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Case Report

Primary Ewing Sarcoma in Spinal Epidural Space: Report of Three Cases and Review of the Literature

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Summary

Ewing sarcoma (ES) is the most common malignant bone tumor in children younger than 10 years of age. Extraosseous ES (EES) arising from the spinal epidural space is extremely rare. We aimed to report herein three cases of primary spinal epidural EES and to review the related literature. We report our experience with three cases of primary spinal epidural EES in a single institution (aged 34, 14, and 65 years). The patients were admitted with complaints of weakness of the lower extremities and urinary retention. Magnetic resonance imaging (MRI) showed an epidural mass with cord compression at T4-T6, L2-L3 and T7-T8 levels, respectively. All three patients underwent laminectomy; total resection of the epidural mass was performed in two patients and gross total resection in one patient. Immunohistochemical examinations revealed ES. All patients underwent chemotherapy and radiotherapy after surgery. No evidence of recurrence or metastasis was detected after 18 and 16 months, respectively, for the first two cases. In the third patient, gross total resection was performed due to tumor infiltration and invasion to the surrounding tissue, and residual tumor in the surrounding tissue was noted on MRI for the 14-month follow-up period.

Key words: Ewing Sarcoma,Primary, Spinal Epidural

Primer Spinal Epidural Ewing Sarkoma: Üç Olgu Sunumu ve Literatürün Gözden Geçirilmesi

Özet

Ewing sarkoma (ES) 10 yaş altı çocuklarda en sık görülen malign kemik tümörüdür. Spinal epidural mesafeden kaynaklanan ekstraosseus ES (ESS) oldukça nadirdir. Biz burada primer spinal epidural ESS tanısı alan üç vakayı sunmayı ve litaretürü gözden geçirmeyi amaçladık. Tek klinikte tedavi edilen primer spinal epidural ESS tanısı alan üç vakalık deneyimimizi sunuyoruz. Yaşları sırasıyla 34, 14,65 olan hastalar alt ekstremite kuvvetsizliği ve idrar retansiyonu bulguları ile hastanemize başvurmuşlardır. Magnetik rezonans görüntülemede (MRG) sırası ile T4-T6, L2-L3 ve T-T8 seviyelerinde spinal kord kompresyonu yapan epidural kitle tespit edilmiştir. Üç hastaya da dekompresif laminektomi yapılmıştır. İki hastada epidural kitle total çıkartılırken bir hastada kitle gros total çkartılmıştır. İmmunohistokimyasal incelemelerle ES tanısı konulmuştur. Tüm vakalar cerrahi sonrası kemoterapi ve radyoterapi tedavisi görmüşlerdir. İlk iki vaka için sırasıyla 18 ve 16 aylık

takiplerde rezidü yada rekürens gözlenmezken çevre dokulara tümör ünvazyonu ve infiltrasyonuna bağlı gros total rezeksiyon yapılan üçüncü hastada 14 aylık takipler sonrasında MRG'de çevre dokularda rezidü tumör dokusu saptanmıştır. Primer spinal epidural ESS vakalarında total rezeksiyon sonrası kemoterapi ve radyaterapi en etkili tedavi şekli olarak önerilmektedir.

Anahtar Kelimeler: Ewing Sarkoma,Primer, Spinal Epidural

INTRODUCTION

Ewing sarcoma (ES) is the most common malignant bone tumor in children younger than 10 years of age and is characterized histologically by small round blue cells with varying degree of neuroectodermal differentiation[1-6,10,12,24,33-38,43-51]. It mostly arises in the long bones and pelvis, while the hands, feet, vertebral bones, and soft tissue are affected considerably less often[1,6,7,13-22,40-44]. Extraosseous ES (EES) was identified by Tefft in 1969[47]. Osseous ES, EES, and peripheral primitive neuroectodermal tumors (pPNET) are generally known today as ES family tumors. Primary spinal PNET and/or spinal extraskeletal ES family tumors are rare lesions appearing in the spinal extradural space[4,5,6,9,12,13,14,25-30,32,40]. EES arising from the spinal epidural space is extremely rare, and to date, only 63 cases of primary EES arising in the spinal epidural space have been reported in the literature. We aimed to report herein our experience with three cases of primary spinal epidural EES in a single institution, seen between January 2012 and July 2013. We describe the clinical presentation and therapeutic strategies, together with a brief review of the literature.

CASE PRESENTATION

Case 1

A 34-year-old female was admitted to our hospital emergency department with complaints of weakness of both lower extremities for 12 hours before admission. Her medical history revealed no other complaint except for back pain for four months. The neurological examination revealed paraparesis muscle power strength score of 2/5 and hypoesthesia below the thoracal (T)6 level. Laboratory examinations revealed no remarkable abnormality. Magnetic resonance imaging (MRI) showed a well-circumscribed posterior extradural mass with cord compression from T4-T6 level (Fig. 1A and 1B). The patient underwent immediate T4-T5-T6 laminectomy, and total resection of a vascular, dark blue-purple, solid epidural mass was performed. Screening for metastasis and primary tumor was done, and neither primary tumor nor metastasis was detected elsewhere in the body. Immunohistochemical examinations revealed a malignant, diffuse homogeneous, small round cell tumor with uniform nuclei and rare rosette formation, consistent with ES. Tumor cells were extensively positive for CD99(Fig. 2) and vimentin, but negative for neuron specific enolase (NSE), CD56, CD20, CD3, synaptophysin, glial fibrillary acidic protein (GFAP), S100, desmin, anti-endomysial antibodies (EMA), and leukocyte common antigen (LCA). Ki-67 proliferation index was approximately 70%. Postoperatively, the patient's paraparesis improved totally, and she was discharged without any complication. The patient received sequential chemotherapy with vincristine, doxorubicin, cyclophosphamide, mesna, ifosfamide, and etoposide, and 4500 cGY tomotherapy in total. She first underwent a multiagent chemotherapy regimen, and thereafter, radiation therapy was delivered in 200 cGY fractioned doses daily. No evidence of recurrence or metastasis was detected after 18 months of follow-up.

Case 2

A 14-year-old previously healthy male was referred to our clinic with complaints of

low back pain, progressive gait disturbance, urinary retention, and weakness of both lower extremities for 20 days before admission. The neurological examination revealed paraparesis muscle power strength score of 3/5 proximally and 2/5 distally, numbness of both lower extremities, increased deep tendon reflexes bilaterally, and presence of the Babinski sign was clearly identified. Laboratory examinations revealed no remarkable contribution. MRI showed one solitary well-circumscribed posterior extradural mass with severe spinal cord compression from lumbar (L)2 to L3 level without foraminal widening (Fig. 3A and 3B). The mass appeared hypointense on both T1- and T2-weighted images with homogeneous contrast enhancement after injection of gadolinium. As a standard procedure in our clinic for spinal tumors, screening for metastasis and primary tumor was done, and neither primary tumor nor metastasis was detected elsewhere in the body. The patient underwent L2-L3 laminectomy, and gross total resection of a hemorrhagic, dark reddish-purple firm epidural mass was performed. During surgery, there was no evidence of extension to vertebral bones or paraspinal tissues. Immunohistochemical examinations revealed a malignant small round cell tumor consistent with ES. The tumoral structure was vascular with pseudocapsule, and rosette formations were present rarely. Tumor cells were rich in glycogen and extensively positive for CD99, vimentin, CD117 and Bcl-2, but negative for NSE, chromogranin, CD20, CD19, CD79a, CD3, terminal deoxynucleotidyl tranferase (Tdt), GFAP, S100, desmin, gross cystic disease fluid protein (GCDFP-15), EMA, and LCA (Fig. 4). Ki-67 proliferation index was approximately 70%. Postoperatively, the patient's paraparesis improved to 4/5 muscle power strength, and he was discharged without urinary retention. The patient received sequential chemotherapy and radiotherapy with the same regimens as in Case 1. No evidence of recurrence or metastasis was detected after 16 months of follow-up.

Case 3

A 65-year-old female was admitted to our hospital with complaints of weakness of both lower extremities for five days prior to admission. Her medical history revealed a complaint of back pain for three months. The neurological examination revealed paraparesis muscle power strength score of 3/5 and hypoesthesia below the T7 level. Laboratory examinations revealed no remarkable abnormality. MRI showed a well-circumscribed posterior extradural mass with cord compression at the T7-T8 level with foraminal widening (Fig. 5A and 5B). The patient underwent immediate T7-T8-T9 laminectomy, and because of tumor infiltration to the vertebral bone structures and surrounding tissue via neural foramina, gross total resection of a vascular, dark blue-purple, solid epidural mass was achieved. Screening for metastasis and primary tumor was done, and neither primary tumor nor metastasis was detected elsewhere in the body. Tumor cells were extensively positive for CD99 and CD56, poorly positive for synaptophysin and CD117, and negative for NSE, CD20, CD3, WT1, periodic acid Schiff (PAS), pan-cytokeratin (Ck), EMA, and LCA. Ki-67 proliferation index was approximately 80%. Immunohistochemical examinations revealed a malignant diffuse homogeneous, necrotic, small round cell tumor with uniform nuclei and frequent rosette formation, consistent with PNET and/or ES family tumors (Fig. 6). Postoperatively, the patient's paraparesis improved to 4/5 muscle power strength, and she was discharged without any complication. The patient received sequential chemotherapy with vincristine, doxorubicin, cyclophosphamide, mesna, ifosfamide, and etoposide, and 4500 cGY tomotherapy in total. She first underwent a multiagent chemotherapy regimen, and thereafter, radiation therapy was delivered in 200

cGY fractionated doses daily. Because of gross total resection due to infiltration and invasion of the tumor to the surrounding tissues, residual tumor in the surrounding tissue and the neural foramina was noted on MRI during 14 months of follow-up.

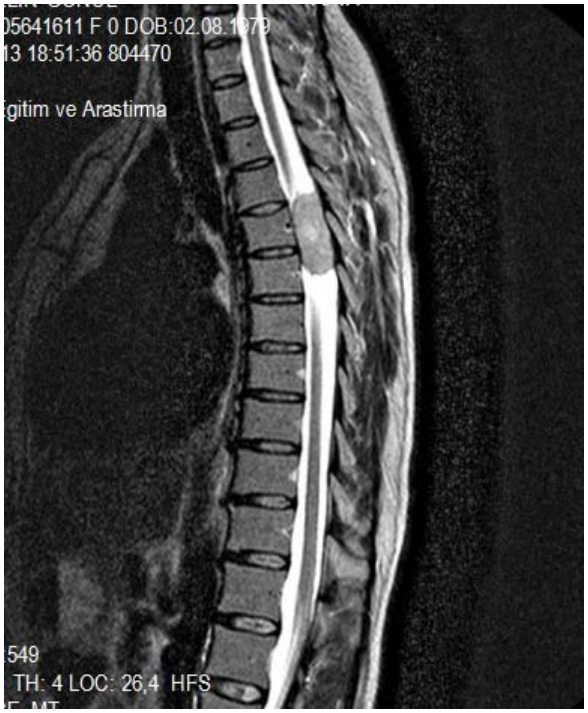

Fig 1A: *Sagital MRI section showing epidural mass with cord compression at T4-T6 level.*

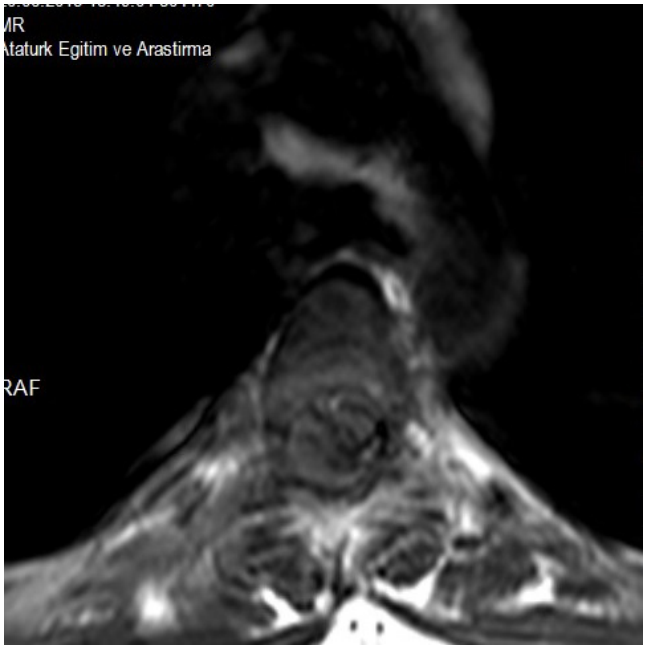

Fig 1B: *Axial MRI section showing epidural mass with cord compression at T4-T6 level.*

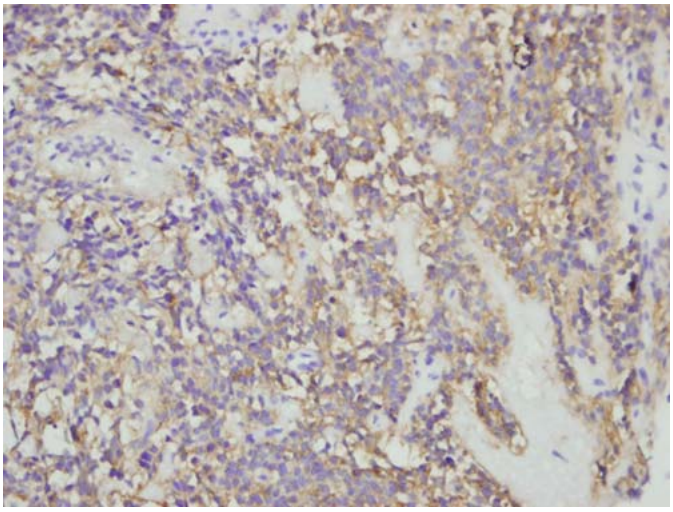

Fig 2: *Uniform cell with darkly staining nuclei and very scanty cytoplasm with strong CD99 immunoreactivity.*

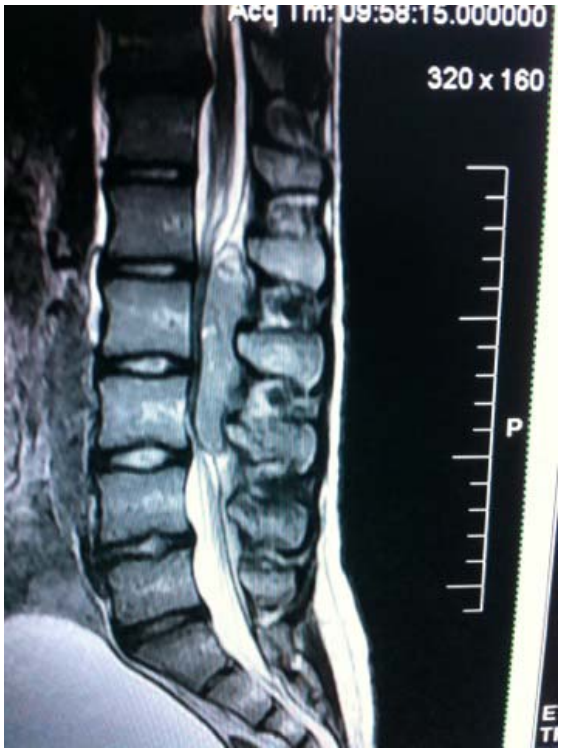

Fig 3A: *Sagital MRI section showing epidural mass with cord compression at L2-L3 level.*

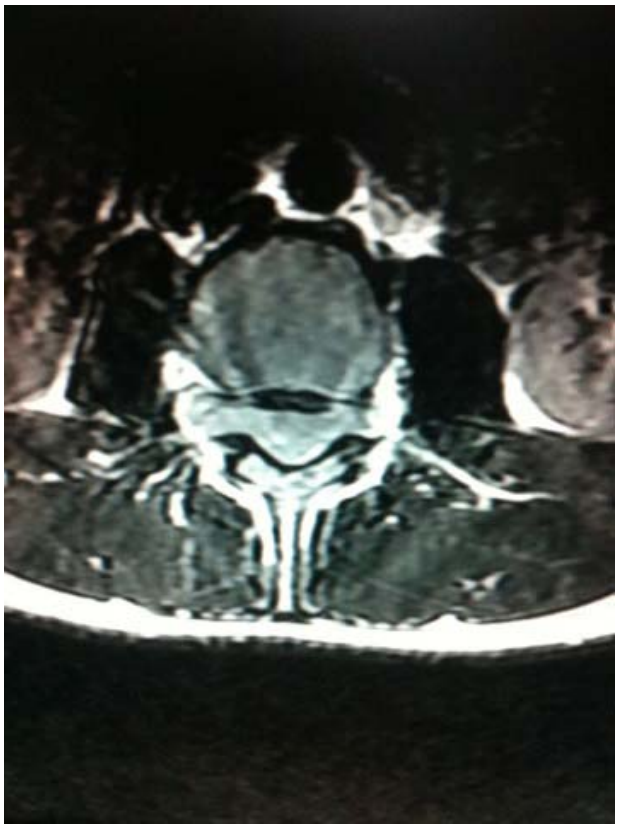

Fig 3B: *Axial MRI section showing epidural mass with cord compression at L2-L3 level.*

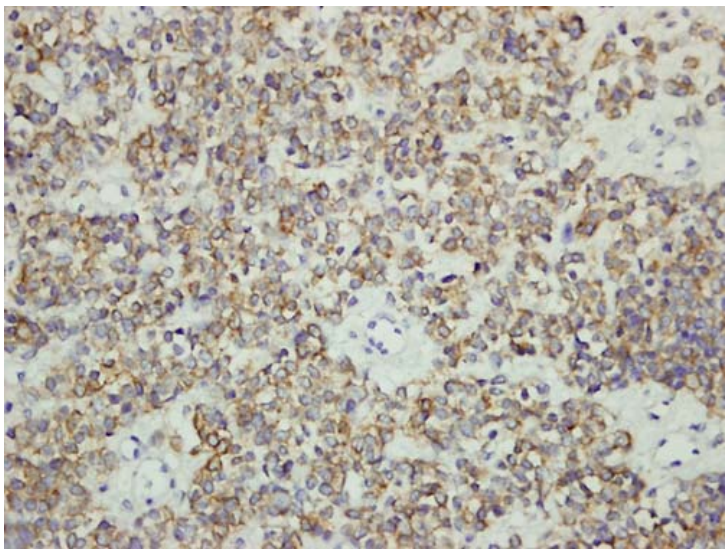

Fig 4: *Small round tumor cells rich in glycogen and extensively positive for CD99.*

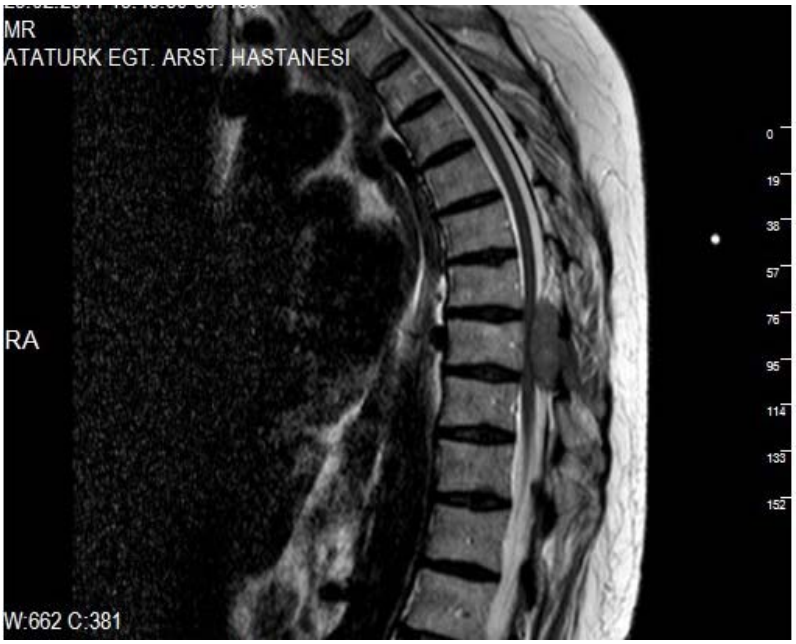

Fig 5A: *Sagital MRI section showing epidural mass with cord compression at T7-T8 level.*

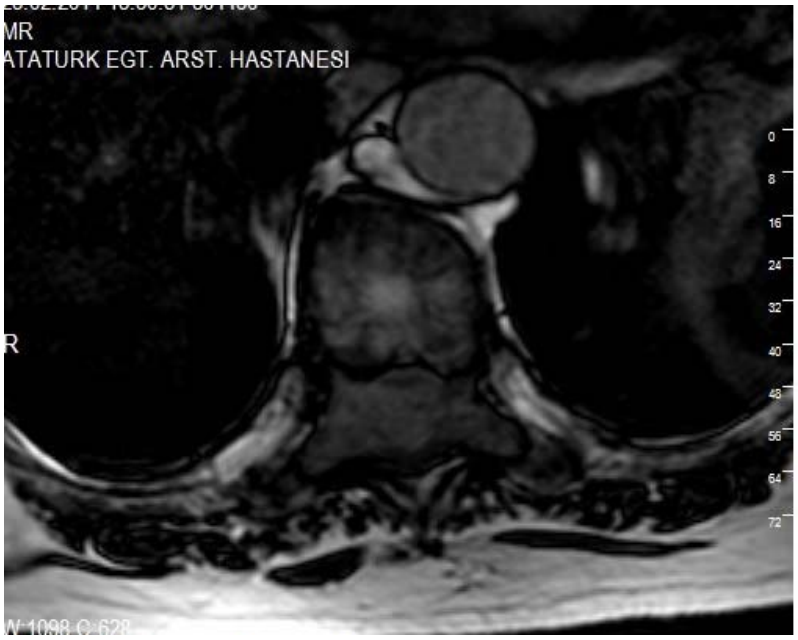

Fig 5B: *Axial MRI section showing epidural mass with cord compression at T7-T8 level.*

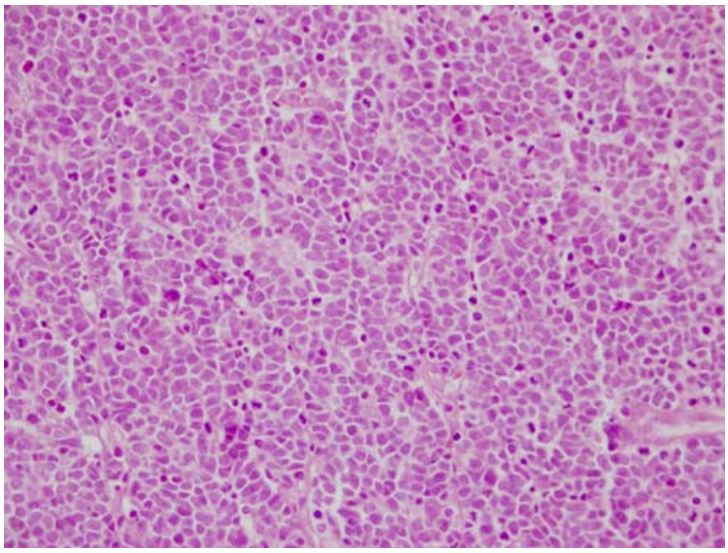

Fig 6: *Diffuse homogeneous, necrotic, small round cell tumor with uniform nuclei and frequent rosette formation with strong membranous staining for CD56 in tumour cells.*

DISCUSSION

ES is a PNET originating from the medullary cavity of the long bones, often arising in the diaphysis or medullary-diaphyseal cavity, and is characterized histologically by small round blue cells with varying degree of neuroectodermal differentiation[1-8,14-22,33,34,40-44,50,51]. It accounts for 6-8% of all malignant primary bone tumors. In 1969, Tefft et al. first described two patients with extraosseous paravertebral and contiguous epidural neoplasms with the morphological features of ES[47]. The terminology of ES family tumors is used today instead of osseous ES, EES, and pPNET. The most frequent sites of EES occurrence are the chest wall, lower extremities, trunk, and pelvis. Primary spinal PNET and/or spinal extraskeletal ES family tumors are rare lesions appearing in the spinal extradural space. Primary spinal PNETs are extremely rare, and most cases involving the spinal cord are drop metastases from primary intracranial tumors via cerebrospinal fluid[8-12,24,26,23,24,29,37,38,40,46,50,51]. To the best of our knowledge, only 63 cases of primary EES arising in the spinal epidural space have been reported in the English literature to date (Table 1).

According to the available reviews, the mean age at diagnosis of patients with spinal epidural EES was between 19.2 and 22.9 years, with a male predominance (66-69.7%). Because of the non-specific symptoms at onset, the mean duration of symptoms before diagnosis ranged between 4.52-4.9 months in the literature[40]. In the literature, presentations of extraskeletal ES arising primarily in the spinal epidural space included back and/or radicular pain, paresis, sensory disturbances, and bladder and bowel dysfunction[1,4,5,7,40,50,51]. The symptoms in our cases were similar to those reported in the literature. The tumor generally tends to spread locally, infiltrating deep fascial spaces, muscles or skeletal structures. In Cases 1 and 2 presented herein, the mass did not infiltrate any adjacent structures, only the epidural space, but in Case 3, infiltration of the tumor to the vertebral bone structures and surrounding tissue via neural foramina was observed. In the literature, the incidence of primary EES arising in the spinal epidural space in the lumbar region is twice that observed in thoracic and cervical regions[40,42,48,50,51]. In our experience with three cases, tumors were located in the thoracic region in two cases and in the lumbar region in one case.

Table 1: Details of previous 63 cases and present three cases of primary EES arising in the spinal epidural space in literature.

Location	*Age/Gender*	*CD 99*	*Treatment*	*Follow up(months)*	*Author(ref No)*
Lumbar	6y/F	neg	S/RT/CT	48	Tefft et al. [47]
Sacral	17y/M	neg	S	1	Angervall et al.[3]
Thoracic	20y/M	neg	S/RT/CT	12	Angervall et al [3]
Lumbar	18y/F	neg	S/RT/CT	6	Angervall et al [3]
Lumbar	18y/M	neg	S/RT/CT	16	Scheithauer et al [41]
Thoracic	27y/F	neg	S/RT/CT	132	Scheithauer et al [41]
Sacral	23y/M	neg	S/RT/CT	12	Mahoney et al [33]
Lumbar	19y/M	neg	S/RT/CT	12	Fink et al [17]
Lumbar	13y/M	neg	S/RT/CT	15	Simonati et al [45]
Thoracic	29y/M	neg	S/RT/CT	6	N'Golet et al [36]
Lumbar	47y/F	neg	S/RT/CT	4	N'Golet et al [36]
Lumbar	10y/M	neg	S/RT/CT	15	Spaziante et al [46]
Lumbar	16y/F	neg	S/CT	NA	Demeocq et al [11]
Lumbar	17y/M	neg	S/RT/CT	9	Ruelle et al [39]
Thoracic	18y/M	neg	S/RT/CT	42	Sharma et al [42]
Lumbar	4y/M	neg	S	5	Machin Valtuena et al [32]
Lumbar	26y/F	neg	S/RT	6	Liu et al [31]
Thoracic	16y/F	neg	S/RT/CT	6	Benmeir et al [7]
Thoracic	7y/M	neg	S/CT	40	Caspers et al [26]
Thoracolumbar	15y/F	neg	S	NA	Allam et al [2]
Lumbar	36y/F	neg	S/RT	96	Christie et al [10]
Thoracic	4y/M	neg	S/RT/CT	76	Akai et al [1]
Lumbar	17y/M	pos	S/RT/CT	23	Dorfmüller et al [13]
Cervical	24y/M	neg	S/RT/CT	12	Kennedy et al [27]
Cervicothoracal	13y/F	pos	S/RT/CT	31	Izycha-Swieszewkaet al [23]
Cervical	38y/M	pos	S/CT	17	Schin et al [43]
Cervicothoracal	22Y/M	pos	S/CT	48	Schin et al [43]
Cervical	29y/F	pos	S/RT/CT	30	Mukhopadhyay et al [34]
Thoracic	18y/M	pos	S/RT/CT	18	Mukhopadhyay et al [34]
Lumbar	22y/M	pos	S/RT/CT	15	Mukhopadhyay et al [34]
Lumbar	31y/M	pos	S/RT/CT	32	Mukhopadhyay et al [34]
Cervical	13y/M	pos	S/RT/CT	11	Mukhopadhyay et al [34]
Thoracic	5y/M	neg	S/RT	8	Virani et al [49]
Lumbar	15y/F	pos	S/RT/CT	8	Kadri et al [25]
Thoracic	12y/F	neg	S/RT/CT	32	Harimaya et al [19]
Cervicothoracal	10y/M	neg	S/RT/CT	22	Harimaya et al [19]
Thoracic	33y/M	pos	S/RT/CT	3	Gandhi et al [18]
Thoracic	16y/M	neg	S/RT/CT	7	Aydin et al [5]
Lumbar	26y/M	pos	S/RT/CT	16	Weber et al [50]
Cervical	7y/F	pos	S/RT/CT	60	Kogawa et al [29]
Thoracic	15y/F	pos	S	NA	Siami-Namini et al [44]
Lumbar	28/F	neg	S/RT/CT	24	Koudelova et al [30]
Thoracic	13y/M	pos	S/RT/CT	NA	Athanassiadou et al [4]

Lumbar	20y/M	pos	S/CT	15	Isefuku et al [22]
Lumbar	8y/F	pos	S/RT/CT	10	He et al [20]
Cervicothoracal	18y/M	pos	S/CT	13	Ozturk et al [38]
Cervical	28y/M	pos	S/RT/CT	18	Bozkurt et al [8]
Cervicothoracal	7y/M	pos	S/RT/CT	108	Erkutlu et al [15]
Thoracic	24y/M	pos	S/RT	14	Feng et al [16]
Sacral	27y/m	neg	S/RT/CT	24	Mushal et al [35]
Lumbar	13y/F	pos	S/CT	14	Ozdemir et al [37]
Thoracic	12y/M	pos	S/RT/CT	20	Hsieh et al [21]
Thoracic	28y/F	pos	S/CT	2	Theeler et al [48]
Thoracic	25y/M	pos	S/RT/CT	6	Kiatsoontorn et al [28]
Thoracic	58y/M	pos	S	25	Jingyu et al [24]
Thoracic	15y/F	pos	S/RT/CT	12	Chang et al [9]
Thorocolumbar	13y/M	pos	S/RT/CT	10	Dogan et al [12]
Cervical	14y/M	pos	S/RT/CT	2	Duan et al [14]
Thoracic	26y/F	pos	S/RT/CT	3	Duan et al [14]
Cervicothoracal	7y/M	pos	S/RT	NA	Duan et al [14]
Thoracic	32y/M	pos	S	1	Duan et al [14]
Sacral	44y/F	pos	S/RT	9	Saeedinia et al [40]
Thoracic	37y/F	pos	S/RT/CT	22	Yasuda et al [51]
lumbar	14y/M	pos	S/RT/CT	14	Present case
Thoracic	34y/F	pos	S/RT/CT	16	Present case
Thoracic	65y/F	pos	S/RT/CT	12	present case

M: Male F: Female S: Surgery RT: Radiotherapy CT: Chemotherapy NA: not avaiable

The differential diagnoses of epidural EES include primary or metastatic malignancies such as lymphoma, leukemic infiltration, and various epidural metastases, such as prostate, breast, and lung malignancies. The occurrence of primary spinal epidural EES/pPNET is unusual, and the pathological distinction is difficult. Advances in the past decade in immunohistochemical methods have shown CD99 expression to be characteristic for ES. Chromosomal studies were performed in approximately 14.8% of cases in the reviewed literature. CD99 has a high specificity for primary intraspinal EES/pPNET. This may obviate the need for complementary chromosomal studies[1,4,6,40,42,49,50,51].

If possible, total surgical resection is the gold standard to achieve diagnosis and decompression, which is usually followed by improvement in the symptoms. In spinal epidural EES/pPNET, it is believed that adjuvant therapies also are indispensable after a laminectomy with tumor resection to avoid a local recurrence or distant metastasis. In the literature, the recommended dose of radiation therapy for spinal epidural EES/pPNET varies between 3000 Gy and 5600 Gy in fractionated doses[40-48,49,50,51]. In our cases, a total dose of 4500 cGY radiation therapy was delivered in daily 200 cGY fractionated doses. Probably due to the limited number of reported cases, no certain therapeutic protocol has yet to be applied for primary spinal epidural EES/pPNET. Even though adjuvant chemotherapy is proposed for ES, this was not performed in some of the reports, mostly due to age limitations, early mortality, or lack of patient compliance.

The chemotherapeutic agents most commonly used are vincristine, doxorubicin, cyclophosphamide, ifosfamide, and actinomycin-D[3-12,33,36,38,40,50,51]. In our cases, combination chemotherapy with six courses of vincristine, doxorubicin, cyclophosphamide, mesna, ifosfamide, and etoposide was used. Combinations of surgery, chemotherapy and radiotherapy have been used for more successful results, but the clinical results of spinal epidural EES/pPNET are very poor, even if adjuvant therapies are administered. The five-year survival rate for spinal epidural EES/pPNET has been reported to range from 0-37.5%[40]. The poor prognosis may be a result of incomplete resections. In two of our cases, a complete resection could be performed because there was no evidence of infiltration or adhesion in the surrounding tissues. However, in the third case, because of tumor infiltration to the vertebral bone structures and surrounding tissue via the neural foramina, gross total resection was achieved. The follow-up periods for Cases 1-3 were 18, 16 and 14 months, respectively. For each patient, MRI gadolinium was performed radiologically at the 1st, 3rd, 6th and 12th months after surgery during the neurological examination of the patients. The first and second cases showed no evidence of recurrent or residual tumor during the follow-up period. In the third case, who underwent gross total resection due to infiltration and invasion of the tumor to the surrounding tissue, total reduction of the tumor filling the thecal sac and residual tumor in the surrounding tissue and the neural foramina were noted on MRI. The neurological examinations of all cases improved immediately after surgery and remained stable during the follow-up period.

CONCLUSION

ES in the spinal epidural space is extremely rare. A pathological differential diagnosis is difficult. The number of reported cases of small round cell tumors in the spine have increased in recent years with the immunohistochemical study improvements. CD99 has a high specificity for primary spinal epidural EES/pPNET, so a thorough immunohistochemical study including CD99 is sufficient for the pathological diagnosis. Presentation of spinal epidural ES is generally with pain, paresis, sensory disturbances, and bladder and bowel dysfunction. Because limited evidence regarding the therapeutic aspects of these tumors, treatment protocols cannot be formulated definitely yet but early and total resection of the tumor combined with radiation and chemotherapy is recommended as the therapeutic strategy for spinal epidural EES.

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