Case Report

Primary spinal primitive neuroectodermal tumor: A single center series with literature review

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Context: Primary spinal primitive neuroectodermal tumor (PNET) of the central nervous system has a low incidence. The intraspinal case is very rare. Around 30 cases have been reported so far. We summarized the cases of primary spinal PNET available in the database of our institute, either intramedullary or extramedullary cases. Then we did literature review of the same disease.

Findings: There were eight cases of primary spinal PNET available in our database, with one intramedullary case and seven extramedullary cases. Surgical resection was performed. The histology diagnosis was PNET. Perioperative image examinations of the whole central nervous system (CNS) were performed to exclude tumors other than spinal cord origin. Then during literature review, 33 reports of the disease were included. The preoperative diagnosis rate was low. The disease had a high recurrence rate and poor prognosis given available treatment.

Conclusion: Primary spinal primitive neuroectodermal tumor is of high malignancy. Little is known due to its quite low incidence. The prognosis is poor due to lacking of effective treatment strategy. Present treatment strategy is referred to other common CNS malignancies like glioma. Further investigation of the disease is necessary.

Keywords: Spinal, Intramedullary, Extramedullary, Primitive neuroectodermal tumor (PNET), Primary

Introduction

Primitive neuroectodermal tumor (PNET) is a heterogeneous group of central nervous system (CNS) tumors composed of undifferentiated or poorly differentiated neuroepithelial cells. It can involve the whole CNS. The spinal PNET cases are very rare. Around 30 cases have been reported so far. It can locate either intramedullary or extramedullary. We added eight cases of histology confirmed primary spinal PNET of our institute with one intramedullary case and seven extra medullary ones. The results were compared with literatures.

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Case series

There were eight cases of spinal PNET with histology confirmation in the histology database of our institute. Four of them were under 18 years old, two were 18, and two of them were adults. The mean age was 17 years old, range 7–43. Most lesions (5) located at lumber to sacral levels. Two were at the cervical level. One case had multiple foci. Only 1 of them was intramedullary. The other seven were extramedullary and had the tendency of invade out of the spinal canal through interspinal foramen. The symptoms depended on the exact spinal segment involved. Motor dysfunctions and pain were main symptoms.

Neuro-radiology examinations always showed iso- to hypo-intense on T1-weighted image and iso- to hyper-intense on T2-weighted image, with enhancement. In those cases extending out through the interspinal foramen a typical dumbbell shape could be observed.

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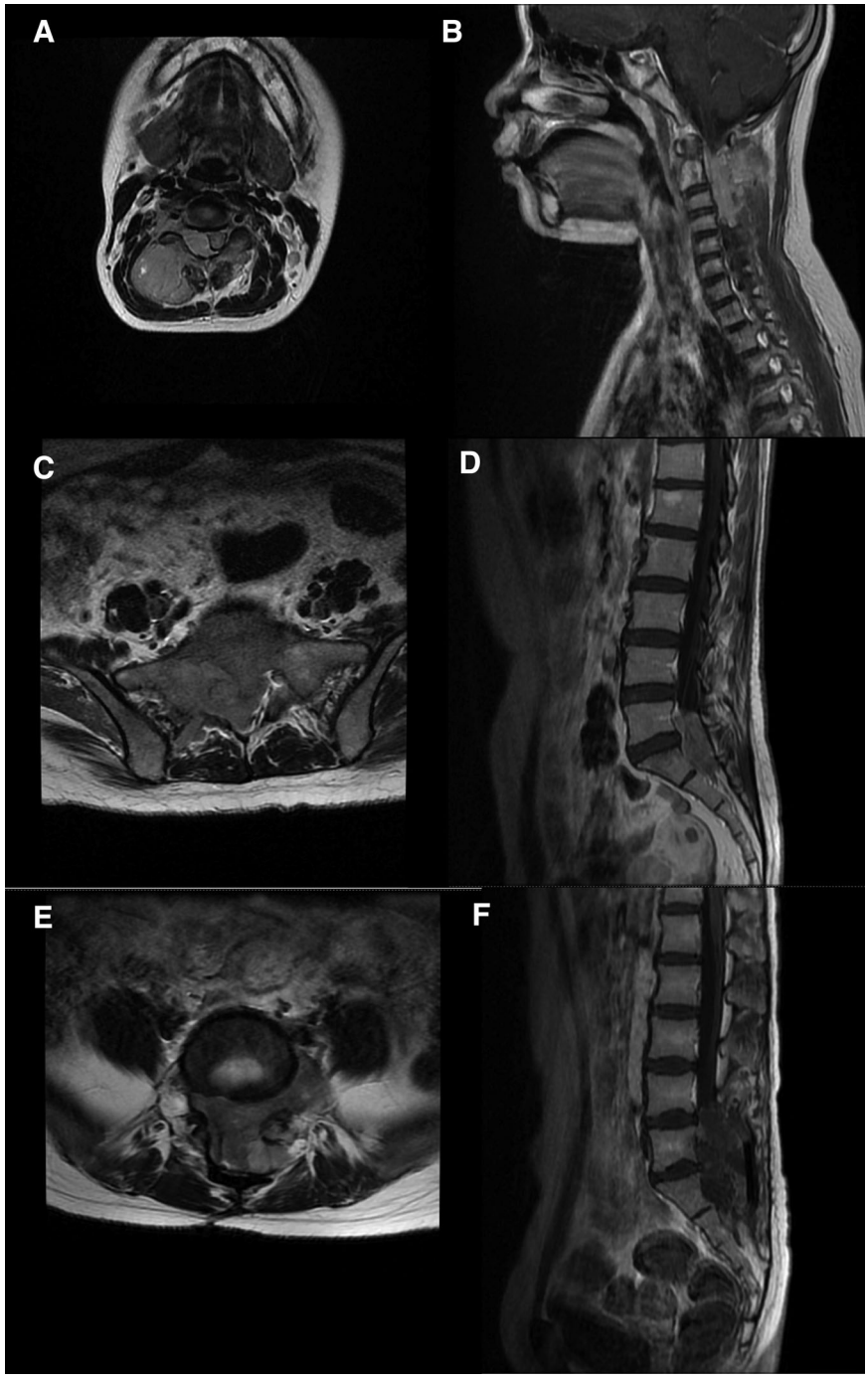

Figure 1 Pre-operative MR scan of case 1, 6, and 7. (A,B: case 1, T2-weighted traverse and T1 enhancement saggital. The lesion located at C2-4, extramedullary, extend extraspinal through interspinal foramen. C,D: case 6, T2-weighted traverse and T1 enhancement saggital. The lesion located at L5-S1, extramedullary, extend extraspinal through interspinal foramen. E,F: case 7, T2-weighted traverse and T1 enhancement saggital. Multiple lesions at L5-S1, extramedullary, extend extraspinal through interspinal foramen.).

Pre-operative diagnosis was not easy due to its rare incidence. None of our cases were suspected as PNET before surgery. The differentiated diagnosis included both malignancies and non-malignant neoplasms. When located intramedullary it might be considered as glioma, lymphoma, sarcoma, or ependymoma, etc. When located extramedullary with interspinal foramen invasion, most were suspected as Schwannoma or neurofibroma, much more commonly seen that had typical dumbbell shape. The whole CNS image examination involving the brain and whole spinal cord were performed for these eight patients,

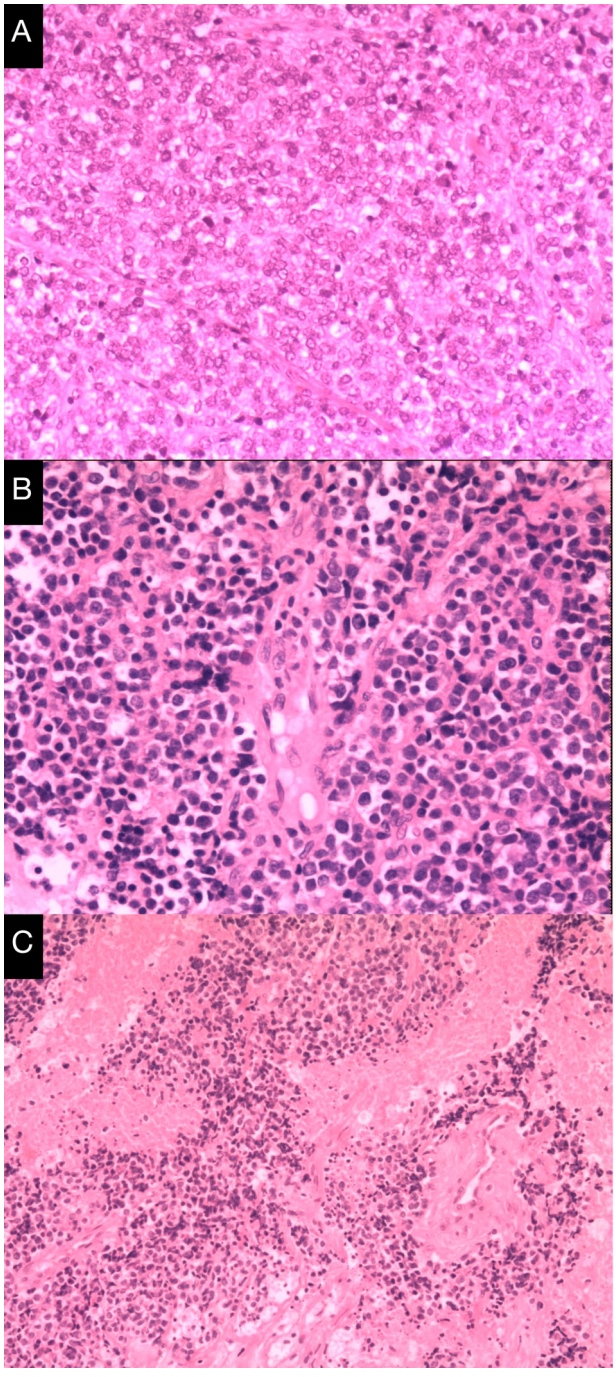

Figure 2 Post-op histology slides of case 1, 6, and 7 with diagnosis of primitive neuroectodermal tumor. (Hematoxylin-eosin stain, original magnification×100. A-C: Case 1, 6, and 7 correspondingly).

either before or after surgery, to exclude secondary spinal cord lesion.

Surgical resection with lamiectomy was first-line treatment for all patients. The operation strategy depended on the exact location of the tumor. For the multiple case that all lesions could not be resected through a single approach, the lesion with most prominent symptom was resected first. The extent of resection was defined according to both intra-operative evaluation and post-operative MR scan. Gross total resection was reached for seven extra medullary cases. For the intramedullary case, the entity of the tumor was similar to glioma and extensive resection was not applicable for the protection of the spinal cord functions. Subtotal resection was performed for this case. All specimen were sent for pathological examination and were confirmed as PNET. Adjuvant radiotherapy was recommended for all patients. Chemotherapy should also be considered although no standard guideline existed yet for chemotherapy of spinal PNET. However, the compliance of patients varied. Three patients were lost to follow-up, aged 7, 18, and 43 at the admission. For the rest five patients, including three under 18, one 18 years old, and one above 18, were all died during five years of follow-up. One pediatric patient went on to take chemotherapy and died from recurrence nine months later. One pediatric patient took both radiotherapy and chemotherapy and died from recurrence 12 months later. One pediatric and one adult patient did not receive any adjuvant therapy and died without exact time of death. One patient of 18 years old was already a recurrent lesion at the first admission to our institute. After the operation, she received radiotherapy and died 16 months later. All the adjuvant radiotherapy and chemotherapy were offered by other institutes and no detailed strategy or regimen was available (Figs. 1 and 2) (Table 1).

Review of literature

The PubMed online database was searched in July 2018, with the query of "((spinal cord[Title/Abstract]) OR intramedullary[Title/Abstract]) AND primitive neuroectodermal tumor[Title/Abstract]". Fifty-eight articles were generated. Four were not English. Twenty-one were not about spinal PNET, but focused on lesions of other histology or PNET of locations other than spinal region. Thirty-three primary spinal PNET were included, seven of which with no available full text (Table 2).

Discussion

PNET is a heterogeneous group of tumors composed of undifferentiated or poorly differentiated neuroepithelial cells, WHO grade IV. According to differentiations of cell types the tumor is further classified into neuroblastomas with only neuronal differentiation, ganglioneuroblastomas if ganglion cells are also present, medulloepitheliomas with features of neural tube

Table 1 Summary of primary spinal primitive neuroectodermal tumor of our institute.

	Gender	Age (yr.)	Location	MR	Other signs on image examination	Other case information	Adjuvant therapy	Follow-up
1	F	9	C2–4	T1-T2-, homogeneous enhancement.	Extramedullary, Extend extraspinal through interspinal foramen.	—	Chemotherapy	Recurrent and died 9 month later.
2	M	9	C2–7	T1↓T2↑, prominent enhancement.	Intramedullary.	—	Radiotherapy & Chemotherapy	Recurrent and died 12 months later.
3	F	18	T11–S1	T1-T2-↑, heterogeneous enhancement.	Extramedullary, Multiple.	A recurrence at admission.	Radiotherapy	Recurrent and died 16 months later.
4	F	25	L5–S1	T1↓T2↑, prominent enhancement.	Extramedullary, Extend extraspinal through interspinal foramen.	—	No	Died (Family were reluctant to offer time of death).
5	F	7	L4	T1-T2-, homogeneous enhancement.	Extramedullary, Extend extraspinal through interspinal foramen.	—	Not clear	Loss
6	F	43	L5–S1	Heterogeneous T1/T2, prominent enhancement.	Extramedullary, Extend extraspinal through interspinal foramen.	—	Not clear	Loss
7	F	18	L5–S1	T1-T2↑, slight enhancement.	Extramedullary, Extend extraspinal through interspinal foramen.	A recurrence at admission.	Not clear	Loss
8	M	7	S1–3	T1-T2-, medium enhancement.	Extramedullary.	—	No	Died (Family were reluctant to offer time of death).

M, male; F, female; yr., years old; -, iso-intensive; ↑, hyper-intensive; ↓, hypo-intensive.

formation, and ependymoblastomas with ependymoblastic rosettes formation.

Precise incidence is not clearly known. Intraspinal case is very rare comparing to intracranial location. Around 30 cases have been reported so far. We reported eight cases. Only one of them was intramedullary. Then 33 literatures were identified with the keywords of spinal cord or intraspinal and primitive neuroectodermal tumor, with 21 reports of intramedullary PNET of the spinal cord with 24 cases in all and 12 cases of extramedullary PNET, either intradural or extradural. The earliest one was a pediatric intramedullary case reported by Freyer DR *et al.*[21] dating back to 1989. Most were sporadic cases. Mulholland CB *et al.*[6] reported a case with concomitant NF1 disease in 2011. Features common to all CNS PNET include early onset and aggressive clinical behavior. For all of our eight cases, the mean age at diagnosis was 17 years old. There was no age information of three intramedullary cases from the 33 literatures; however, 2 of them were pediatric cases. The mean age of the rest 33 cases in literatures were 26.9, with 26.6 for intramedullary cases and 27.6 for extramedullary cases respectively. The ratio of M:F was 2:6 of our cases and was 15:15 of the 30 cases in literatures with information available. Signs and symptoms are related to the site of origin of the tumor. Lumbar-sacral region was most common, including conus medullaris and cauda equina. However, the pan spinal level could be involved. In our series, five involved lumbar-sacral region, two involved cervical segment, and two invaded extremely long segments from thoracic to sacral level. In the 36 cases reviewed, four were cervical, four were cervical-thoracic, 10 were thoracic, six were thoracic-lumbar, and five were lumbar-sacral lesions. Two invaded the whole spinal cord segments. Three cases were lacking in location details. The whole CNS could be affected, especially for those intramedullary cases. Both Kwon OK *et al.*[18] and Ogasawara H *et al.*[20] reported a intramedullary case each with intracranial seeding. Alexiou GA *et al.*[4] reported a two-month-old female of cervical-thoracic intramedullary PNET with concomitant hydrocephalus. Chen YC *et al.*[13] also reported a intramedullary case with intracranial hypertension as an initial manifestation. The image examination results were similar to any other CNS malignancies originated from the neural stem cells, like glioma, lymphoma, etc. and pre-operative diagnosis rate was quite low due to its rare incidence. The differentiation diagnosis included other common spinal malignancies such as glioma, ependymoma, and lymphoma when located intramedullary and from those neoplasms such as Schwannoma and

Table 2 Review of the literatures of primary spinal primitive neuroectodermal tumor.

Author	Date of publication	Patient information (gender, age/yr.)	Spinal segment	Location	Extent of resection	Adjuvant therapy	Follow-up	Other
Wang G *et al.*[1]	2017 Dec	M, 26	Lumbar	Intramedullary	GTR	Radiotherapy & Chemotherapy (TMZ) after the 2nd operation	Recurrence 9 months later, received 2nd surgery and adjuvant therapy. PFS for 5 more months.	—
Sharma *P et al.*[2]	2016 Apr-Jun	M, 11	Cervical	Intramedullary	Near total removal	No details.	No details.	—
Harbhajanka A *et al.*[3]	2012 Jan	F, 18	Thoracic-Lumbar	Intramedullary	Tumor decompression	Awaiting chemoradiotherapy.	Awaiting adjuvant therapy.	—
Alexiou GA *et al.*[4]	2013 Feb	F, 0 (2 months)	Cervical-Thoracic	Intramedullary	Radical resection (some small tumor remnants left) + VP-shunt	Chemotherapy (Head Start II protocol).*[1]	No recurrence 9 months later.	Hydrocephalus since 33 weeks' gestation.
Coumans JV *et al.*[5]	2012 Jan	M, 26	Cervical-Thoracic	Intramedullary	GTR	Radiotherapy and chemotherapy (back-bone regimen).*[2]	PFS after adjuvant therapy.	—
Mulholland CB *et al.*[6]	2011 Oct	M, 27	Cervical	Intramedullary	80% resected	Chemotherapy.	Died 3 months later.	Associated with NF1.
Fujisawa H *et al.*[7]	2011 Feb	M, 65	Cervical-Thoracic	Intramedullary	Partial resection	Radiotherapy.*[3]	Survive 6 months later.	20 years after pineal tumor and hydrocephalus.
Tsutsumi S *et al.*[8]	2010 Apr	M, 39	Thoracic-Lumbar	Intramedullary	Incomplete resection	Radioatherapy.*[4]	Died 11 months later.	—
Otero-Rodríguez A *et al.*[9]	2009 Aug	M, 1 (17 months)	Thoracic	Intramedullary	Near total removal	Chemotherapy.	Recurrence 6 months later.	—
Kumar R *et al.*[10]*	2007	-, 8	Thoracic	Intramedullary	Not available	Not available.	Not available.	—
		-, 9	Holocord	—	Not available	Not available.	Not available.	—
		-, 18	Cervical	Extramedullary	Not available	Not available.	Not available.	—
Jain A *et al.*[11]	2006 Jun	F, 54	Cervical	Intramedullary	Partial excision	Radiotherapy.	Awaiting chemotherapy.	—
De Tommasi A *et al.*[12]	2006 Mar	M, 38	Thoracic	Intramedullary	Biopsy	Chemotherapy.*[5]	Died 18 months later.	—
Chen YC *et al.*[13]	2005 Aug	F, 19	Cervical-Thoracic	Intramedullary	Biopsy	Chemotherapy & radiotherapy. *[6]	Died 9 months later.	Concomitant pregnancy & IH.
Albrecht CF *et al.*[14]*	2003 Jan	F, 29	Thoracic	Intramedullary	No details (multifocal)	Radiotherapy and chemotherapy.*[7]	Died 17 months later.	—
		F, 49	Lumbar	Extramedullary	GTR	Radiotherapy and chemotherapy.*[7]	Died 23 months later.	—
Mawrin C *et al.*[15]	2002 Jan	M, 69	Thoracic	Intramedullary	Partial removal	Radiotherapy. *[8]	Died 12 weeks later.	—

Continued

Table 2 ***Continued***

Author	Date of publication	Patient information (gender, age/ yr.)	Spinal segment	Location	Extent of resection	Adjuvant therapy	Follow-up	Other
Meltzer CC *et al.*[16]	1998 Jul	M, 30	Cervical-Conus medullaris.	Intramedullary	No details	Radiotherapy and chemotherapy.*[9]	Died 1 year later.	FDG PET investigation in a recurrent case.
Deme S *et al.*[17]*	1997 Dec	F, 22	Thoracic-Lumbar	Intramedullary	GTR	Radiotherapy and chemotherapy.	Recurrence 10 weeks later.	—
Kwon OK *et al.*[18]*	1996 Oct	F, 0 (3 months)	Thoracic	Intramedullary	Biopsy	Chemotherapy.	Died 21 days later.	With intracranial seeding.
Brunberg JA *et al.*[19]	1991 Nov	Pediatric	—	Intramedullary	No details	No details.	No details.	MR and sonography studies in 11 pediatric intramedullary lesions, including one PNET case.
Ogasawara H *et al.*[20]*	1992 Apr	-	—	Intramedullary	Not available	Radiotherapy and chemotherapy.	Not available	With intracranial seeding.
Freyer DR *et al.*[21]*	1989	Pediatric	—	Intramedullary	Not available	Not available.	Not available.	—
Eghbal K *et al.*[22]	2017 Mar 9	F, 38	Lumbar	Extramedullary	Total resection	No details.	Survive 6 months later.	—
Rege SV *et al.*[23]	2016 Oct-Dec	F, 8	Thoracic	Extramedullary	Complete excision	Radiotherapy. *[10]	Survive after adjuvant therapy.	—
Meng XT *et al.*[24]	2015 Apr	F, 60	Lumbar	Extramedullary	Complete removal	Radiotherapy. *[11]	Recurrence 4 months later, died 8 months later.	—
Chan SH *et al.*[25]	2015 Feb	M, 7	Lumbar-Sacral	Extramedullary	Biopsy (twice)	Chemotherapy & radiotherapy.	Died 2.5 years later.	—
Venkataraman S *et al.*[26]	2013 Apr	F, 19	Thoracic-Lumbar	Extramedullary	GTR	Chemotherapy.	Awaiting chemotherapy.	—
Hung PC *et al.*[27]	2007 Oct	F, 16	Thoracic-Lumbar	Extramedullary	No details	Chemotherapy & local radiotherapy.	No details.	—
Nutman A *et al.*[28]*	2007 Jan-Feb	F, 19	Thoracic-Lumbar	Extramedullary	No details	Radiotherapy (entire cranio-spinal axis irradiation) & chemotherapy with autologous stem cell rescue.	PFS 24 months later.	—
Aydin MV *et al.*[29]	2004 Oct	M, 16	Thoracic	Extramedullary	Totally excision	Radiotherapy and chemotherapy.*[12]	PFS 7 months later.	—
Fabre E *et al.*[30]	2006 Jul	M, 70	Cauda equina	Extramedullary	Partial resection	Radiotherapy and chemotherapy.*[13]	Survive 1 year later.	—
Isotalo PA *et al.*[31]	2000 Aug	M, 52	Cauda equina	Extramedullary	Debulking	Radiotherapy. *[14]	PFS 1 year later.	—
Akai T *et al.*[32]	1998 Aug	M, 4	Thoracic	Extramedullary	GTR	Radiotherapy and chemotherapy.*[15]	PFS 6 years 4 months later.	—

Continued

Table 2 *Continued*

Author	Date of publication	Patient information (gender, age/ yr.)	Spinal segment	Location	Extent of resection	Adjuvant therapy	Follow-up	Other
Papadatos D *et al.*[33]	1998 Apr	F, 22	Thoracic	Extramedullary	Debulking	Radiotherapy and chemotherapy.*[16]	PFS 1 year later.	—

yr., years old; -, details not available due to no full text available; GTR, gross total resection; TMZ, temozolomide; PFS, progression-free survival; NF1, neurofibromatosis type I; IH, intracranial hypertension.
*No full text available.
*1–*16 Refer to supplement table 1 for details of available adjuvant therapy.

neurofibroma when located extramedullary. Meltzer CC *et al.*[16] discussed the PET characteristic of a recurrent case. Brunberg JA *et al.*[19] also mentioned one pediatric intramedullary PNET in a study of a MR and sonography results investigation of 11 intramedullary lesions, but the details of the case was not offered. Surgical resection with laminectomy is recommended as early. Sometimes the aggressive resection is not applicable due to its close relationship with spinal cord, especially for those intramedullary cases. Adjuvant radiotherapy and chemotherapy are also necessary. However, no standard guideline existed yet for radiochemotherapy of spinal PNET. We're lacking in datas of detailed adjuvant therapy. In the literature review, some oncologists referred to glioma treatment strategies, and some referred to medulloblastoma. With lacking of standard and effective therapies the prognosis for all CNS PNET is bleaker especially for infants less than two years old at the time of diagnosis. The recurrence and mortality rate is high. Of our cases with available follow-up data, all patients died and three of them died around one year after operation. According to literatures, most patients die within two years given all available treatment methods for now. Only one exception was observed in Akai T *et al.*'s report[32] about a four-year-old male who survived more than six years after total resection and adjuvant radiochemotherapy. After the surgery, the patient underwent focal irradiation (36 Gy) and combination chemotherapy with cyclophosphamide, pirarubicin, cisplatin, and etoposide postoperatively. Chemotherapy was performed 14 times during three years. There is still a long way to go for the understanding of the disease.

Conclusion

Spinal PNET is a quite rare group of tumors composed of heterogeneous undifferentiated or poorly differentiated neuroepithelial cells. It's highly malignant. The pre-operative diagnosis based on image examinations was a challenge and should be differentiated from other CNS malignancies like glioma, lymphoma, and ependymoma when located intramedullary and from those common CNS neoplasms like Schwannoma and neurofibroma when located extramedullary. The medical history was important for clinical evaluation. The tumor tends to have an early onset and aggressive clinical behavior. Positive interventions should be considered as early for suspected cases. However, the prognosis is quite poor and there's still a lot of unknown areas of spinal PNET. Multi-center cooperation may be a way to perform further investigations of this rare disease.

Disclaimer statements

Consent The study is approved by Institutional Review Board of Beijing Tiantan Hospital affiliated to Capital Medical University. Written informed consent was obtained from each patient for the publication of this study including case presentation and images. Copies of the written consents are available.

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