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CLINICAL STUDY

Clinical presentation and long-term outcome of primary spinal peripheral primitive neuroectodermal tumors

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Abstract Primary spinal peripheral primitive neuroectodermal tumors (pPNETs) are extremely rare entities that predominantly occur in children and young adults. Few studies have reported more than three cases. There are no current optimum treatment strategies due to the paucity of data. Here, we present 13 patients (nine females and four males) with primary intraspinal pPNETs who were surgically treated from April 2008 to February 2014. Histopathologic findings revealed the expression of CD99 in all cases. Limb weakness was the most common initial symptom (11/13, 85 %). The tumors were located mainly at the cervical level (6/13, 46 %) and in the epidural space (10/13, 77 %). The radiological diagnosis was neurinoma or meningioma in most cases (10/13, 77 %). Gross total resection was achieved in 77 % (10/13) of patients. During a mean follow-up of 25.5 months, local relapse occurred in 8 (61.5 %) patients and distant metastases occurred in 8 (61.5 %) patients. The overall 1-year survival rate was 77 % (10/13), and the overall 2-year survival rate was 54 % (7/13). The 2-year survival rate was 57.1 % in patients with adjuvant chemotherapy and 50 % in those without chemotherapy. Gross total resection and adjuvant radiotherapy with or without chemotherapy demonstrated a longer survival period (1-year survival rate: 100 %; 2-year survival rate: 86 %). Our data showed that primary spinal pPNETs are extremely rare and aggressive tumors with a poor prognosis. Radical resection is advocated. Gross total resection combined with adjuvant radiation may help to significantly improve patient survival period. Chemotherapy may also help to slightly prolong patient life.

Keywords Primary peripheral primitive neuroectodermal tumors · Spinal surgery · Spinal tumors

Introduction

Primary spinal primitive neuroectodermal tumors (PNETs) are poorly differentiated malignant tumors that usually occur in children and adolescents. PNETs include two categories: CNS PNETs or central PNETs and Ewing sarcoma/PNETs or peripheral PNETs. In recent classification by WHO, central PNETs (cPNETs) and medulloblastomas were subdivided under embryonic tumors [1]. Unlike cPNETs, which are referred to as tumors arising in the central nervous system (CNS) [2], peripheral PNETs (pPNETs) are non-CNS tumors derived from the neural crest [3], belonging to the Ewing sarcoma family of tumors (ESFTs) [4]. Primary spinal pPNETs are extremely rare entities. In the literature, slightly more than 100 cases of primary spinal pPNETs have been reported. Due to the limited reports, the epidemiology of primary spinal PNETs is unclear and the prognosis is very poor. Although multidisciplinary treatment has been well established as the standard treatment strategy for intracranial PNETs, there is no current standard treatment protocol for primary spinal pPNETs. Here, we review our series of 13 patients and discuss the clinical course, treatment and outcome of primary spinal pPNETs.

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Methods

Patient population

Between April 2008 and February 2014, 13 patients with a definite pathological diagnosis of primary spinal pPNETs were treated at the Department of Neurosurgery in Beijing Tiantan Hospital and Beijing Jishuitan Hospital. This study included nine female and four male patients. The age at presentation ranged from 4 to 47 years (mean 19.8 years). The details of the patients' baseline clinical characteristics are presented in Table 1. The inclusion criteria were primary spinal PNETs with the expression of CD99. The exclusion criteria were those with CNS PNETs, unavailable pathological data, incomplete follow-up, dissemination from the intracranial locations or any evidence of metastatic disease as revealed by brain MRI, chest CT, bone scan, bone marrow biopsy and CSF cytology. The natural history was based on the time span from the initial onset of the disease until surgery (Table 1).

Surgical treatment

Under general anesthesia, a dorsal approach was made through laminectomy in all patients. Neurophysiological monitoring was used. The tumors were located in the epidural space in 10 cases and in the intradural-extramedullary space in three cases. For those with epidural tumors, the dura mater was not opened. For those with intra- and extra-spinal tumors, the incision was extended according to tumor location. For those with intFradural tumors, prior to opening the dura mater, the location of the tumor was confirmed using an intraoperative ultrasonography device, which guided the extent of bone removal. At surgery, the tumors appeared as reddish or reddish-gray and soft lesions with abundant blood supply. The tumor margin appeared to be well demarcated. Intraoperative frozen sections showed undifferentiated small round cells. Under microsurgical conditions, gross total resection of the tumors was achieved in ten patients. Spinal fixation was performed through synthetic vertebral fixation devices in six patients to reduce vertebral mobility and avoid possible damage to the spinal cord and spinal roots. None of the patients experienced notable immediate-postoperative complications.

Adjuvant therapy

Two to four weeks after the initial surgery, the patients were referred to clinical oncologists. However, the use of chemotherapy or radiotherapy was determined by patient age, Karnofsky performance status scale (KPS) and patient preference. The pre- and post-operative KPS scores of the patients are listed in Table 1. Patients with a KPS $\geq$ 70 after surgery were suggested to undergo chemotherapy. The vincristine, doxorubicin, cyclophosphamide (VAC) or vincristine, ifosfamide, doxorubicin, etoposide (VIDE) protocol was recommended for chemotherapy. Radiotherapy was initiated 2 weeks after surgery for those who did not receive chemotherapy. For those with chemotherapy, radiotherapy was initiated concurrently or at a later stage, according to patient tolerance and compliance. The patients' complete

Table 1 Clinical characteristics of 13 patients with primary spinal pPNETs

Pat.	Age/sex	Clinical symptoms	History	Level	Location	Preoperative diagnosis	KPS	
							Pre-op	Post-op
1	47/F	Neck and shoulder pain	3 months	C1–2	Epidural	Meningioma	90	90
2	11/F	rt UE pain and weakness	1 month	C6–7	Epidural	Neurinoma	70	80
3	4/F	lt UE Pain and weakness	10 days	C2–6	Epidural	Neurinoma	50	50
4	8/F	LE weakness	20 days	T10–L1	Epidural	Nerurinoma	60	70
5	17/F	rt LE weakness, incontinence	21 days	L5–S1	Epidural	Nerurinoma	70	80
6	43/M	Lumbago and scelalgia	3 months	L3–4	Epidural	Neurinoma	90	90
7	19/M	Sudden quadriplegia, incontinence	1 days	C5–7	Epidural	Hematoma	40	40
8	17/F	Neck pain, rt limbs weakness	15 days	C3–5	Intradural	Meningioma	80	90
9	43/F	LE weakness, incontinence	1 month	L5–S1	Intradural	Neurinoma	70	70
10	9/F	Neck pain, UE weakness	7 days	C2–4	Epidural	Sarcoma	60	70
11	16/F	LE weakness, incontinence	3 months	L5–S1	Intradural	Neurinoma	70	80
12	7/M	LE weakness, incontinence	2 months	S1–3	Epidural	Neurofibroma	80	80
13	16/M	LE weakness, incontinence	2 months	T4–8	Epidural	Neurinoma	70	60

Pat. Patient number, *KPS* Karnofsky performance status, *lt* left, *rt* right, *LE* lower extremity, *UE* upper extremity, *Pre-op* preoperative, *Post-op* postoperative

blood count and liver and kidney function were examined regularly to determine further adjuvant therapy.

Follow-up data

All patients underwent clinical and spinal MR imaging follow-up. Positron emission tomography-computed tomography (PET/CT) was used in some cases to reveal distant metastasis. The long-term treatment outcome was based on the follow-up from the time of surgery to the most recent medical information. The follow-up period ranged from 9 to 86 months (mean 25.5 months).

Results

Initial clinical presentation

The clinical presentation showed considerable variability (Table 1). The time interval between symptomatic onset and initial surgery was within 3 months (range 1 day–3 months; mean 40 days). The most common symptom at presentation was weakness in the limbs (in 11 cases), followed by pain (in six cases) and incontinence (in six cases). One patient presented sudden quadriplegia and incontinence because of tumor apoplexy, which led to acute spinal cord compression (Case 7). All patients had localized lesions, and none had metastatic disease at initial presentation.

Magnetic resonance data

The pPNETs were located throughout the spinal axis, but mainly at the cervical (6 cases) and lumbosacral levels (three cases) (Table 1). The tumors were located solely in the spinal canal in six cases. Intra and extra spinal communicating tumors were found in six cases (including dumbbell tumors). One was located in the foraminal space. A brain MRI, chest CT and bone scan did not reveal evidence of metastatic disease. The preoperative diagnosis was neurinoma in eight patients, meningioma in two patients, neurofibroma in one patient, sarcoma in one patient and hematoma in one patient. As revealed by postoperative MR imaging, gross total resection of the tumors was achieved in ten patients (Fig. 1).

Pathologic findings

The tumors presented uniform findings, showing well-circumscribed, reddish or reddish-gray soft tissues with an abundant blood supply. Because the primary preoperative diagnosis was mainly neurinoma, meningioma or neurofibroma, the histological findings were surprising. Light microscopic histological examination of hematoxylin-

eosin-stained slides revealed highly cellular tumors consisting mainly of small round undifferentiated cells with hyperchromatic nuclei and a small cytoplasmatic wall. No well-defined Homer-Wright rosettes were found (Fig. 2a). High mitotic activity and necroses were presented. Immunohistochemistry using anti-MIB-1 (Ki 67) antibodies revealed a high proliferative index in most cases. Further staining revealed CD99 (MIC2) (+) in all patients (Fig. 2b). Vimentin was positive in 10 cases. Strong immunoreactivity for FLI-1 was detected in 8 patients. Fluorescence in situ hybridization and chromosomal study were not performed in this series.

Treatment modalities and long-term outcome

As listed in Table 2, the treatment modalities were gross total resection with adjuvant chemotherapy and radiotherapy in five patients, partial resection with adjuvant chemotherapy and radiotherapy in one patient, gross total resection with adjuvant chemotherapy in one patient, gross total resection with adjuvant radiotherapy in two patients, partial resection with adjuvant radiotherapy in two patients and gross total resection without adjuvant therapy in two patients. During follow-up, eight patients had local recurrence (Table 2; Fig. 3) and four patients underwent a second or third operation. The distant metastatic sites was the lung in five patients, sternum in two patients, rib in one patient, mediastinum in one patient and lumbar spinal canal in one patient (Table 2; Fig. 3). The overall 1-year survival rate was 77 % (10/13) and the 2-year survival rate was 54 % (7/13). The 1- and 2-year survival rates were 71 and 57.1 %, respectively, in patients with adjuvant chemotherapy, while they were 83 and 50 %, respectively, in patients without chemotherapy. Gross total resection and adjuvant radiotherapy with or without chemotherapy showed a relatively longer survival period (1-year survival rate: 100 %; 2-year survival rate: 86 %). However, whether adjuvant chemotherapy or radiotherapy or both were applied, partial resection of the tumors resulted in the rapid progress of local recurrence and distant metastasis, leading to a short survival period. Patients with early distant metastasis after surgery had a relatively shorter survival period. Due to the limited number of patients, statistical analysis was not used in this study.

Discussion

Concept and classification of PNETs

Primary spinal PNETs are very rare soft tissue neoplasms in both children and young adults [5]. In 1973,Hart and Earle formally introduced the concept and diagnostic criteria of PNETs, proposing that PNETs are undifferentiated
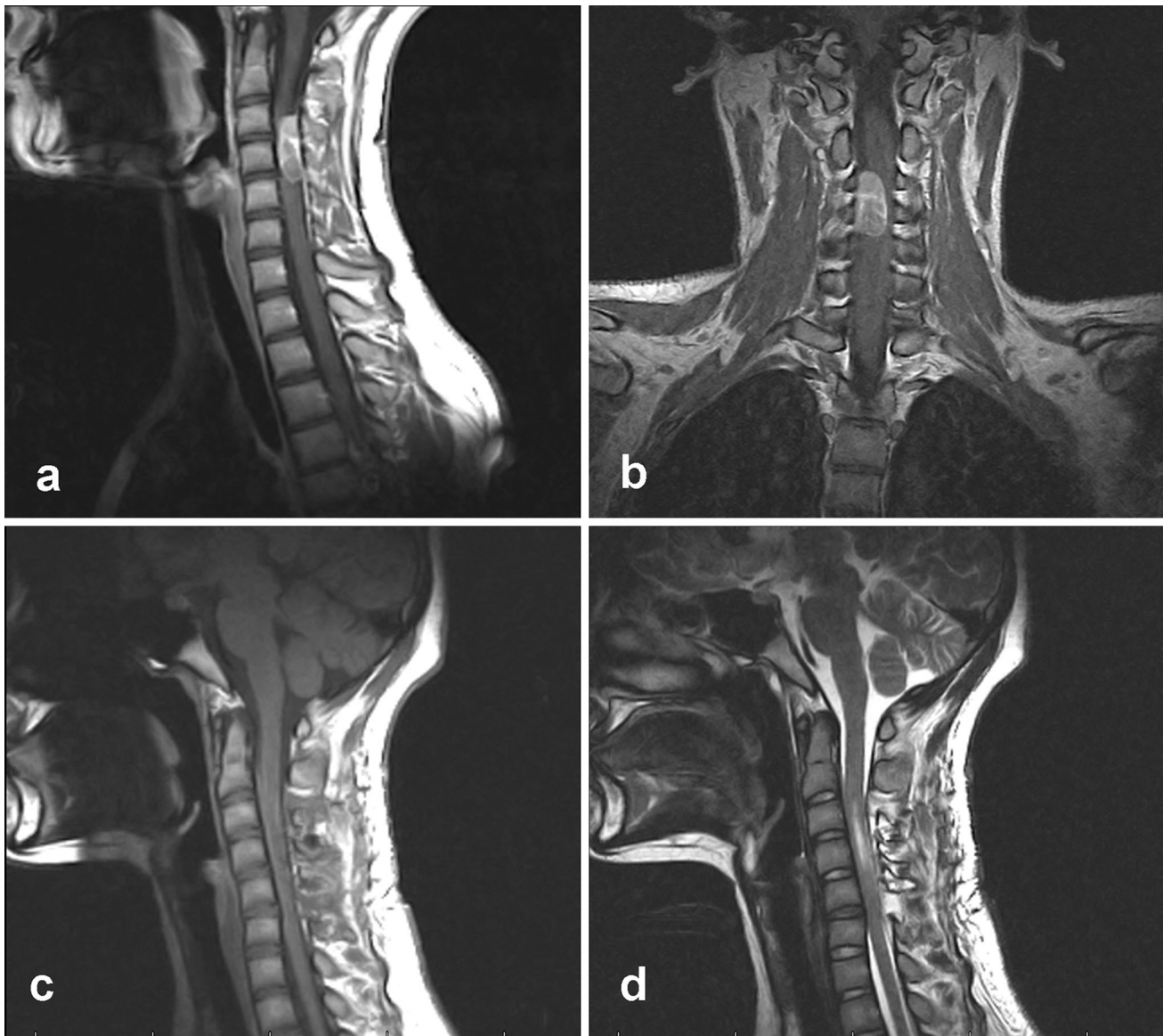
Fig. 1 Case 8. **a, b** shows a moderate to prominent contrast-enhanced intradural lesion at the C3–5 level on sagittal and coronal T1-weighted MRI. 1 week after surgery, sagittal T1-weighted MRI (**c**) and T2-weighted MRI (**d**) show gross total resection of the tumor

malignant tumors of intracranial origin [2]. The World Health Organization classification in 1993 included cerebral medulloblastoma-like tumors as supratentorial PNETs [6]. In the third edition of the World Health Organization classification, PNETs were defined as embryonic tumors composed of undifferentiated or poorly differentiated neuroepithelial cells that have the capacity for or display divergent differentiation along neuronal astrocytic, ependymal, muscular or melanotic lines [7]. In recent classification by WHO, central PNETs (cPNETs) and medulloblastomas were subdivided under embryonic tumors [1]. Central PNET are referred to as neoplasms arising in the CNS but located outside the posterior fossa. pPNETs are non-CNS tumors derived from the neural crest

[3], belonging to the ESFTs [4]. Primary intraspinal PNETs are extremely rare. These tumors may originate at all levels of the spine and can be intramedullary, intra- and extramedullary, extramedullary, or epidural. Because PNETs frequently disseminate or seed throughout the CNS, most cases of PNETs involving the spinal cord are "drop" metastases from primary intracranial tumors. For the correct diagnosis of spinal PNETs, the "drop" metastases of intracranial origin must be excluded [8, 9].

Epidemiology of primary spinal pPNETs

Primary spinal pPNETs are rare entities. Slightly more than 100 cases have been reported in the literature. Most were
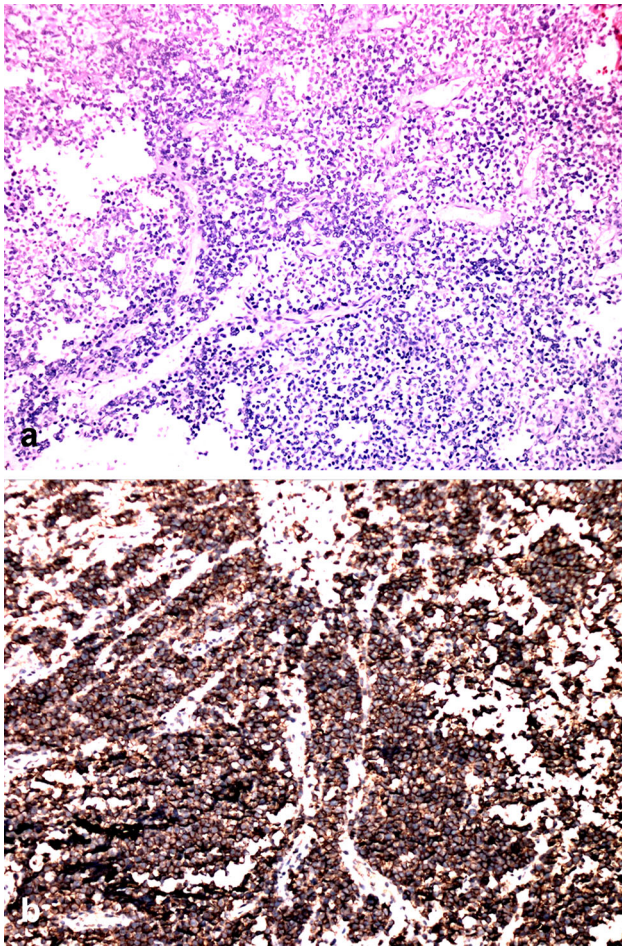
Fig. 2 Case 8. **a** The light microscopic photograph shows a typical highly cellular pPNET tumor consisting of undifferentiated small round cells with frequent mitoses. **b** Immunohistochemistry shows CD 99 immunoreactivity in pPNET tumor cells

reports in the past 15 years with one or two cases and only four studies reported more than three cases [10–13]. It is unreliable to have an accurate epidemiology from these case reports. Engelhard et al. reported that spinal PNETs account for <1 % of the primary tumors in their 430 cases [14]. From 2008 to 2014, 3012 patients with primary spinal tumors were admitted to our department. We conclude that primary spinal pPNETs account for approximately 0.4 % of the primary spinal tumors treated at our department. In the recent two literature reviews of primary spinal pPNETs, a nearly 2:1 male sex preponderance was found [15, 16]. However, in our series, 69 % (9/13) were female and 31 % (4/13) were male, which is just contrary to their findings. Previous studies have asserted that primary spinal PNETs are most prevalent in children and young adults [4, 15–18]. Our study is consistent with those results. The mean age at presentation was 19.8 years. Additionally 77 % (10/13) of the patients were under the age of 20 years and 23 % (3/13) were in their 40s.

Clinical presentation

The clinical presentation of primary spinal pPNETs varied according to tumor locations and involved structures. In a recent meta-analysis of reported cases in the literature, muscle weakness is the most common symptom. Sensory symptoms, local pain, and radiculopathy are also common presentations [16]. In our series, 85 % (11/13) of the patients presented with varied degrees of limb weakness. Incontinence was found in 46 % (6/13) patients, mainly due to the location of the tumors. Patients may present with neck and shoulder pain mimicking cervical spondylosis (Case 1) or lumbago and scelalgia mimicking lumbar disc herniation (Case 6), particularly in adults. Additionally these patients would not be aware of their disease until a later stage, such as Case 1 and Case 6, who are in their 40s. The mean duration of symptoms before surgery was 40 days, much less than previously reported [16]. In 2011, Ellis et al. [15] reported the first case with intratumoral hemorrhage that resulted in acute spinal cord compression and neurological decline. Case 7 in our series presented with sudden quadriplegia and incontinence, which is the second reported case of intratumoral hemorrhage.

Radiological features

Ellis et al. [15] reported that spinal PNETs are typically hypo—to isointense on T1-weighted MR imaging and iso—to hyperintense on T2-weighted imaging. Our findings are consistent with those results. Their study showed that there was often minimal contrast enhancement [15]. Tsutsumi et al. [19] reviewed the literature and found that varying enhancement was noted. Moderate to prominent contrast enhancement were found in most of our cases. A recent meta-analysis showed that approximately half of the primary intraspinal pPNET cases occur in the lumbar spine [16]. Tsutsumi et al. [19] also reported that the thoracic spine was the most frequently affected area. In our series, 55 % (6/11) of the tumors were located at the cervical level and 27 % (3/11) at L5/S1 level, which is contrary to previous findings. Also in the recent meta-analysis, the author reported their case is the first female and the sixth patient with sacral epidural primary intraspinal pPNET [16]. Case 12 in our series is the sixth male and seventh patient in this category, and the patient is currently in good condition now. The radiographic findings of primary spinal pPNETs are usually not helpful in diagnosis and differential diagnosis, as was stated by previous studies [15, 19]. Radiological diagnosis may be neurinoma, meningioma, neurofibroma, especially neurinoma. Other diagnoses may be ependymoma or astrocytoma [15]. Most primary spinal pPNETs are epidural lesions and may often occupy the

Table 2 Treatment modality and long-term outcome of the 13 patients with primary spinal pPNETs

Pat.	Surgery	Chemotherapy	Radiotherapy	Recurrence	Reoperation	Post-surgical metastasis	Follow-up (m)
1	GTR	VAC	50 Gy	Yes	Twice	None	Died at 86
2	GTR	VIDE	35 Gy	None	None	Lung	Died at 25
3	PR	None	30 Gy	Yes	None	Sternum	Died at 10
4	GTR	VAC	50 Gy	None	None	None	Died at 32
5	GTR	VIDE	50 Gy	Yes	None	Sternum, lung	Died at 15
6	GTR	None	50 Gy	None	None	None	Alive at 70
7	GTR	None	None	None	None	Lung, rib	Died at 18
8	GTR	VIDE	45 Gy	Yes	Once	Lumbar spinal canal	Alive at 25
9	PR	VAC	50 Gy	Yes	None	Lung	Died at 11
10	GTR	VIDE	None	Yes	None	Mediastinum	Died at 9
11	GTR	None	None	Yes	Twice	None	Died at 40
12	GTR	None	45 Gy	None	None	None	Alive at 38
13	PR	None	50 Gy	Yes	Once	Lung	Died at 13

GTR Gross total resection; *Pat.* patient number; *PR* partial resection; *VAC* vincristine, doxorubicin, cyclophosphamide; *VIDE* vincristine, ifosfamide, doxorubicin, etoposide

intraspinal and extraspinal space. Intradural locations are less frequent. Intramedullary location is extremely rare.

Diagnosis

PNETs are poorly differentiated small round blue cell tumors with hyperchromatic nuclei and features of neural differentiation, rarely with typical Homer–Wright rosettes [20]. cPNETs and pPNETs are often distinguishable according to their morphological features. Correct diagnosis depends on immunohistochemistry and cytogenetic analysis. In the literature, nearly half of the reports on primary spinal pPNETs did not make a histopathologic distinction between cPNET and pPNET [16]. Kampman et al. recently summarized the distinguishing features between cPNET and pPNET [4]. Immunocytochemical staining can distinguish between pPNET and cPNET by demonstrating the expression of MIC2 glycoprotein (CD99) in pPNET and showing the presence of the specific chimeric gene of EWS-FLI1 in pPNET [4]. The membrane protein FLI1 (Friend leukemia virus integration 1) are also commonly expressed in pPNETs [21–24]. Immunohistochemical staining showed that the tumor cells expressed CD99 in all 13 patients in our series, consistent with the diagnosis of pPNETs. FLI-1 was positive in 62 % (8/13) of the patients, which further confirmed the diagnosis of pPNETs. Cytogenetic analysis has shown that chromosomal translocation (11;22) (q24;q12) presents in more than 90 % of cases [8, 25, 26]. The presence of an (11;22) (q24;q12) translocation may be the strongest diagnostic tool for pPNETs [15]. However, chromosomal studies were

performed in only a small portion (approximately 1/7) of the reported cases in the literature [16].

Treatment options

There are no current standard therapeutic strategies for primary spinal pPNETs. However, surgical removal of the tumors is the cornerstone of therapy [20]. Although tumor relapses and metastasis might occur even with gross total resection, radical resection is still recommended to prevent further neurological decline, improve quality of life, allow early mobilization and achieve sufficient volume reduction for further oncological management [18]. Gross total resection was achieved in 77 % (10/13) of patients in our series without causing further neurological damage. A standard laminectomy with preservation of the facet joints should be performed [15]. Intraoperative neurophysiological monitoring should be used. An ultrasonography device is advocated to guide the extent of bone removal and tumor resection. The tumor margins are usually well demarcated. Frozen sections should also be advocated during surgery. Spinal fixation should be performed in selected patients to reduce vertebral mobility and avoid possible damage to adjacent essential structures.

Due to the paucity of data, the benefit of adjuvant therapy remains unclear. A recent meta-analysis showed that adjuvant chemotherapy improved the 1- and 2-year survival rates after total or subtotal tumor resection [16]. The VAC or VIDE protocol was used in our patients with adjuvant chemotherapy. Although the 1-year survival rate in patients with adjuvant chemotherapy was slightly lower than that in those without chemotherapy (71 vs 83 %), the
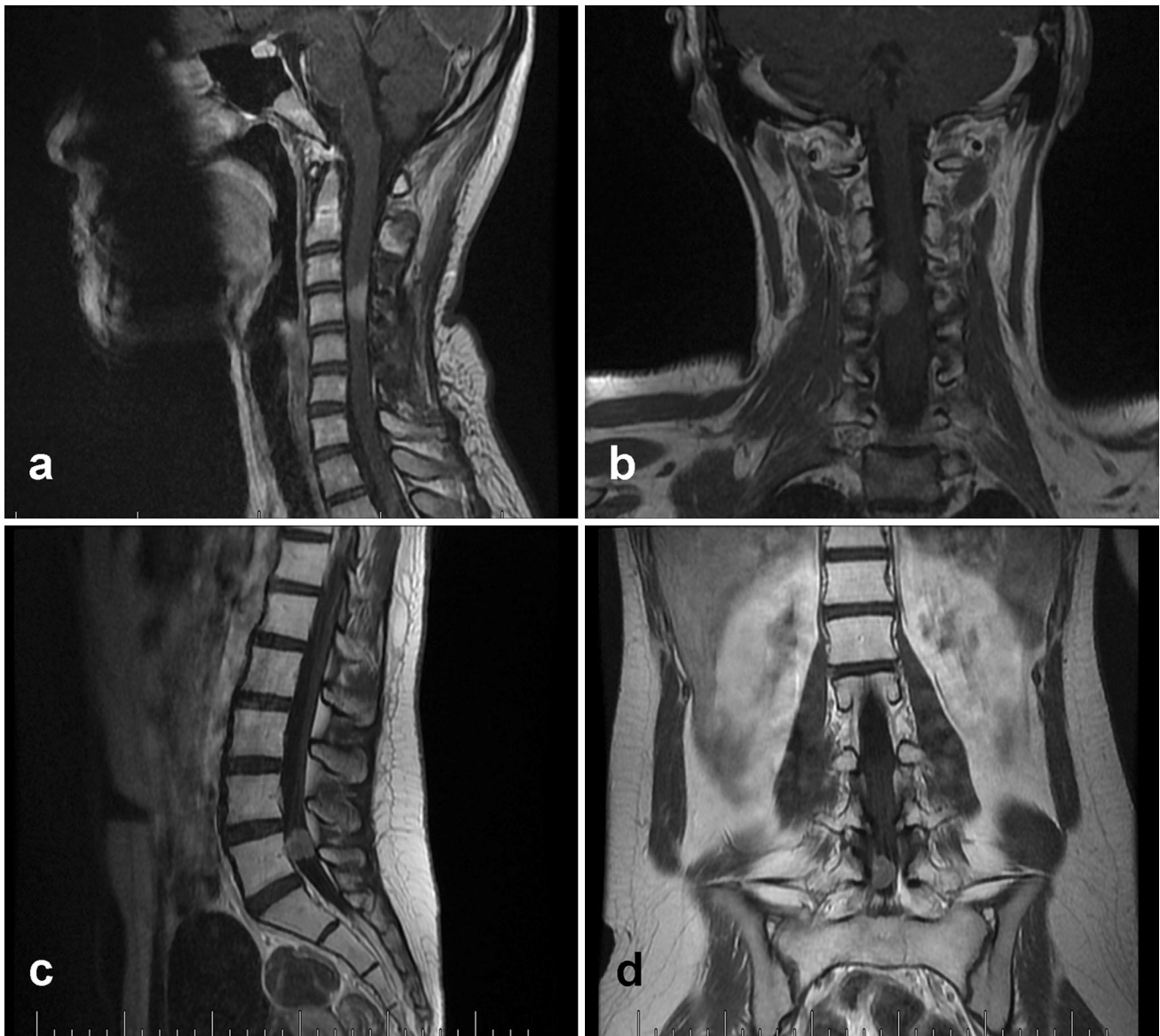
Fig. 3 MRI of Case 8 2 years after surgery. **a, b** Local recurrence of the tumor on sagittal and coronal T1-weighted contrast MRI. **c, d** Tumor dissemination at the L5 level on sagittal and coronal T1-weighted contrast MRI

2-year survival rate was relatively higher in patients with chemotherapy (57.1 vs 50 %). Gross total resection and adjuvant radiotherapy with or without chemotherapy had a relatively longer survival period (1-year survival rate: 100 %; 2-year survival rate: 86 %). Our experience showed that radiotherapy was relatively more important than adjuvant chemotherapy in prolonging the survival period. However, gross total resection should be the prerequisite. Patients with partial resection of tumors may survive for a period of <1 year even with adjuvant chemotherapy and/or radiotherapy. Radiation strategies varied in different reports. Controversies exist regarding the optimal radiation strategy, the indications of full neural

axis radiation and dosing in the treatment of primary spinal PNETs [27]. In the literature, total doses ranged from 30 to 60 Gy [15]. In our series, the total doses employed ranged from 30 to 50 Gy. None of our patients received the combination of high-dose chemotherapy and autologous stem cell rescue as a supplement of surgery and radiotherapy. However, this treatment modality has shown promising results in previous reports [28, 29].

Prognosis

Primary spinal pPNETs are aggressive malignant tumors that lead to a lower 2-year survival rate [16]. Due to the

limited reports in the literature, the prognostic factors are unclear. Regarding our series, partial resection, local recurrence and distant metastasis may predict a shorter survival period. However, gross total resection and radiation can significantly improve the survival rate of the patients. Adjuvant chemotherapy combined with gross total resection can also slightly prolong patient life. Patients with this tumor entity have a low 3-year survival rate (40 % in our series) and seldom survive 5 years after diagnosis (two patients in our series). Three patients were alive at our last follow-up. Two patients were uneventful and led a normal life (Case 6 and 12). Case 8 has experienced local recurrence and lumbar spinal canal dissemination of the tumor (Fig. 3). And this patient will undergo surgery at our department or another hospital. We will continue to follow up these three patients.

Conclusions

Primary spinal pPNETs are extremely rare and aggressive tumors with a poor prognosis. Clinical presentation varies from patient to patient. Radiological features may lead to misdiagnosis. Diagnosis of this disease depends on histopathologic findings. There is no standard treatment protocol due to the rarity of this disease. Microsurgical resection of the tumor is the mainstay of treatment. Gross total resection combined with adjuvant radiation may help to improve the survival period of the patients. Chemotherapy may also help to slightly prolong patient life.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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