

Case Report

Primary spinal extradural Ewing's sarcoma (primitive neuroectodermal tumor): Report of a case and meta-analysis of the reported cases in the literature

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Abstract

Background: Primary spinal primitive neuroectodermal tumors (PNET) and/or spinal extraskeletal Ewing's sarcoma family tumors (ESET) are rare lesions appearing in the spinal extradural space. One hundred forty-one primary spinal PNETs, including 29 intramedullary lesions, have been reported in the literature. Encountering a case of primary epidural EES/peripheral PNET (pPNET) in sacral level, which is the fifth one occurring at this level in the literature, we have tried to conduct a meta-analysis of the reported cases.

Case Description: A 44-year-old lady with epidural EES/pPNET is reported here. She was once operated for L5/S1 herniated disc, which did not ameliorate her symptoms. The clinical, imaging, surgical, and histopathologic characteristics of our case are presented and wide search of the literature is also done. All the reports were level 3 or less evidences and most of the series had missing parts. 106 cases of primary intraspinal (extradural/extramedullary-intradural) EES/pPNET and 29 cases of primary intramedullary PNET (CNS-PNET) have been reported in the literature. The most common clinical presentation in both entities was muscle weakness proportionate to the tumor location. Distant metastasis occurred in 38 of 99 (38%) cases of primary intraspinal EES/pPNET, while the rate of metastasis was 48% in patients with PNETs occurring in the intramedullary region ($P > 0.05$). One-year survival rate of the patients who underwent chemo-radiation after total or subtotal resection was better than those who did not receive chemotherapy or radiotherapy, or did not have total or subtotal resection. However, this difference was not repeated in 2-year survival rate in any of the tumor groups.

Conclusion: It seems that total or subtotal removal of the tumor and adjuvant chemo- and radiation therapy can improve the outcome in these patients.

Key Words: Ewing's sarcoma, primitive neuroectodermal tumor, spine

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INTRODUCTION

Primary spinal primitive neuroectodermal tumors (PNET) and/or spinal extraskeletal Ewing's sarcoma family tumors (ESET) are rare lesions appearing in the spinal extradural space.^[2,81,116] Undifferentiated round cell tumors include inhomogeneous group of malignant tumors which may arise in any organ because of their embryonic origin. A subgroup of these tumors named "PNET" may affect the CNS primarily.^[2,94] The origin of PNET in CNS seems to be the matrix or germinal cells of the embryonic neural tube. The well-known tumor of this subgroup is medulloblastoma which is a primary cerebellar tumor and the most common primary posterior fossa tumor in

children, comprising 20% of all the intracranial tumors in this age group.^[94] The classification of tumors of CNS published by World Health Organization (WHO) in 1993 designated other cerebral medulloblastoma-like tumors as supratentorial PNET.^[33,63,64] In the more recent classification by WHO, these tumors were subdivided under medulloblastoma as CNS-PNETs.^[65,76] Even though spine seeding secondary to intracranial medulloblastoma is common, primary spinal intramedullary CNS-PNET occurs rarely^[2,81,116] and only 29 cases have been reported in 22 series so far [Table 1]. Among the undifferentiated round cell tumors such as neuroblastoma, non-Hodgkin's lymphoma, and rhabdomyosarcoma, it seems that PNETs have similarities to Ewing's sarcoma (ES).^[21,34] ES is

Table 1: Details of 29 cases of primary spinal intramedullary CNS-primitive neuroectodermal tumors extracted from 22 reports

Author	Year	Age/Sex	Location of Tumor	Treatment	Follow-up (month)	Out come	CD99	t (11:22)
Kosnic <i>et al.</i>	1978	<10y/NA	Conus Medullaris	STR/CT/RT	<12	Dead	NA	NA
Jackche <i>et al.</i>	1988	15y/F	Conus Medullaris	STR/CT/RT	18	Dead	NA	NA
Freyer <i>et al.</i>	1989	7y/M	T4 – S3	Biopsy/CT/RT	20	Dead	NA	NA
Kwon <i>et al.</i>	1996	3m/F	T7 – L5	Biopsy/CT	15 Days	Dead	NA	NA
Deme <i>et al.</i>	1997	22y/F	Conus Medullaris	STR/CT/RT	15	Alive	NA	NA
Mottle <i>et al.</i>	1997	<17y/F	C3 – L2	Biopsy/CT/RT	NA	NA	NA	NA
Miller <i>et al.</i>	1997	NA	NA	NA	NA	NA	NA	NA
Miller <i>et al.</i>	1997	NA	NA	NA	NA	NA	NA	NA
Meltzer <i>et al.</i>	1998	25y/M	C3 – Conus Medullaris	STR/CT/RT	60	Dead	NA	NA
Papdatos <i>et al.</i>	1998	23y/F	T10 – T11	STR/CT/RT	12	Alive	NA	NA
Weil <i>et al.</i>	2001	21y/M	T10 – T11	STR/CT/RT	30	Alive	+	+
Mawrin <i>et al.</i>	2002	69y/M	C7 – T3	STR/RT	3	Dead	NA	NA
Mawrin <i>et al.</i>	2002	38y/M	NA	STR/CT/RT	18	Dead	NA	NA
Albrecht <i>et al.</i>	2003	29y/F	T2 & T10 – T11	Biopsy/CT/RT	17	Dead	–	–
Chen <i>et al.</i>	2005	19y/F	Cervico-thoracic	Biopsy/RT	9	Dead	–	NA
Kampman <i>et al.</i>	2006	3y/M	C2 – C6	STR	1	Dead	–	NA
Jain <i>et al.</i>	2006	54y/F	C2 – C5	STR/RT	NA	NA	–	NA
Detommasi <i>et al.</i>	2006	38y/M	T1 – T3	Biopsy/CT	18	Dead	–	NA
Kumar <i>et al.</i>	2007	9y/F	T9 – L1	TTR/CT/RT	18	Alive	NA	NA
Kumar <i>et al.</i>	2007	18y/M	Cervico-thoracic	Biopsy/CT/RT	6	Alive	+	NA
Han <i>et al.</i>	2008	17y/M	Conus Medullaris	STR/CT/RT	24	Dead	NA	NA
Han <i>et al.</i>	2008	40y/F	Conus Medullaris	TTR/CT/RT	8	Alive	NA	NA
Oto-Rodriguez <i>et al.</i>	2009	1.5y/M	T3 – T10	STR/CT	6	Alive	–	NA
Benesh <i>et al.</i>	2010	1.5y/F	Medulla Oblongata – T3	TTR/CT	6	Dead	–	NA
Benesh <i>et al.</i>	2010	14.5y/F	C2 – T1	STR/CT/RT	44	Alive	–	NA
Benesh <i>et al.</i>	2010	10m/F	T10 – L2	Biopsy /CT	6	Dead	–	NA
Benesh <i>et al.</i>	2010	2y/M	T7 – T10	Biopsy/CT/RT Autologus stem cell rescue	40	Alive	–	NA
Ellis <i>et al.</i>	2011	27y/M	C5 – C6	STR/CT	28	Alive	–	–
Gollard <i>et al.</i>	2011	27y/F	T5 – T11	Biopsy/CT/RT Autologus stem cell rescue	132	Alive	–	NA

CT: Chemotherapy, F: Female, M: Male, NA: Not Available, RT: Radiotherapy, STR: Sub-total tumor resection, TTR: Total tumor resection, y: year

one of the childhood tumors mostly affecting skeletal tissues.^[93,108] Tefft *et al.* in 1969 introduced the first case of ES without skeletal involvement,^[108] and since then, several cases of extraskeletal ES (EES) have been reported. Osseous ES, EES, Askin's tumor, and peripheral PNET (pPNET) are nowadays generally known as Ewing's sarcoma family tumors (ESFTs).^[47,84,109] Occurrence of CNS-PNET (as we call it in our report) or primary intraspinal EES/pPNET (extradural/intradural) in the spine is unusual, and we intend to report our case of EES/pPNET which is the *fifth one occurring in the sacral level*, describe the clinical presentation, and make a meta-analysis of the reports in the literature.

CASE REPORT

A 44-year-old woman was referred to an orthopedic clinic in a city hospital, complaining of low back pain (LBP) of several years duration. Her severe sciatalgia had exacerbated since 6 months before admission. The diagnosis of L5/S1 disc herniation compressing S1 root on the left side was made and she underwent operation. It was a no-contrast standard lumbosacral magnetic resonance imaging (MRI). At operation, L5 and partial S1 laminectomy followed by bilateral S1 foraminotomy, and bilateral L5/S1 discectomy was performed. Two weeks after the operation, the patient's symptoms exacerbated and paresthesia appeared in the left buttock. Paresthesia of the perineal region and urinary incontinency were also added to her previous complaints. On admission to our department, the muscle forces of the lower limb were intact both proximally and distally, but pin prick sensation was disturbed in S1, S2, and S3 dermatomes, and Achilles tendon reflex was absent in the left side. However, anal sphincter tone was intact. Re-evaluation of the previous preoperative lumbosacral MRI revealed that in addition to the L5/S1 bulged disc, there was an extradural dorsally located mass at S1, S2, and S3 levels. The new contrast-enhanced MRI revealed a 3 × 2 × 2 cm extradurally located tumor, extending from lower edge of S1 down to S2/S3 interspace. The tumor was hypointense

in both T1 and T2 images and enhanced homogeneously after contrast material injection. Scalloping of the posterior aspect of the S2 vertebra was also detectable [Figure 1a–d]. In the second operation, the previous laminectomy was extended from lower edge of L5 down to S3. A reddish gray tumor located in the extradural space, extending from S1 root axilla down to the S3 root, could be excised totally. There was neither tumor invasion to the dura or intradural space, nor any bone involvement detectable under microscopic observation. Histopathologic examination revealed a highly cellular neoplasm composed of diffuse sheets of tumor cells having monomorphic, round to oval, finely vesicular nuclei and occasional nucleoli with indistinct cytoplasmic border. Delicate fibrovascular septae surrounded the tumor mass along with intra tumoral extensions. In some foci, tumor cells gathered in groups around small vessels (pseudo-rosette appearance). There were nerve bundle entrapments within the tumor nests. Several groups of mitotic figures were noted, but no necrosis was detected [Figure 2a and b].

Immunohistochemical (IHC) staining showed that the tumor cells stained positively for neuron-specific enolase, synaptophysin, and chromogranin, suggestive of neuronal differentiation of the tumor. Tumor cells also expressed CD99, consistent with the diagnosis of ES/PNET [Figure 2c]. Ki-67 proliferative index showed about 10–15% proliferative activity. Other markers such as leukocyte common antigen (LCA), epithelial membrane antigen (EMA), cytokeratin (CK), desmin, smooth muscle actin (SMA), and myogenin were negative. Fluorescence *in situ* hybridization and chromosomal study were not performed.

The postoperative course was uneventful and all her symptoms including radicular pain and sphincter problems improved rapidly. The patient was referred for radiotherapy as the adjuvant therapy. In the last re-evaluation of the patient after 18 months, there was no sign of tumor recurrence in MRI.

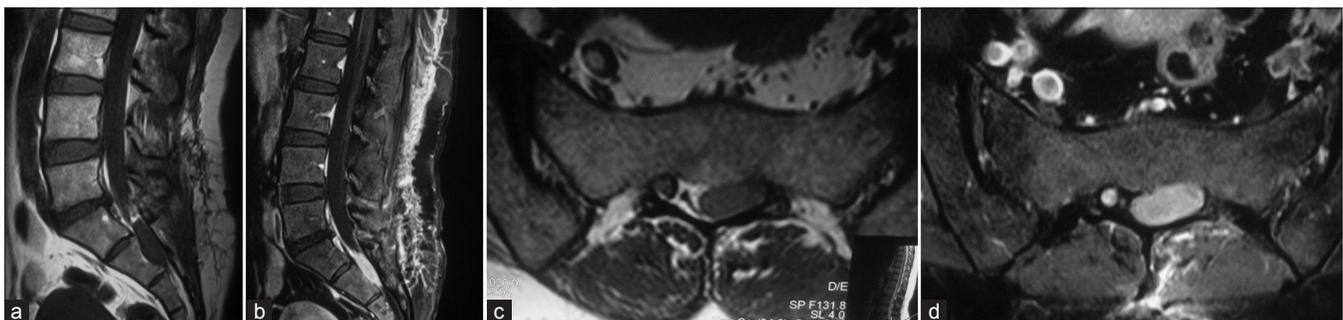


Figure 1: (a) Sagittal T1-W MRI without contrast injection, before the first surgery. An extradural hyposignal lesion is observed at S1–S3 level, which was neglected in the first intervention. (b) Sagittal T1 MRI with contrast from the lumbosacral region after the first operation. Homogenous enhancement of the lesion is observed. (c and d) Axial T1 MRI views of the lesion with and without contrast, after the first operation

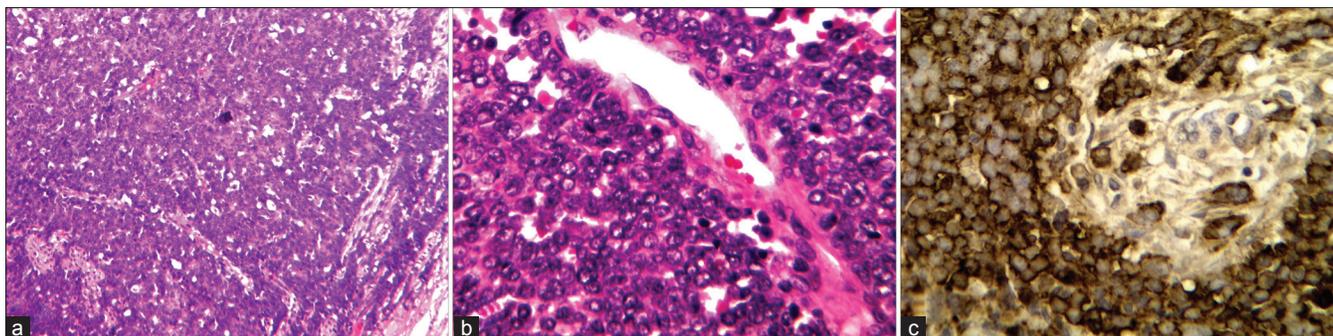


Figure 2: (a and b) Hematoxylin and Eosin staining of the tumor under low- and high-power microscopic fields revealing a highly cellular neoplasm composed of diffuse sheets of tumor cells having monomorphic, round to oval, finely vesicular nuclei and occasional nucleoli with indistinct cytoplasmic border. In some foci, tumor cells are grouped around small vessels (pseudo-rosette appearance). Several groups of mitotic figures were noted, but no necrosis was detected. (c) Immunohistochemistry study for CD99 depicting tumor cells highly positive for the marker

Method

Article selection

After our wide search using Tehran University of Medical Sciences electronic resources (www.tums.ac.ir) and motor searches of Pubmed, Ovid, and EBSCO using the key words, spinal primitive neuroectodermal tumor and spinal extraskeletal Ewing sarcoma, 106 abstracts were found in the form of case series and case reports, which reported 141 cases of primary intraspinal EES/pPNET. Full texts of all the articles were collected from different electronic and paper archives including English, French, Spanish, and Italian articles. The earliest articles were published by Smith *et al.*^[106] and Tefft *et al.*^[108] in 1969 and the latest by Gollard *et al.*^[37] in Feb 2011. Patients' information including age, sex, clinical signs and symptoms, duration of symptoms, family history, location of the tumor, metastasis, recurrences, therapeutic methods, duration of follow-up, and eventual outcome were all extracted from resources. As the articles were reported from various clinical departments (e.g. Neurosurgery, Orthopedics, Radiology, Oncology, Pathology, Pediatrics), different aspects of the disease were reviewed in each, and this led to neglecting some other aspects resulting in missed values regarding some subjects. In some of them with missing data about the mode of therapy, final outcome, or follow-up of the patients, the authors were contacted via e-mail directly for the required information. In spite of sending e-mail to 20 authors, only one reply was received.^[89]

Statistical analysis

After collecting and classifying the information, the data were analyzed utilizing SPSS version 13.0.

For analysis of the numeric variables such as age, Kolmogorov-Smirnov test was used to evaluate normal distribution of the data upon which we could decide to utilize parametric versus non-parametric tests to compare the data. Chi-square test (χ^2) was used when comparing two nominal or ordinal variables such as 1-year survival

in patients receiving different therapies. Independent sample *t*-test was used to evaluate numerical variable among two populations (e.g. age in different subgroups). *P*-values less than 0.05 were considered statistically significant.

RESULTS OF THE META-ANALYSIS

Considering the rarity of primary intraspinal EES/pPNET as a pathologic diagnosis and scarce information on this entity in the references, we decided to review the literature on the issue. By now, 106 cases^[1-5,7-9,12-14,16,17,19,23,25-32,36,38,41-50,52-54,56-62,66-68,70,71,73,77-79,81,84,86-90,92,93,95,97-113,115,116] of primary intraspinal EES/pPNET (extradural/intradural/extramedullary lesions) and 29 cases^[3,11,18,20,22,28,35,37,40,51,52,55,69,71,72,80,82,83,85,91,94,114] of primary intramedullary PNET (CNS-PNET) have been reported in the literature [Tables 1 and 2]. In some studies, neither intra- nor extramedullary location of the tumor was mentioned, so they were not included in any of the groups in our review (i.e. 135 cases out of 141).^[10,15,69,96] The average age of occurrence for primary intraspinal EES/pPNET was 22.9 ± 13.9 and for CNS-PNET was 19.5 ± 12.8 , and this difference was not statistically significant (χ^2 , $P > 0.05$). The youngest and the eldest patients with primary intraspinal EES/pPNET were 40 days and 70 years old, respectively, whereas these age extremes for CNS-PNET patients were 3 months and 69 years. The proportion of primary intraspinal EES/pPNET and CNS-PNET in different age groups is summarized in Table 3. *Our case was 41 years old and present in the elder side of the reported cases.*

Among 107 patients with primary intraspinal EES/pPNET, 71 (66%) were males, whereas of 26 patients with CNS-PNET, 12 (46%) were males and the gender of three patients was unidentified. Duration of symptoms before diagnosis was 4.52 ± 7.01 months and 2.80 ± 3.40 months, respectively, in patients with primary intraspinal EES/pPNET and CNS-PNET. The most common clinical

Table 2: Summary of the cases of primary spinal primitive neuroectodermal tumors-Ewing's sarcoma family tumors reported in the literature

Author	Reference number	Year	Age/Sex	Location of Tumor	Treatment	Follow-up (month)	Outcome	CD99	t (11:22)
Smith <i>et al.</i>	106	1969	24 y/M	Cauda Equina	STR/RT	10	Dead	NA	NA
Tefft <i>et al.</i>	108	1969	6 y/F	L4/ Extradural	STR/RT/CT	48	Dead	NA	NA
Angervali <i>et al.</i>	7	1975	17 y/M	S1-S2/ Extradural	TTR	1	Dead	NA	NA
Angervali <i>et al.</i>	7	1975	20 y/M	T2-T5/ Extradural	STR/RT/CT	12	Dead	NA	NA
Angervali <i>et al.</i>	7	1975	18 y/F	L5/ Extradural	TTR/RT/CT	6	Dead	NA	NA
Scheithauer <i>et al.</i>	100	1978	18 y/M	L1/ Extradural	TTR/RT/CT	16	Alive	NA	NA
Scheithauer <i>et al.</i>	100	1978	27 y/F	T4-T6/ Extradural	STR/RT/CT	132	Alive	NA	NA
Mahoney <i>et al.</i>	78	1978	23 y/M	S1/ Extradural	Biopsy/RT/CT	12	Dead	NA	NA
Fink <i>et al.</i>	32	1979	19 y/M	L2-L3/ Extradural	STR/RT/CT	12	Alive	NA	NA
Simonati <i>et al.</i>	105	1981	13 y/M	L3/ Extradural	TTR/RT/CT	15	Alive	NA	NA
N'Golet <i>et al.</i>	88	1982	29 y/M	T1-T3/ Extradural	TTR/RT/CT	6	Alive	NA	NA
N'Golet <i>et al.</i>	88	1982	47 y/F	L4/ Extradural	TTR/RT/CT	4	Dead	NA	NA
Spazinate <i>et al.</i>	107	1983	10 y/M	L4-L5/ Extradural	STR/RT/CT	15	Dead	NA	NA
Demeocq <i>et al.</i>	23	1983	16 y/F	L3-L4/ Extradural	STR/CT	NA	NA	NA	NA
Kepes <i>et al.</i>	58	1985	24 y/M	Cauda Equina	TTR/RT/CT	18	Dead	NA	NA
Kepes <i>et al.</i>	58	1985	56 y/M	Cauda Equina	STR/RT	36	Alive	NA	NA
Kepes <i>et al.</i>	58	1985	39 y/M	Cauda Equina	STR/RT	42	Dead	NA	NA
Ruelle <i>et al.</i>	98	1986	17 y/M	L3-L4/ Extradural	STR/RT/CT	9	Dead	NA	NA
Sharma <i>et al.</i>	102	1986	18 y/M	T10/ Extradural	STR/RT/CT	42	Dead	NA	NA
Machin Valtuena <i>et al.</i>	77	1987	4 y/M	L1/ Extradural	TTR	5	Dead	NA	NA
Liu <i>et al.</i>	73	1987	26 y/F	L5-S1/ Extradural	STR/RT	6	Alive	NA	NA
Sevich <i>et al.</i>	101	1987	26 y/M	C2-C3/Intradural-Extramedullary	TTR/RT	36	Dead	NA	NA
Jaksche <i>et al.</i>	52	1988	26 y/M	T8-L2/ Intradural-Extramedullary	STR/RT/CT	36	Dead	NA	NA
Benmeir <i>et al.</i>	12	1991	16 y/F	T8-T10/ Extradural	TTR/RT/CT	6	Alive	NA	NA
Kaspers <i>et al.</i>	56	1991	7 y/M	T12-L1/ Extradural	STR/CT	40	Alive	NA	NA
Ogasawara <i>et al.</i>	90	1992	16 y/F	Cauda Equina	STR/RT/CT	29	Alive	NA	NA
Kinsella <i>et al.</i>	62	1993	14 y/F	NA	STR/RT/CT	48	Alive	NA	NA
Mc Dermott <i>et al.</i>	81	1994	47 y/M	Cauda Equina	Biopsy/RT/CT	16	Dead	NA	NA
Wasserberg <i>et al.</i>	112	1994	41 y/M	T1-T7/ Intradural-Extramedullary	TTR	36	Alive	NA	NA
Allam <i>et al.</i>	5	1994	15 y/F	T12-L2/ Extradural	Biopsy/NA	NA	NA	NA	NA
Christie <i>et al.</i>	19	1997	36 y/F	Lumbar/ Extradural	STR/RT	96	Dead	NA	NA
Hisoaka <i>et al.</i>	44	1997	14 y/M	Cauda Equina	STR	3	Alive	+	+
Koot <i>et al.</i>	68	1998	2 y/F	C1-C6/ Intradural-Extramedullary	STR	3 Days	Dead	NA	NA
Akai <i>et al.</i>	1	1998	4 y/M	T8-T9/ Extradural	TTR/RT/CT	76	Alive	NA	NA
Dorfmueller <i>et al.</i>	26	1999	17 y/M	L3-L4/ Extradural	TTR/RT/CT	23	Alive	+	+
Isotalo <i>et al.</i>	48	2000	52 y/M	Cauda Equina	STR/RT	12	Alive	+	NA
Kennedy <i>et al.</i>	57	2000	24 y/M	C1-C5/ Extradural	STR/RT/CT	13	Alive	NA	NA
Izyscha-swieszewka <i>et al.</i>	50	2001	13 y/F	C7-T11/ Extradural	Biopsy/RT/CT	31	Alive	+	+
Shin <i>et al.</i>	103	2001	38 y/M	C5-C7/ Extradural	STR/CT	17	Alive	+	NA
Shin <i>et al.</i>	103	2001	22 y/F	C7-T1/ Extradural	STR/CT	48	Alive	+	NA
Mukhopadhyay <i>et al.</i>	86	2001	29 y/F	C3-C5/ Extradural	STR/RT/CT	30	Alive	+	NA
Mukhopadhyay <i>et al.</i>	86	2001	18 y/M	T8/ Extradural	STR/RT/CT	18	Alive	+	NA
Mukhopadhyay <i>et al.</i>	86	2001	22 y/M	L5-S1/ Extradural	Biopsy/RT/CT	15	Alive	+	NA
Mukhopadhyay <i>et al.</i>	86	2001	31 y/M	L3-L4/ Extradural	STR/RT/CT	32	Alive	+	NA
Mukhopadhyay <i>et al.</i>	86	2001	13 y/M	C3-C5/ Extradural	STR/RT/CT	11	Alive	+	NA

Contd...

Table 2: Contd...

Author	Reference number	Year	Age/Sex	Location of Tumor	Treatment	Follow-up (month)	Outcome	CD99	t (11:22)
Virani <i>et al.</i>	111	2002	5 y/M	T1-T4/ Extradural	STR/RT	8	Alive	NA	NA
Yavus <i>et al.</i>	116	2002	18 y/F	Cauda Equina	STR/RT/CT	25	Alive	NA	NA
Reihani-Kermani <i>et al.</i>	97	2002	22 y/F	T12/ Intradural-Extramedullary	TTR/RT	9	Alive	NA	NA
Martinez-Quinones <i>et al.</i>	79	2002	40 y/M	Cauda Equina	NA	NA	NA	NA	NA
Kadri <i>et al.</i>	54	2002	15 y/F	L2-L3/ Extradural	STR/RT/CT	8	Alive	+	NA
Uesaka <i>et al.</i>	110	2002	11 y/F	C7-T1/ Intradural-Extramedullary	STR/NA	NA	NA	+	NA
Izycka-swieszewska <i>et al.</i>	49	2003	26 y/M	C4-C6/ Intradural-Extramedullary	STR/RT	3	Dead	+	-
Albrecht <i>et al.</i>	3	2003	49 y/F	Cauda Equina	TTR/RT/CT	23	Alive	+	NA
Harimaya <i>et al.</i>	42	2003	12 y/F	T1-T3/ Extradural	STR/RT/CT	32	Dead	NA	NA
Harimaya <i>et al.</i>	42	2003	10 y/M	C6-T3/ Extradural	STR/RT/CT	22	Dead	NA	NA
Harimaya <i>et al.</i>	42	2003	30 y/F	C2-C4/ Intradural-Extramedullary	STR/RT/CT	14	Dead	NA	NA
Harimaya <i>et al.</i>	42	2003	14 y/M	Cauda Equina	TTR/CT	67	Alive	NA	NA
Gandhi <i>et al.</i>	36	2003	33 y/M	T5-T9/ Extradural	TTR/RT/CT	3	Alive	+	NA
Aydin <i>et al.</i>	9	2004	16 y/M	Thoracic/ Extradural	TTR/RT/CT	7	Alive	NA	NA
Akyuz <i>et al.</i>	2	2004	31 y/F	Cauda Equina	STR/RT/CT	4	Dead	+	NA
Kim <i>et al.</i>	61	2004	17 y/M	Cauda Equina with conus medullaris invasion	STR/RT	4	Alive	+	NA
Weber <i>et al.</i>	113	2004	26 y/M	L1/ Extradural	TTR/RT/CT	16	Alive	+	NA
Kogawa <i>et al.</i>	67	2004	7 y/F	C2-C4/ Extradural	STR/RT/CT	60	Alive	+	NA
Bohn Sarmiento <i>et al.</i>	13	2005	37 y/M	Cauda Equina	STR/RT	6	Dead	+	NA
Woestenborghs <i>et al.</i>	115	2005	11 y/M	C4-T2/ Intradural-Extramedullary	STR/CT	NA	NA	+	+
Siarni-Namini <i>et al.</i>	104	2005	15 y/F	T3-T7/ Extradural	STR/NA	NA	NA	+	+
Mobely <i>et al.</i>	84	2006	32 y/M	Cauda Equina	TTR/RT/CT	12	Dead	+	+
Faber <i>et al.</i>	30	2006	70 y/M	Cauda Equina	STR/RT/CT	12	Alive	+	+
Koudelova <i>et al.</i>	70	2006	28 y/F	L1-L2/ Extradural	STR/RT/CT	24	Alive	NA	NA
Athanassiadou <i>et al.</i>	8	2006	13 y/M	T9/ Extradural	STR/RT/CT	NA	NA	+	+
Isefuku <i>et al.</i>	47	2006	20 y/M	L5-S1/ Extradural	STR/CT	15	Dead	+	+
Nutman <i>et al.</i>	89	2007	19 y/F	Cauda Equina	TTR/RT/CT/ Autologous stem cell rescue	78	Alive	+	NA
Kumar <i>et al.</i>	71	2007	8 y/M	C2-C4/ Intradural-Extramedullary with Extradural extension	TTR	8	Alive	NA	NA
Perry <i>et al.</i>	95	2007	27 y/M	Cauda Equina	TTR/RT/CT	72	Alive	+	-
Perry <i>et al.</i>	95	2007	16 y/F	Cauda Equina	STR/RT/CT	5	Alive	+	+
He <i>et al.</i>	43	2007	8 y/F	L4-L5/ Extradural	STR/RT/CT	10	Dead	+	NA
Sahu <i>et al.</i>	99	2007	11 y/M	NA/ Intradural-Extramedullary	STR/RT/CT	NA	NA	+	NA
Ozturk <i>et al.</i>	93	2007	18 y/M	C6-T1/ Extradural	TTR/CT	13	Alive	+	NA
Bozkurt <i>et al.</i>	14	2007	28 y/M	C3-C5/ Extradural	TTR/RT/CT	18	Alive	+	NA
Erkutlu <i>et al.</i>	29	2007	7 y/M	C5-T1/ Extradural	TTR/RT/CT	108	Alive	+	NA
Feng <i>et al.</i>	31	2008	24 y/M	T8-T10/ Extradural	TTR/RT	14	Alive	+	-
Mushal <i>et al.</i>	87	2008	27 y/M	S1-S2/ Extradural	TTR/RT/CT	24	Alive	NA	NA
Cai <i>et al.</i>	16	2008	3 y/M	NA/ Extradural	TTR/NA	6	Alive	+	NA

Contd...

Table 2: Contd...

Author	Reference number	Year	Age/Sex	Location of Tumor	Treatment	Follow-up (month)	Outcome	CD99	t (11:22)
Ozdemir <i>et al.</i>	92	2008	13 y/F	L2-L3/ Extradural	TTR/CT	14	Dead	+	NA
Hareh <i>et al.</i>	41	2008	26 y/M	Cauda Equina	TTR/RT/CT	6	Alive	+	NA
Hsieh <i>et al.</i>	46	2008	12 y/M	T7-T9/ Extradural	TTR/RT/CT	20	Alive	+	NA
Hrabalek <i>et al.</i>	45	2009	29 y/M	T9-T10/ Intradural- Extramedullary with Extradural extension	STR/CT	4	Dead	+	+
Theeler <i>et al.</i>	109	2009	28 y/F	Thoracic/ Extradural	TTR/CT	2	Alive	+	+
Kiatsoontorn <i>et al.</i>	59	2009	25 y/M	T7/ Extradural	TTR/RT/CT	6	Alive	+	NA
Jingyu <i>et al.</i>	53	2009	19 y/F	C4-C7/ Intradural- Extramedullary	STR/RT/CT	10	Alive	+	NA
Jingyu <i>et al.</i>	53	2009	46 y/M	T1-T2/ Intradural- Extramedullary	TTR/RT/CT	14	Alive	+	NA
Jingyu <i>et al.</i>	53	2009	58 y/M	T4/ Extradural	TTR	25	Alive	+	NA
Jingyu <i>et al.</i>	53	2009	14 y/M	T11-T12/ Intradural- Extramedullary	TTR/RT/CT	6	Alive	+	NA
Chang <i>et al.</i>	17	2009	15 y/F	T2-T4/ Extradural	TTR/RT/CT	12	Alive	+	NA
Alexander <i>et al.</i>	4	2009	45 y/M	C3-C5/ Intradural- Extramedullary	STR/RT	13	Alive	+	+
Dogan <i>et al.</i>	25	2009	13 y/M	T11-L1/ Extradural	TTR/RT/CT	10	Alive	+	NA
Klimo <i>et al.</i>	66	2009	10 y/M	Cauda Equina	STR/RT/CT	12	Alive	+	NA
Kim <i>et al.</i>	60	2009	32 y/F	C3-C5/Intradural- Extramedullary	TTR/RT/CT	20	Alive	+	NA
Duan <i>et al.</i>	27	2010	14 y/M	C2-C4/ Extradural	STR/RT/CT	2	Alive	+	NA
Duan <i>et al.</i>	27	2010	26 y/F	T4-T7/ Extradural	STR/RT/CT	3	Alive	+	NA
Duan <i>et al.</i>	27	2010	7 y/M	C6-T2/ Extradural	STR/RT	NA	NA	+	NA
Duan <i>et al.</i>	27	2010	8 y/M	Cauda Equina	STR/RT/CT	NA	NA	+	NA
Duan <i>et al.</i>	27	2010	25 y/M	Cauda Equina	STR/RT/CT	6	Alive	+	NA
Duan <i>et al.</i>	27	2010	32 y/M	T12/ Extradural	STR	1	Alive	+	NA
Gurkanlar <i>et al.</i>	38	2010	40 days/M	Cauda Equina with conus medullaris invasion	TTR/CT	6	Dead	+	NA
Ellis <i>et al.</i>	28	2011	35 y/M	Cauda Equina	STR	2	Alive	+	+
Present case	-	2011	44 y/F	S1-S3/Extradural	TTR/RT	9	Alive	+	NA

CT: Chemotherapy, F: Female, M: Male, NA: Not Available, RT: Radiotherapy, STR: Sub-total tumor resection, TTR: Total tumor resection, y: year

Table 3: The proportion of primary intra-spinal extraskeletal ES/peripheral primitive neuroectodermal tumors and central nervous system-primitive neuroectodermal tumors in different age groups

	< 10 Years	10-20 Years	20-50 Years	> 50 Years
EES/pPNET	17 (16)	39 (36)	47 (44)	4 (4)
CNS-PNET	9 (33)	6 (22)	10 (37)	2 (8)

EES/pPNET: extraskeletal ES/peripheral primitive neuroectodermal tumors, CNS-PNET: Central nervous system-primitive neuroectodermal tumors, Figures in parentheses are in percentage

presentation in both entities was muscle weakness proportionate to the tumor location. Other clinical symptoms and their incidences are summarized in Table 4. Our case was a lady complaining of LBP of about 4 years duration, who presented with aggravation

of sciatalgia during the previous 6 months and signs compatible with the location of the tumor.

The incidence of primary intraspinal EES/pPNET in lumbar region is twice as much as in thoracic and cervical regions. Only 5% of these tumors have been reported in sacral spine and our case is one of these rare occurrences. On the other hand, CNS-PNET is distributed equally throughout the spine [Table 5]. Distant metastasis occurred in 38 of 99 (38%) cases of primary intraspinal EES/pPNET, while this rate was 12 of 25 (48%) patients with CNS-PNET (χ^2 , $P > 0.05$). However, extra-CNS distant metastases were significantly more common in patients with primary intraspinal EES/pPNET [Table 6]. In our case which was an extradural intraspinal EES/pPNET, there has been no evident metastasis in 18 months follow-up.

Table 4: Summarizing the clinical findings of the cases in the two groups

	Motor deficit	Local pain	Gait disturbance	Radicular pain	Sphincter dysfunction	Myelopathy	Hydrocephalous
EES/pPNET	67 (71)	66 (70)	47 (50)	38 (40)	47 (50)	8 (9)	1 (1)
CNS-PNET	21 (84)	11 (44)	15 (60)	31 (33)	15 (60)	4 (16)	3 (2)

EES/pPNET: extraskelatal ES/peripheral primitive neuroectodermal tumors, CNS-PNET: Central nervous system-primitive neuroectodermal tumors, Figures in parentheses are in percentage

Table 5: Demonstrating the distribution of the lesion along the spine

	Cervical	Thoracic	Conus medularis	Lumbosacral		
				Cauda equina	Lumbar (epidural)	Sacral (epidural)
EES/pPNET	23 (22)	27 (26.5)	-	26 (25.5)	22 (21)	6 (5)
CNS-PNET	8 (31)	9 (34.5)	9 (34.5)	-	-	-

EES/pPNET: extraskelatal ES/peripheral primitive neuroectodermal tumors, CNS-PNET: Central nervous system-primitive neuroectodermal tumors, Figures in parentheses are in percentage

Table 6: Showing the rate of metastasis in different series

	CNS Metastasis			Distance Metastasis			
	Brain	Spine	Total	Lung	Bone	Multi organ	Total
EES/pPNET	9 (9)	13 (13)	18 (18)	11 (11)	7 (7)	5 (5)	23 (23)
CNS-PNET	7 (28)	8 (32)	12 (48)	0	0	1 (4)	1 (4)

EES/pPNET: extraskelatal ES/peripheral primitive neuroectodermal tumors, CNS-PNET: Central nervous system-primitive neuroectodermal tumors, Figures in parentheses are in percentage

Duration of follow-up for patients with primary intraspinal EES/pPNET and CNS-PNET was 20.5 ± 23.2 and 21.0 ± 23.3 months, respectively, in different series reported in the literature. One-year and 2-year survival rates of the patients (without considering modality of therapy) were not significantly different between the two tumor types (χ^2 , $P > 0.05$) [Table 7].

Among the 106 patients with primary intraspinal EES/pPNET who underwent surgery, 5 (5%) had only biopsy taken, 57 (54%) had subtotal, and 44 (41%) had total tumor excision. Eighty patients (78%) with primary intraspinal EES/pPNET had radiotherapy and 77 (75%) received chemotherapy as the adjuvant therapy. Of 27 patients with CNS-PNET, 10 (37%) cases had biopsy, 14 (52%) had subtotal, and 3 (11%) had total tumor resection. Eighteen patients with CNS-PNET (67%) underwent radiotherapy and 23 (85%) had chemotherapy after surgery. Among patients with primary intraspinal EES/pPNET, 64 cases received both radio- and chemotherapies after total/subtotal tumor resection. Fifteen patients with CNS-PNET were managed in a similar way. *We managed our case with gross total excision of the tumor and radiotherapy only.*

One-year survival rate of the patients who underwent chemo-radiation therapy after total or subtotal resection of the lesion was better than that of those who did not receive chemotherapy or radiotherapy or did not have total or subtotal resection. This difference was statistically significant for patients with CNS-PNET (χ^2 , $P < 0.05$) and marginally nonsignificant for primary intraspinal

EES/pPNET patients (χ^2 , $P = 0.056$). However, this difference was not repeated in 2-year survival rate in any of the tumor groups (χ^2 , $P > 0.05$) [Table 8]. Again, combination of chemo-radiation and total/subtotal surgery reduced the rate of distant metastasis in CNS-PNET patients (χ^2 , $P < 0.05$) but not in primary intraspinal EES/pPNET group (χ^2 , $P = 0.163$) [Table 9]. *We undertook radiotherapy as the adjuvant mode of therapy and have not encountered any sign of local recurrence or distant metastasis after 18 months follow-up.*

DISCUSSION

Pathology: The occurrence of CNS-PNET and primary intraspinal EES/pPNET in spine is unusual, and if it happens, the pathological distinction is difficult.^[69] The authors had adopted the general term of primary spinal PNET or spinal EES before 2000. Advances in the recent decade in cytogenetic and IHC methods have shown chromosomal translocations especially in t(11;22) (q24;q12) gene and CD99 expression to be characteristics for ES, while in CNS-PNET a normal chromosomal arrangement is observed and the tumor cells are negative for CD99 marker.^[6,24,39,74,75] In our review, only 75 cases out of 135 patients underwent IHC evaluations for CD99, which were mostly after 2000 [Tables 1 and 2]. All the 61 patients with primary intraspinal EES/pPNET were positive for CD99, but this happened in only 2 of 14 patients with CNS-PNET. Chromosomal studies were performed in only 20 of 135 patients reviewed from the literature [Tables 1 and 2]. Considering these findings,

Table 7: Survival rate in different series

	After 1 year follow-up (Alive/Total)	After 2 years follow-up (Alive/Total)
EES/pPNET	58/72 (80.6)	27/52 (51.9)
CNS-PNET	16/22 (72.7)	7/19 (36.8)

EES/pPNET: extraskelatal ES/peripheral primitive neuroectodermal tumors,
CNS-PNET: Central nervous system-primitive neuroectodermal tumors, Figures in parentheses are in percentage

Table 8: The rate of survival in different groups undergoing adjuvant therapies

	After 1 year follow-up (Alive/Total)		After 2 years follow-up (Alive/Total)	
	Surgery + CT + RT	Others	Surgery + CT + RT	Others
EES/pPNET	37/42 (88)	21/30 (70)	17/29 (59)	10/23 (44)
CNS-PNET	9/9 (100)	7/13 (54)	4/6 (67)	3/13 (23)

EES/pPNET: extraskelatal ES/peripheral primitive neuroectodermal tumors,
CNS-PNET: Central nervous system-primitive neuroectodermal tumors, Figures in parentheses are in percentage

Table 9: The rate of distant metastasis in different groups

	Surgery + CT + RT	Others
EES/pPNET	19/59 (32)	18/39 (46)
CNS-PNET	1/8 (12.5)	11/17 (65)

EES/pPNET: extraskelatal ES/peripheral primitive neuroectodermal tumors,
CNS-PNET: Central nervous system-primitive neuroectodermal tumors, Figures in parentheses are in percentage

CD99 has a high specificity for primary intraspinal EES/pPNET. This may obviate the need for chromosomal studies, though their application can be complementary. *The IHC and CD99 confirmed the presumptive diagnosis in our patient.*

Demography: It seems that primary intraspinal EES/pPNET is more prevalent than CNS-PNET in spine as their reported cases were four times more common than CNS-PNET patients. Contrary to the previous belief that primary intraspinal EES/pPNET and CNS-PNET are more common in childhood, our evaluations and analysis showed that less than one-sixth of primary intraspinal EES/pPNET and less than one-third of CNS-PNET occur in children younger than 10 years of age, and they both occur mostly in young adults. Both primary intraspinal EES/pPNET and CNS-PNET occur rarely after 50 years of age. CNS-PNET occurs equally in both sexes, but primary intraspinal EES/pPNET shows a male sex propensity.

Presentation: The most common symptom in both tumor groups is muscle weakness. However, sensory symptoms, local pain, and radiculopathy are more common in primary intraspinal EES/pPNET. The symptoms mimic spinal disc herniation in any case. The same problem happened in our patient who first underwent discectomy

while the tumor could hardly be diagnosed on MRI. Although CNS-PNET equally affects spine in different regions, around half of the primary intraspinal EES/pPNET cases happen in lumbar spine. Only five patients with sacral primary intraspinal EES/pPNET have been reported and they were all males. *Our case is the first female patient with sacral epidural primary intraspinal EES/pPNET.*

Clinical course: Primary intraspinal EES/pPNET and CNS-PNET follow completely different behavior regarding metastasis. Extra CNS metastasis in CNS-PNET is a rare event, while half of the patients developed metastasis to CNS during follow-up, which is the issue comparable with the medulloblastoma patients. Contrarily, CNS metastasis occurs in less than one-fifth of patients with primary intraspinal EES/pPNET, while extra CNS metastasis occurs frequently, with lung being the most common site, followed by the skeletal system. One-year survival is not different between the two tumor groups; however, two-year survival rate is slightly more in patients with primary intraspinal EES/pPNET.

Treatment options: No certain therapeutic protocol has been applied for all the patients with CNS-PNET or primary intraspinal EES/pPNET. This is mostly due to the limited number of the reported cases. Accordingly, primary intraspinal EES/pPNET and CNS-PNET of spine are treated as extraspinal ES and medulloblastoma, respectively. Surgical treatment is necessary to achieve diagnosis and decompression, which is usually followed by improvement of symptoms. Even though adjuvant chemotherapy is proposed both for ES and medulloblastoma, this was not performed in some of the reports mostly due to age limitations, early mortality, or lack of compliance of the patients. Our data analysis shows that chemotherapy improves 1- and 2-year survival rates after total or subtotal tumor resection in both primary intraspinal EES/pPNET and CNS-PNET patients, respectively. This difference was statistically significant only in 1-year survival rate of patients with CNS-PNET. Adjuvant chemotherapy may reduce CNS metastasis in cases with CNS-PNET [Table 9].

Prognosis: Primary intraspinal EES/pPNET and CNS-PNET are both aggressive malignant tumors leading to mortality within 2 years after diagnosis in nearly half and two-thirds of the patients, respectively. Age is one of the important prognostic factors in both tumors as survival reduces at both age extremes. However, survival did not show any differences regarding gender of the patients. It seems that total or subtotal tumor resection combined with both radiation and chemotherapy improves the outcome of the patients significantly.

CONCLUSION

The reported cases of undifferentiated small round cell tumors in the spine have increased in number in recent

years. Our review and analysis showed that CNS-PNET and EES/pPNET of spine have different clinical courses, necessitating further histopathologic evaluations including that of CD99 and t(11;22)(q24;q12) to distinguish these entities from each other. Tumor location is an important clue in differentiating the two, as CNS-PNETs are mostly intramedullary in contrast with EES/pPNETs which are often extramedullary.

Due to limited evidence regarding the therapeutic aspects of these tumors, no definite protocol can be formulated for their treatment and the best mode of therapy should be individualized for each case. However, our review supports the fact that total/subtotal tumor removal followed by adjuvant chemo-radiation is associated with the best clinical outcome.

Future studies should mainly focus on finding evidences denoting the best treatment strategies for these tumors. Autologous stem cell rescue besides adjuvant chemotherapy has been associated with prolonged survival in some reports,^[27,29,72] which can be the matter of further investigation in the future.

REFERENCES

- Akai T, Iizuka H, Kadaya S, Nojima T, Kohno M. Primitive neuroectodermal tumor in the spinal epidural space: Case report. *Neurol Med Chir (Tokyo)* 1998;38:508-11.
- Akyüz M, Demiral AN, Güner IE, Uçar T, Tuncer R. Primary primitive neuroectodermal tumor of cauda equina with intracranial seeding. *Acta Neurochir (Wien)* 2004;146:525-8.
- Albrecht CF, Weiss E, Schulz-Schaeffer WJ, Albrecht T, Fauser S, Wickboldt J, et al. Primary intraspinal primitive neuroectodermal tumor: Report of two cases and review of the literature. *J Neurooncol* 2003;61:113-20.
- Alexander HS, Koleda C, Hunn MK. Peripheral Primitive Neuroectodermal Tumor (pPNET) in the cervical spine. *J Clin Neurosci* 2010;17:259-61.
- Allam K, Sze G. MR of primary extraosseous Ewing sarcoma. *AJNR Am J Neuroradiol* 1994;15:305-7.
- Ambros IM, Ambros PF, Strehl S, Kovar H, Gadner H, Salzer-Kuntschik M. MIC2 is a specific marker for Ewing's sarcoma and peripheral primitive neuroectodermal tumors. Evidence for a common histogenesis of Ewing's sarcoma and peripheral primitive neuroectodermal tumors from MIC2 expression and specific chromosome aberration. *Cancer* 1991;67:1886-93.
- Angervall L, Enzinger FM. Extraskelatal neoplasm resembling Ewing's sarcoma. *Cancer* 1975;36:240-51.
- Athanassiadou F, Tragiannidis A, Kourti M, Papageorgiou T, Kotoula V, Kontopoulos V, et al. Spinal epidural extraskelatal Ewing sarcoma in an adolescent boy: A case report. *Pediatr Hematol Oncol* 2006;23:263-7.
- Aydin MV, Sen O, Ozel S, Kayaselcuk F, Caner H, Altinors N. Primary primitive neuroectodermal tumor within the spinal epidural space: Report of a case and review of the literature. *Neurol Res* 2004;26:774-7.
- Baum ES, Morgan ER, Dal Centro MC, West PM. Review of experience with primitive neuroectodermal tumors of childhood. In: Humphrey GB, Dehner LP, editors. *Pediatric Oncology I*. The Hague: Martinus Nijhoff; 1981. p. 239-42.
- Benesch M, Sperl D, von Bueren AO, Schmid I, von Hoff K, Warmuth-Metz M, et al. Primary central nervous system primitive neuroectodermal tumors (CNS-PNETs) of the spinal cord in children: Four cases from the German HIT database with a critical review of the literature. *J Neurooncol* 2011;104:279-86.
- Benmeir P, Sagi A, Hertzanu Y, Zirkin H, Rosenberg L, Peiser J, et al. Primary and secondary spinal epidural extraskelatal Ewing's sarcoma. Report of two cases and review of the literature. *Spine (Phila Pa 1976)* 1991;16:224-7.
- Bohn Sarmiento U, Aguiar Bujanda D, Camacho Galán R, Rivero Vera JC, Aguiar Morales J. Lumbar region intra-spinal primitive neuroectodermal tumor (PNET) combined with neurofibromatosis type I. *Clin Transl Oncol* 2005;7:464-7.
- Bozkurt G, Ayhan S, Turk CC, Akbay A, Soylemezoglu F, Palaoglu S. Primary extraosseous Ewing sarcoma of the cervical epidural space. Case illustration. *J Neurosurg Spine* 2007;6:192.
- Bruno LA, Rorke LB, Norris DG. Primitive neuroectodermal tumors of infancy and childhood. In: Humphrey GB, Dehner LP, editors. *Pediatric Oncology I*. The Hague: Martinus Nijhoff; 1981. p. 265-7.
- Cai C, Zhang Q, Shen C, Hu X. Primary intraspinal primitive neuroectodermal tumor: A case report and review of literature. *J Pediatr Neurosci* 2008;3:154-6.
- Chang SI, Tsai MC, Tsai MD. An unusual primitive neuroectodermal tumor in the thoracic epidural space. *J Clin Neurosci* 2010;17:261-3.
- Chen YC, Tang LM, Chen CJ, Jung SM, Chen ST. Intracranial hypertension as an initial manifestation of spinal neuroectodermal tumor. *Clin Neurol Neurosurg* 2005;107:408-11.
- Christie DR, Bilous AM, Carr PJ. Diagnostic difficulties in extraosseous Ewing's sarcoma: A proposal for diagnostic criteria. *Australas Radiol* 1997;41:22-8.
- De Tommasi A, De Tommasi C, Occhiogrosso G, Cimmino A, Parisi M, Sanguedolce F, et al. Primary intramedullary primitive neuroectodermal tumor (PNET): Case report and review of the literature. *Eur J Neurol* 2006;13:240-3.
- Delattre O, Zucman J, Melot T, Garau XS, Zucker JM, Lenoir GM, et al. The Ewing family of tumors--A subgroup of small round-cell tumors defined by specific chimeric transcripts. *N Engl J Med* 1994;331:294-9.
- Deme S, Ang LC, Skaf G, Rowed DW. Primary intramedullary primitive neuroectodermal tumor of the spinal cord: Case report and review of the literature. *Neurosurgery* 1997;41:1417-20.
- Demeocq F, Fonck Y, Legros M, Chazal J, Plagne R, Dauplat J. Extraskelatal Ewing's sarcoma. Anatomico-clinical study of a new case. *Pediatric* 1983;38:475-8. (Article in French)
- Dierick AM, Roels H, Langlois M. The immunophenotype of Ewing's sarcoma. An immunohistochemical analysis. *Pathol Res Pract* 1993;189:26-32.
- Dogan S, Leković GP, Theodore N, Horn EM, Eschbacher J, ReKate HL. Primary thoracolumbar Ewing's sarcoma presenting as isolated epidural mass. *Spine (Phila Pa 1976)* 2009;9:9-14.
- Dorfmueller G, Würtz FG, Umschaden HW, Kleinert R, Ambros PF. Intraspinal primitive neuroectodermal tumor: Report of two cases and review of the literature. *Acta Neurochir (Wien)* 1999;141:1169-75.
- Duan XH, Ban XH, Liu B, Zhong XM, Guo RM, Zhang F, et al. Intraspinal primitive neuroectodermal tumor: Imaging findings in six cases. *Eur J Radiol* 2011;80:426-31.
- Ellis JA, Rothrock RJ, Moise G, McCormick PC 2nd, Tanji K, Canoll P, et al. Primitive neuroectodermal tumors of the spine: A comprehensive review with illustrative clinical cases. *Neurosurg Focus* 2011;30:E1.
- Erkutlu I, Buyukhatipoglu H, Alptekin M, Ozsarac C, Buyukbese I, Gok A. Primary spinal epidural extraosseous Ewing's sarcoma mimicking a spinal abscess. *Pediatr Hematol Oncol* 2007;24:537-42.
- Fabre E, Guillemin R, Chretien F, Le Guerinel C, Duffau H. Peripheral primitive neuroectodermal tumor of the cauda equina in an elderly patient. Case report. *J Neurosurg Spine* 2006;5:68-71.
- Feng JF, Liang YM, Bao YH, Pan YH, Jiang JY. Multiple primary primitive neuroectodermal tumors within the spinal epidural space with non-concurrent onset. *J Int Med Res* 2008;36:366-70.
- Fink LH, Meriwether MW. Primary epidural Ewing's sarcoma presenting as a lumbar disc protrusion. Case report. *J Neurosurg* 1979;51:120-3.
- Fletcher CD, Unni KK, Mertens F. World Health Organization Classification of Tumors: Pathology and Genetics of Tumors of Soft Tissue and Bone. Lyon: IARC Press; 2002.
- Folpe AL, Goldblum JR, Rubin BP, Shehata BM, Liu W, Dei Tos AP, et al. Morphologic and immunophenotypic diversity in Ewing family tumors: A study of 66 genetically confirmed cases. *Am J Surg Pathol* 2005;29:1025-33.
- Freyer DR, Hutchinson RJ, McKeever PE. Primary primitive neuroectodermal tumor of the spinal cord associated with neural tube defect. *Pediatr Neurosci* 1989;15:181-7.
- Gandhi D, Goyal M, Belanger E, Modha A, Wolffe J, Miller W. Primary epidural Ewing's sarcoma: Case report and review of literature. *Can Assoc Radiol J* 2003;54:109-13.
- Gollard RP, Rosen L, Anson J, Mason J, Khoury J. Intramedullary PNET of the spine: Long-term survival after combined modality therapy and subsequent

- relapse. *J Pediatr Hematol Oncol* 2011;33:107-12.
38. Gurkanlar D, Korkmaz E, Gurler IE, Gokhan G, Kazan S. Multilevel primary intraspinal PNETs in an infant associated with hydrocephalus. *Turk Neurosurg* 2010;20:82-5.
 39. Gyure KA, Prayson RA, Estes ML. Extracerebellar primitive neuroectodermal tumors: A clinicopathologic study with bcl-2 and CD99 immunohistochemistry. *Ann Diagn Pathol* 1999;3:276-80.
 40. Han IH, Kuh SU, Chin DK, Kim KS, Jin BH, Cho YE. Surgical treatment of primary spinal tumors in the conus medullaris. *J Korean Neurosurg Soc* 2008;44:72-7.
 41. Haresh KP, Chinikkatti SK, Prabhakar R, Rishi A, Rath GK, Sharma DN, et al. A rare case of intradural extramedullary Ewing's sarcoma with skip metastasis in the spine. *Spinal Cord* 2008;46:582-4.
 42. Harimaya K, Oda Y, Matsuda S, Tanaka K, Chuman H, Iwamoto Y. Primitive neuroectodermal tumor and extraskeletal Ewing sarcoma arising primarily around the spinal column: Report of four cases and a review of the literature. *Spine (Phila Pa 1976)* 2003;28:E408-12.
 43. He SS, Zhao J, Han KW, Hou TS, Hussain N, Zhang SM. Primitive neuroectodermal tumor of lumbar spine: Case report. *Chin Med J (Engl)* 2007;120:844-6.
 44. Hisaoka M, Hashimoto H, Murao T. Peripheral primitive neuroectodermal tumor with ganglioneuroma-like areas arising in the cauda equina. *Virchows Arch* 1997;431:365-9.
 45. Hrabálek L, Kalita O, Swebisova H, Ehrmann J Jr, Hajduch M, Trojanec R, et al. Dumbbell-shaped peripheral primitive neuroectodermal tumor of the spine: Case report and review of the literature. *J Neurooncol* 2009;92:211-7.
 46. Hsieh CT, Chiang YH, Tsai WC, Sheu LF, Liu MY. Primary spinal epidural Ewing sarcoma: A case report and review of the literature. *Turk J Pediatr* 2008;50:282-6.
 47. Isefuku S, Seki M, Tajino T, Hakozaiki M, Asano S, Hojo H, et al. Ewing's sarcoma in the spinal nerve root: A case report and review of the literature. *Tohoku J Exp Med* 2006;209:369-77.
 48. Isotalo PA, Agbi C, Davidson B, Girard A, Verma S, Robertson SJ. Primary primitive neuroectodermal tumor of the cauda equina. *Hum Pathol* 2000;31:999-1001.
 49. Izycka-Swieszewska E, Debiec-Rychter M, Wasag B, Wozniak A, Gasecki D, Plata-Nazar K, et al. A unique occurrence of a cerebral atypical teratoid/rhabdoid tumor in an infant and a spinal canal primitive neuroectodermal tumor in her father. *J Neurooncol* 2003;61:219-25.
 50. Izycka-Swieszewska E, Stefanowicz J, Debiec-Rychter M, Rzepko R, Borowska-Lehman J. Peripheral primitive neuroectodermal tumor within the spinal epidural space. *Neuropathology* 2001;21:218-21.
 51. Jain A, Jalali R, Nadkarni TD, Sharma S. Primary intramedullary primitive neuroectodermal tumor of the cervical spinal cord. Case report. *J Neurosurg Spine* 2006;4:497-502.
 52. Jaksche H, Wöckel W, Wernert N. Primary spinal medulloblastomas? *Neurosurg Rev* 1988;11:259-65.
 53. Jingyu C, Jinning S, Hui M, Hua F. Intraspinal primitive neuroectodermal tumors: Report of four cases and review of the literature. *Neurol India* 2009;57:661-8.
 54. Kadri PA, Mello PM, Olivera JG, Braga FM. Primary lumbar epidural Ewing's sarcoma: Case report. *Arq Neuropsiquiatr* 2002;60:145-9. (Article in Portuguese)
 55. Kampman WA, Kros JM, De Jong TH, Lequin MH. Primitive neuroectodermal tumors (PNETs) located in the spinal canal: The relevance of classification as central or peripheral PNET: Case report of a primary spinal PNET occurrence with a critical literature review. *J Neurooncol* 2006;77:65-72.
 56. Kaspers GJ, Kamphorst W, van de Graaff M, van Alphen HA, Veerman AJ. Primary spinal epidural extrasosseous Ewing's sarcoma. *Cancer* 1991;68:648-54.
 57. Kennedy JG, Eustace S, Caulfield R, Fennelly DJ, Hurson B, O'Rourke KS. Extraskeletal Ewing's sarcoma: A case report and review of the literature. *Spine (Phila Pa 1976)* 2000;25:1996-9.
 58. Kepes JJ, Belton K, Roessmann U, Ketcherside WJ. Primitive neuroectodermal tumors of the cauda equina in adults with no detectable primary intracranial neoplasm--Three case studies. *Clin Neuropathol* 1985;4:1-11.
 59. Kiatsoontorn K, Takami T, Ichinose T, Chokyu I, Tsuyuguchi N, Ohsawa M, et al. Primary epidural peripheral primitive neuroectodermal tumor of the thoracic spine. *Neurol Med Chir (Tokyo)* 2009;49:542-5.
 60. Kim SW, Shin H. Primary intradural extrasosseous Ewing's sarcoma. *J Korean Neurosurg Soc* 2009;45:179-81.
 61. Kim YW, Jin BH, Kim TS, Cho YE. Primary intraspinal primitive neuroectodermal tumor at conus medullaris. *Yonsei Med J* 2004;45:533-8.
 62. Kinsella TJ. Extraskeletal Ewing's sarcoma. *J Clin Oncol* 1993;11:489.
 63. Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumors. *Brain Pathol* 1993;3:255-68.
 64. Kleihues P, Cavenee WK. World Health Organization Classification of Tumors: Pathology and Genetics: Tumors of the Nervous System. Lyon: IARC Press; 1997.
 65. Kleihues P, Cavenee WK. World Health Organization Classification of Tumors: Pathology and Genetics: Tumors of the Nervous System. 2nd ed. Lyon: IARC Press; 2000.
 66. Klimo P Jr, Codd PJ, Grier H, Goumnerova LC. Primary pediatric intraspinal sarcomas. Report of 3 cases. *J Neurosurg Pediatr* 2009;4:222-9.
 67. Kogawa M, Asazuma T, Iso K, Koike Y, Domoto H, Aida S, et al. Primary cervical spinal epidural Extra-osseous Ewing's sarcoma. *Acta Neurochir (Wien)* 2004;146:1051-3.
 68. Koot RW, Hennevelde HT, Albrecht KW. [Two children with unusual causes of torticollis: Primitive neuroectodermal tumor and Grisel's syndrome.]. *Ned Tijdschr Geneesk* 1998;142:1030-3. (Article in Dutch)
 69. Kosnik EJ, Boesel CP, Bay J, Sayers MP. Primitive neuroectodermal tumors of the central nervous system in children. *J Neurosurg* 1978;48:741-6.
 70. Koudelová J, Kunesová M, Koudela K Jr, Matejka J, Novák P, Prausová J. [Peripheral primitive neuroectodermal tumor--PNET.]. *Acta Chir Orthop Traumatol Cech* 2006;73:39-44. (Article in Czech)
 71. Kumar R, Reddy SJ, Wani AA, Pal L. Primary spinal primitive neuroectodermal tumor: Case series and review of the literature. *Pediatr Neurosurg* 2007;43:1-6.
 72. Kwon OK, Wang KC, Kim CJ, Kim IO, Chi JG, Cho BK. Primary intramedullary spinal cord primitive neuroectodermal tumor with intracranial seeding in an infant. *Childs Nerv Syst* 1996;12:633-6.
 73. Liu HM, Yang WC, Garcia RL, Noh JM, Malhotra V, Leeds NE. Intraspinal primitive neuroectodermal tumor arising from the sacral spinal nerve root. *J Comput Tomogr* 1987;11:350-4.
 74. Lombart-Bosch A, Machado I, Navarro S, Bertoni F, Bacchini P, Alberghini M, et al. Histological heterogeneity of Ewing's sarcoma/PNET: An immunohistochemical analysis of 415 genetically confirmed cases with clinical support. *Virchows Arch* 2009;455:397-411.
 75. Lombart-Bosch A, Navarro S. Immunohistochemical detection of EWS and FLI-1 proteins in Ewing sarcoma and primitive neuroectodermal tumors: Comparative analysis with CD99 (MIC-2) expression. *Appl Immunohistochem Mol Morphol* 2001;9:255-60.
 76. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK. WHO Classification of Tumors of the Central Nervous System. 4th ed. Lyon: IARC; 2007.
 77. Machin Valtueña M, Garcia-Sagredo JM, Muñoz Villa A, Lozano Giménez C, Aparicio Meix JM. 18q-syndrome and extraskeletal Ewing's sarcoma. *J Med Genet* 1987;24:426-8.
 78. Mahoney JP, Ballinger WE Jr, Alexander RW. So-called extraskeletal Ewing's sarcoma. Report of a case with ultrastructural analysis. *Am J Clin Pathol* 1978;70:926-31.
 79. Martínez-Quiñones JV, de Antonio A, Hernandez G, Moratinos P, Hijosa M. Primitive neuroectodermal tumor of the cauda equina. Report of a case. *Neurocirugía (Astur)* 2002;13:46-9. (Article in Spanish)
 80. Mawrin C, Synowitz HJ, Kirches E, Kutz E, Dietzmann K, Weis S. Primary primitive neuroectodermal tumor of the spinal cord: Case report and review of the literature. *Clin Neurol Neurosurg* 2002;104:36-40.
 81. McDermott VG, el-Jabbour JN, Sellar RJ, Bell J. Primitive neuroectodermal tumor of the cauda equina. *Neuroradiology* 1994;36:228-30.
 82. Meltzer CC, Townsend DW, Kottapally S, Jadali F. FDG imaging of spinal cord primitive neuroectodermal tumor. *J Nucl Med* 1998;39:1207-9.
 83. Miller DC, Rorke LB, Weinberg J, Allen JC, Epstein FJ. Histopathologic diagnoses of intramedullary spinal cord tumors in children. *J Neuropathol Exp Neurol* 1997;56:607.
 84. Mobley BC, Roulston D, Shah GV, Bijwaard KE, McKeever PE. Peripheral primitive neuroectodermal tumor/Ewing's sarcoma of the craniospinal vault: Case reports and review. *Hum Pathol* 2006;37:845-53.
 85. Mottl H, Koutecky J. Treatment of spinal cord tumors in children. *Med Pediatr Oncol* 1997;29:293-5.
 86. Mukhopadhyay P, Gairola M, Sharma M, Thulkar S, Julka P, Rath G. Primary spinal

- epidural extraosseous Ewing's sarcoma: Report of five cases and literature review. *Australas Radiol* 2001;45:372-9.
87. Musahl V, Rihn JA, Fumich FE, Kang JD. Sacral intraspinal extradural primitive neuroectodermal tumor. *Spine J* 2008;8:1024-9.
 88. N'Golet A, Pasquier B, Pasquier D, Lachard A, Couderc P. Extraskeletal Ewing's sarcoma of the epidural space. A report of two new cases with literature review (author's transl). *Arch Anat Cytol Pathol* 1982;30:10-3. (Article in French)
 89. Nutman A, Postovsky S, Zaidman I, Elhasid R, Vlodavsky E, Kreiss Y, et al. Primary intraspinal primitive neuroectodermal tumor treated with autologous stem cell transplantation: Case report and review of the literature. *Pediatr Hematol Oncol* 2007;24:53-61.
 90. Ogasawara H, Kiya K, Kurisu K, Muttaqin Z, Uozumi T, Sugiyama K, et al. Intracranial metastasis from a spinal cord primitive neuroectodermal tumor: Case report. *Surg Neurol* 1992;37:307-12.
 91. Otero-Rodríguez A, Hinojosa J, Esparza J, Muñoz MJ, Iglesias S, Rodríguez-Gil Y, et al. Purely intramedullary spinal cord primitive neuroectodermal tumor: Case report and review of the literature. *Neurocirugia (Astur)* 2009;20:381-7.
 92. Ozdemir N, Usta G, Minoglu M, Erbay AM, Bezircioglu H, Tunakan M. Primary primitive neuroectodermal tumor of the lumbar extradural space. *J Neurosurg Pediatr* 2008;2:215-21.
 93. Ozturk E, Mutlu H, Sonmez G, Vardar Aker F, Cinar Basekim C, Kizilkaya E. Spinal epidural extraskeletal Ewing sarcoma. *J Neuroradiol* 2007;34:63-7.
 94. Papadatos D, Albrecht S, Mohr G, del Carpio-O'Donovan R. Exophytic primitive neuroectodermal tumor of the spinal cord. *AJNR Am J Neuroradiol* 1998;19:787-9.
 95. Perry R, Gonzales I, Finlay J, Zacharoulis S. Primary peripheral primitive neuroectodermal tumors of the spinal cord: Report of two cases and review of the literature. *J Neurooncol* 2007;81:259-64.
 96. Priest J, Dehner LP, Sung JH, Nesbit ME. Primitive neuroectodermal tumors. Embryonal gliomas of childhood. A clinicopathologic study of 12 cases. In: Humphrey GB, Dehner LP, editors. *Pediatric oncology*. The Hague: Martinus Nijhoff; 1981. p. 247-64.
 97. Reihani-Kermani H, Amizadeh B. Primary intraspinal primitive neuroectodermal tumors: Report of a case. *Arch Iran Med* 2002;5:262-6.
 98. Ruelle A, Boccardo M. Epidural extraskeletal Ewing's sarcoma simulating a herniated disk. Clinical case. *Riv Neurol* 1986;56:183-8. (Article in Italian)
 99. Sahu JK, Seth R, Karak A, Thavaraj V, Kabra SK. Primitive neuroectodermal tumor presenting as cauda equina syndrome. *Indian J Med Paediatr Oncol* 2007;28:34-7.
 100. Scheithauer BW, Egbert BM. Ewing's sarcoma of the spinal epidural space: Report of two cases. *J Neurol Neurosurg Psychiatry* 1978;41:1031-5.
 101. Sevick RJ, Johns RD, Curry BJ. Primary spinal primitive neuroectodermal tumor with extraneural metastases. *AJNR Am J Neuroradiol* 1987;8:1151-2.
 102. Sharma BS, Khosla VK, Banerjee AK. Primary spinal epidural Ewing's sarcoma. *Clin Neurol Neurosurg* 1986;88:299-302.
 103. Shin JH, Lee HK, Rhim SC, Cho KJ, Choi CG, Suh DC. Spinal epidural extraskeletal Ewing sarcoma: MR findings in two cases. *AJNR Am J Neuroradiol* 2001;22:795-8.
 104. Siami-Namini K, Shuey-Drake R, Wilson D, Francel P, Perry A, Fung KM. A 15-year-old female with progressive myelopathy. *Brain Pathol* 2005;15:265-7.
 105. Simonati A, Vio M, Iannucci AM, Bricolo A, Rizzuto N. Lumbar epidural Ewing sarcoma. Light and electron microscopic investigation. *J Neurol* 1981;225:67-72.
 106. Smith DR, Hardman JM, Earle KM. Metastasizing neuroectodermal tumors of the central nervous system. *J Neurosurg* 1969;31:50-8.
 107. Spaziante R, de Divitiis E, Giamundo A, Gambardella A, Di Prisco B. Ewing's sarcoma arising primarily in the spinal epidural space: Fifth case report. *Neurosurgery* 1983;12:337-41.
 108. Tefft M, Vawter GF, Mitus A. Paravertebral: "Round cell" tumors in children. *Radiology* 1969;92:1501-9.
 109. Theeler BJ, Keylock J, Yoest S, Forouhar M. Ewing's sarcoma family tumors mimicking primary central nervous system neoplasms. *J Neurol Sci* 2009;284:186-9.
 110. Uesaka T, Amano T, Inamura T, Ikezaki K, Inoha S, Takamatsu M, et al. Intradural, extramedullary spinal Ewing's sarcoma in childhood. *J Clin Neurosci* 2003;10:122-5.
 111. Virani MJ, Jain S. Primary intraspinal primitive neuroectodermal tumor (PNET): A rare occurrence. *Neurol India* 2002;50:75-80.
 112. Wasserberg J, Al-Sarraj S, Bridges LR. Peripheral neuroepithelioma presenting as a spinal cord tumor. *Br J Neurosurg* 1994;8:497-9.
 113. Weber DC, Rutz HP, Lomax AJ, Schneider U, Lombriser N, Zenhausem R, et al. First spinal axis segment irradiation with spot-scanning proton beam delivered in the treatment of a lumbar primitive neuroectodermal tumor. Case report and review of the literature. *Clin Oncol (R Coll Radiol)* 2004;16:326-31.
 114. Weil RJ, Zhuang Z, Pack S, Kumar S, Helman L, Fuller BG, et al. Intramedullary Ewing sarcoma of the spinal cord: Consequences of molecular diagnostics. Case report. *J Neurosurg* 2001;95 Suppl 2:270-5.
 115. Woestenborghs H, Debiec-Rychter M, Renard M, Demaerel P, Van Calenberghe F, Van Gool S, et al. Cytokeratin-positive meningeal peripheral PNET/Ewing's sarcoma of the cervical spinal cord: Diagnostic value of genetic analysis. *Int J Surg Pathol* 2005;13:93-7.
 116. Yavuz AA, Yaris N, Yavuz MN, Sari A, Reis AK, Aydin F. Primary intraspinal primitive neuroectodermal tumor: Case report of a tumor arising from the sacral spinal nerve root and review of the literature. *Am J Clin Oncol* 2002;25:135-9.