as: Wu L, Wang L, Zou W, Yang J, Jia W, Xu Y. Clinical features and surgical outcomes of primary spinal anaplastic meningioma: a cases series and literature review. *Transl Cancer Res* 2023;12(5):1325-1334. doi: 10.21037/tcr-22-2505