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
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 an 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.\(^9\) The classification of tumors of CNS published by World Health Organization (WHO) in 1993 designated other cerebral medulloblastoma-like tumors as supratentorial PNET.\(^13,65,64\) 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

| Author            | Year | Age/Sex | Location of Tumor | Treatment | Follow-up (month) | Out come | CD99 | CD99 t (11:22) |
|-------------------|------|---------|-------------------|-----------|-------------------|----------|------|----------------|
| Kosnic et al.     | 1978 | <10y/NA | Conus Medullaris  | STR/CT/RT | <12               | Dead     | NA   | NA             |
| Jackche et al.    | 1988 | 15y/F   | Conus Medullaris  | STR/CT/RT | 18                | Dead     | NA   | NA             |
| Freyer et al.     | 1989 | 7y/M    | T4 – S3           | Biopsy/CT/RT | 20         | Dead     | NA   | NA             |
| Kwon et al.       | 1996 | 3m/F    | T7 – L5           | Biopsy/CT | 15 Days           | Dead     | NA   | NA             |
| Deme et al.       | 1997 | 22y/F   | Conus Medullaris  | STR/CT/RT | 15                | Alive    | NA   | NA             |
| Mottle et al.     | 1997 | <17y/F  | C3 – L2           | Biopsy/CT/RT | NA           | NA       | NA   | NA             |
| Miller et al.     | 1997 | NA      | NA                | NA        | NA                | NA       | NA   | NA             |
| Miller et al.     | 1997 | NA      | NA                | NA        | NA                | NA       | NA   | NA             |
| Meltzer et al.    | 1998 | 25y/M   | C3 – Conus Medullaris | STR/CT/RT | 60              | Dead     | NA   | NA             |
| Papdatos et al.   | 1998 | 23y/F   | T10 – T11         | STR/CT/RT | 12               | Alive    | NA   | NA             |
| Weil et al.       | 2001 | 21y/M   | T10 – T11         | STR/CT/RT | 30               | Alive    | +    | +              |
| Mawrin et al.     | 2002 | 69y/M   | C7 – T3           | STR/RT    | 3                 | Dead     | NA   | NA             |
| Mawrin et al.     | 2002 | 38y/M   | NA                | STR/CT/RT | 18               | Dead     | NA   | NA             |
| Albrecht et al.   | 2003 | 29y/F   | T2 & T10 – T11    | Biopsy/CT/RT | 17         | Dead     | _    | _              |
| Chen et al.       | 2005 | 19y/F   | Cervico-thoracic  | Biopsy/RT | 9                 | Dead     | _    | NA             |
| Kampman et al.    | 2006 | 3y/M    | C2 – C6           | STR       | 1                 | Dead     | _    | _              |
| Jain et al.       | 2006 | 54y/F   | C2 – C5           | STR/RT    | NA                | NA       | _    | _              |
| Detommasi et al.  | 2006 | 38y/M   | T1 – T3           | Biopsy/CT | 18               | Dead     | _    | _              |
| Kumar et al.      | 2007 | 9y/F    | T9 – L1           | TTR/CT/RT | 18               | Alive    | NA   | NA             |
| Kumar et al.      | 2007 | 18y/M   | Cervico-thoracic  | Biopsy/CT/RT | 6           | Alive    | _    | _              |
| Han et al.        | 2008 | 17y/M   | Conus Medullaris  | STR/CT/RT | 24               | Dead     | NA   | NA             |
| Han et al.        | 2008 | 40y/F   | Conus Medullaris  | TTR/CT/RT | 8                | Alive    | NA   | NA             |
| Oto-Rodriguez et al. | 2009 | 1.5y/M | T3 – T10         | STR/CT    | 6                 | Alive    | _    | _              |
| Benesh et al.     | 2010 | 1.5y/F  | Medulla Oblongata – T3 | TTR/CT | 6                | Dead     | _    | _              |
| Benesh et al.     | 2010 | 14.5y/F | C2 – C1          | STR/CT/RT | 44               | Alive    | _    | _              |
| Benesh et al.     | 2010 | 10m/F   | T10 – L2         | Biopsy/CT | 6                | Dead     | _    | _              |
| Benesh et al.     | 2010 | 2y/M    | T7 – T10         | Biopsy/CT/RT | 40          | Alive    | _    | _              |
| Ellis et al.      | 2011 | 27y/F   | C5 – C6           | STR/CT    | 28               | Alive    | _    | _              |
| Gollard et al.    | 2011 | 27y/F   | T5 – T11         | Biopsy/CT/RT | 132        | Alive    | _    | _              |

CT: Chemo therapy, F: Female, M: Male, NA: Not Available, RT: Radiotherapy, STR: Sub-total tumor resection, TTR: T otal tumor resection, y: year
one of the childhood tumors mostly affecting skeletal tissues.[63,108] 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).[67,84,109] 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 \textit{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 buttoc. 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 homogenously 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 \textit{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.
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 ($\chi^2$) 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 [1-5,7-9,12-14,16,17,19,23,25-32,36,38,41-50,52-54,56-62,66-68,70,71,73,75-79,81,84,86-90,92,93,95,97-113,115,116] 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 ($\chi^2$, $P > 0.05$). 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 et al.          | 106              | 1969 | 24 y/M  | Cauda Equina      | STR/RT    | 10               | Dead    | NA             |
| Tefft et al.          | 108              | 1969 | 6 y/F   | L4/ Extradural    | STR/RT/CT | 48               | Dead    | NA             |
| Angervali et al.      | 7                | 1975 | 17 y/M  | S1-S2/ Extradural | TTR       | 1                | Dead    | NA             |
| Angervali et al.      | 7                | 1975 | 20 y/M  | T2-T5/ Extradural | STR/RT/CT | 12               | Dead    | NA             |
| Angervali et al.      | 7                | 1975 | 18 y/F  | L5/ Extradural    | STR/RT/CT | 6                | Dead    | NA             |
| Scheithauer et al.    | 100              | 1978 | 18 y/M  | L1/ Extradural    | TTR/RT/CT | 16               | Alive   | NA             |
| Scheithauer et al.    | 100              | 1978 | 27 y/F  | T4-T6/ Extradural | STR/RT/CT | 132              | Alive   | NA             |
| Mahoney et al.        | 78               | 1978 | 23 y/M  | S1/ Extradural    | Biopsy/RT/CT | 12   | Dead    | NA             |
| Fink et al.           | 32               | 1979 | 19 y/M  | L2-L3/ Extradural | STR/RT/CT | 12               | Alive   | NA             |
| Simonati et al.       | 105              | 1981 | 13 y/M  | L3/ Extradural    | TTR/RT/CT | 15               | Alive   | NA             |
| N’Golet et al.        | 88               | 1982 | 29 y/M  | T1-T3/ Extradural | TTR/RT/CT | 6                | Alive   | NA             |
| N’Golet et al.        | 88               | 1982 | 47 y/F  | L4/ Extradural    | TTR/RT/CT | 4                | Dead    | NA             |
| Spaziano et al.       | 107              | 1983 | 10 y/M  | L4-L5/ Extradural | STR/RT/CT | 15               | Dead    | NA             |
| Demeocq et al.        | 23               | 1983 | 16 y/F  | L3-L4/ Extradural | STR/CT    | NA               | NA      | NA             |
| Kepes et al.          | 58               | 1985 | 24 y/M  | Cauda Equina      | TTR/RT/CT | 18               | Dead    | NA             |
| Kepes et al.          | 58               | 1985 | 56 y/M  | Cauda Equina      | STR/RT    | 36               | Alive   | NA             |
| Kepes et al.          | 58               | 1985 | 39 y/M  | Cauda Equina      | STR/RT    | 42               | Dead    | NA             |
| Ruelle et al.         | 98               | 1986 | 17 y/M  | L3-L4/ Extradural | STR/RT/CT | 9                | Dead    | NA             |
| Sharma et al.         | 102              | 1986 | 18 y/M  | T10/ Extradural   | STR/RT/CT | 42               | Dead    | NA             |
| Machin Valtuena et al.| 77               | 1987 | 4 y/M   | L1/ Extradural    | TTR       | 5                | Dead    | NA             |
| Liu et al.            | 73               | 1987 | 26 y/F  | L5-S1/ Extradural | STR/RT    | 6                | Alive   | NA             |
| Sevich et al.         | 101              | 1987 | 26 y/M  | C2-C3/Intradural-Extradural | TTR/RT | 36 | Dead | NA |
| Jaksche et al.        | 52               | 1988 | 26 y/M  | T8-L2/ Intradural-Extradural | STR/RT/CT | 36 | Dead | NA |
| Benmeir et al.        | 12               | 1991 | 16 y/F  | T8-T10/ Extradural | TTR/RT/CT | 6               | Alive   | NA             |
| Kaspers et al.        | 56               | 1991 | 7 y/M   | T12-L1/ Extradural | STR/CT    | 40               | Alive   | NA             |
| Ogasawara et al.      | 90               | 1992 | 16 y/F  | Cauda Equina      | STR/RT/CT | 29               | Alive   | NA             |
| Kinsella et al.       | 62               | 1993 | 14 y/F  | NA                | STR/RT/CT | 48               | Alive   | NA             |
| Mc Dermott et al.     | 81               | 1994 | 47 y/M  | Cauda Equina      | Biopsy/RT/CT | 16   | Dead | NA |
| Wasserberg et al.     | 112              | 1994 | 41 y/M  | T1-T7/ Intradural-Extradural | TTR | 36 | Alive | NA |
| Allam et al.          | 5                | 1994 | 15 y/F  | T12-L2/ Extradural | Biopsy/NA | NA | NA | NA |
| Christie et al.       | 19               | 1997 | 36 y/F  | Lumbar/ Extradural | STR/RT    | 96               | Dead    | NA             |
| Hisoaka et al.        | 44               | 1997 | 14 y/M  | Cauda Equina      | STR       | 3                | Alive + | + |
| Koot et al.           | 68               | 1998 | 2 y/F   | C1-C6/ Intradural-Extradural | STR | 3 Days | Dead | NA |
| Akai et al.           | 1                | 1998 | 4 y/M   | T8-T9/ Extradural | TTR/RT/CT | 76               | Alive   | NA             |
| Dorfmuller et al.     | 26               | 1999 | 17 y/M  | L3-L4/ Extradural | TTR/RT/CT | 23               | Alive   | +             |
| Isotalo et al.        | 48               | 2000 | 52 y/M  | Cauda Equina      | STR/RT    | 12               | Alive   | +             |
| Kennedy et al.        | 57               | 2000 | 24 y/M  | C1-C5/ Extradural | STR/RT/CT | 13               | Alive   | NA             |
| Izycha-swieszewka et al.| 50             | 2001 | 13 y/F  | C7-T11/ Extradural | Biopsy/RT/CT | 31   | Alive | + |
| Shin et al.           | 103              | 2001 | 38 y/M  | C5-C7/ Extradural | STR/CT    | 17               | Alive   | +             |
| Shin et al.           | 103              | 2001 | 22 y/F  | C7-T1/ Extradural | STR/CT    | 48               | Alive   | +             |
| Mukhopadhyay et al.   | 86               | 2001 | 29 y/F  | C3-C5/ Extradural | STR/RT/CT | 30               | Alive   | +             |
| Mukhopadhyay et al.   | 86               | 2001 | 18 y/M  | T8/ Extradural    | STR/RT/CT | 18               | Alive   | +             |
| Mukhopadhyay et al.   | 86               | 2001 | 22 y/M  | L5-S1/ Extradural | Biopsy/RT/CT | 15   | Alive | + |
| Mukhopadhyay et al.   | 86               | 2001 | 31 y/M  | L3-L4/ Extradural | STR/RT/CT | 32               | Alive   | +             |
| Mukhopadhyay et al.   | 86               | 2001 | 13 y/M  | C3-C5/ Extradural | STR/RT/CT | 11               | Alive   | +             |

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

Contd...
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 ($\chi^2$, $P > 0.05$). 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.
Pathology: The occurrence of CNS-PNET and primary intraspinal EES/pPNET in spine is unusual, and if it happens, the pathological distinction is difficult. 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 ES, while in CNS-PNET a normal chromosomal arrangement is observed and the tumor cells are negative for ES. 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**

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 (χ², 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 (75%) 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 (χ², P < 0.05) and marginally nonsignificant for primary intraspinal EES/pPNET patients (χ², P = 0.056). However, this difference was not repeated in 2-year survival rate in any of the tumor groups (χ², P > 0.05) [Table 8]. Again, combination of chemo-radiation and total/subtotal surgery reduced the rate of distant metastasis in CNS-PNET patients (χ², P < 0.05) but not in primary intraspinal EES/pPNET group (χ², P = 0.163) [Table 9].

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

|                | Motor deficit | Local pain | Gait disturbance | Radicular pain | Sphincter dysfunction | Myelopathy | Hydrocephalus |
|----------------|--------------|------------|-----------------|----------------|-----------------------|------------|---------------|
| 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: extraskeletal ES/peripheral primitive neuroectodermal tumor, CNS-PNET: Central nervous system-primitive neuroectodermal tumor, Figures in parentheses are in percentage.

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

|                | Cervical | Thoracic | Conus medularis | Lumbosacral |
|----------------|----------|----------|-----------------|-------------|
|                |          |          |                 |             |
| EES/pPNET      | 23 (22)  | 27 (26.5)| -               | 26 (25.5)   |
| CNS-PNET       | 8 (31)   | 9 (34.5) | 9 (34.5)        | 22 (21)     |

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

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,
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 extraspatial 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 intradural 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.

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