

# Extraskelatal Ewing's sarcoma of the thoracic epidural space: Case report and review of the literature

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**Abstract.** The occurrence of primary extraskelatal Ewing's sarcoma (EES) of the spinal epidural space has been rarely reported in the literature. The clinical, radiologic and pathologic features of a case of EES occurring in the thoracic epidural space are presented. A 37-year-old woman presented with a one-year history of back pain. Magnetic resonance imaging demonstrated an epidural mass at the T8-9 level. Laminectomy and partial resection of the tumor were performed. The differential diagnosis of a spinal epidural mass is broad. Histopathological and molecular cytogenetic examinations confirmed an EES arising from the thoracic epidural space. Despite receiving both chemotherapy and radiotherapy, the patient died of respiratory insufficiency due to medulla oblongata metastasis 22 months after the initial consultation. Awareness of this entity will allow this rare diagnosis to be considered and facilitate appropriate management. A review of the literature on spinal epidural EES is also presented.

## Introduction

Ewing's sarcoma is a malignant neoplasm of uncharacterized mesenchymal cell origin arising in the bones, rarely in soft tissues (1). Extraskelatal Ewing's sarcoma (EES), the extraosseous form of Ewing's sarcoma, was first described by Tefft *et al* in 1969 (2). The most common sites are the chest wall, paravertebral muscles, extremities, buttocks, and retroperitoneal space (3), but involvement of the epidural space is uncommon. To date, the number of reported cases of EES arising from the epidural space remains small (2,4-23). An additional case of

epidural EES is reported, and the literature on epidural EES is reviewed.

## Case report

A 37-year-old woman had a one-year history of back pain. She underwent a checkup in another hospital in October 2006. Magnetic resonance imaging (MRI) showed a well-circumscribed, posterior epidural tumor compressing the spinal cord and extending from T8 to T9 with foraminal widening (Fig. 1A and B). Bone change was not shown by computed tomogram (CT) (Fig. 2). Laminectomy at T8-T9 and partial resection of the tumor were performed. Tumor cells showed uniform small round nuclei containing fine chromatin, scanty eosinophilic cytoplasm, and an indistinct cytoplasmic membrane. The initial clinicohistopathologic impression was atypical meningioma (Fig. 3).

However, the patient developed progressively increasing back pain and gait disturbance in May 2007. MRI showed a recurrent tumor from T8 to T9. Chest radiogram and CT showed no evidence of lung tumor. Since her paraplegia had progressed rapidly, partial resection of the tumor was performed again in June 2007. Histopathological study of the specimens revealed small round cell sarcoma arising from the epidural space (Fig. 4). Proliferation of small, variable, round or polygonal cells with hyperchromatic nuclei and scant cytoplasm was seen. Immunohistochemically, the tumor cells were positive for CD99 and neuron-specific enolase (NSE) and negative for leukocyte common antigen (LCA) and cytokeratins. Based on the histological features and the immunostain results, a diagnosis of EES was favored, and the specimen was submitted for molecular cytogenetic analysis. Fluorescence *in situ* hybridization (FISH) analysis was performed to assess the *EWS* gene locus. Following molecular diagnostic confirmation, the patient was given multiagent chemotherapy with vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (VadCA-I/E) (24). She completed five cycles of chemotherapy, and the tumor showed significant shrinkage. However, 10 months later, a recurrent tumor and intramedullary dissemination were recognized. Partial resection of the tumor was performed again in May 2008. This was followed by radiotherapy of the total cervical and thoracic spine to a dose

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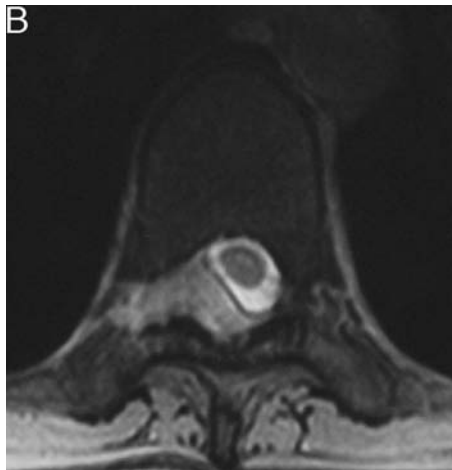
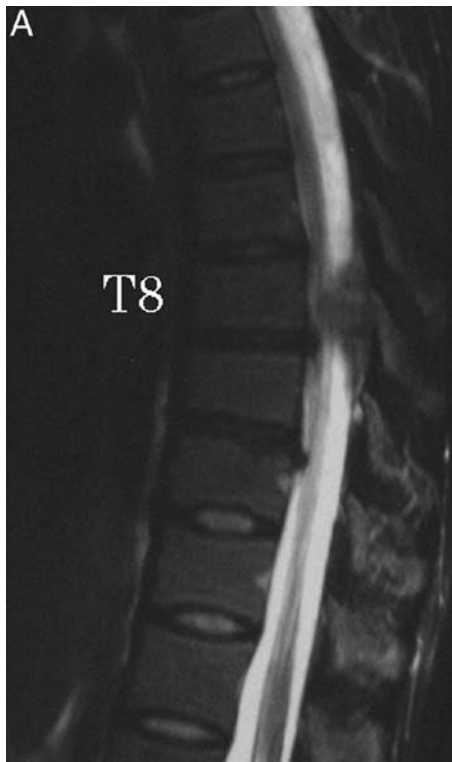


Figure 1. MRI findings at the initial consultation. (A) T2-weighted sagittal imaging. (B) T2-weighted axial imaging. MRI shows a circumscribed, posterior epidural tumor at the T8-9 level that is hyperintense to muscle. The tumor is compressing the spinal cord and extending from T8 to T9, with foraminal widening.

of 45 Gy over 5 weeks. However, the patient died of respiratory insufficiency due to medulla oblongata metastasis 22 months after the initial consultation.

**FISH analysis.** FISH studies of the first specimen were performed on a formalin-fixed, paraffin-embedded tissue section using the Ewing's sarcoma breakpoint region 1 (EWSR1), dual-color, break-apart probe (Vysis, Downer's Grove, IL, USA), which spans the known common breakpoints in the *EWS* gene on chromosome 22q12, as described previously (25,26). Signals were enumerated in 100 nuclei from an invasive area of the tumor located by comparison with hematoxylin and eosin staining. Hybridization signals were



Figure 2. CT myelogram findings. The dura is compressed from the posterolateral side by the epidural mass. Bone change is not obvious.

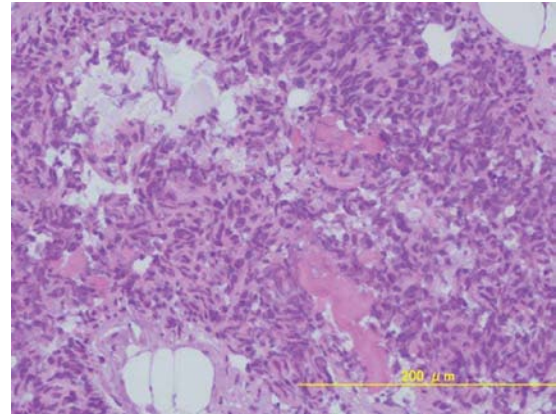


Figure 3. Histological appearance of the first surgical specimen. Tumor cells show uniform small round nuclei containing fine chromatin, scanty eosinophilic cytoplasm, and an indistinct cytoplasmic membrane. The initial clinicohistopathologic impression is atypical meningioma (hematoxylin and eosin stain, Scale bar: 200  $\mu$ m).

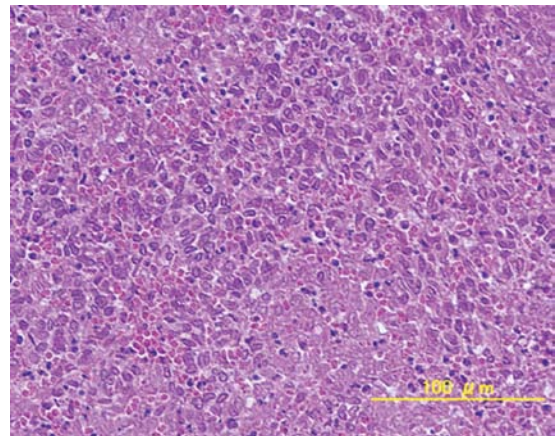


Figure 4. Histological appearance of the second surgical specimen. Diffuse proliferation of small, uniform round cells with hyperchromatic nuclei and scant cytoplasm is observed (hematoxylin and eosin stain, Scale bar: 100  $\mu$ m).

Table I. Reported cases of primary spinal epidural extraskeletal Ewing's sarcoma.

Case (Ref.)	Age (years)/ Gender	Level	Resection	Adjuvant Treatment	Outcome (months)
1 (2)	6/F	L4	Partial	CT, RT	DOD (48)
2 (4)	17/M	S1-2	N/A	None	DOD (1)
3 (4)	20/M	T2-5	Partial	CT, RT	DOD (13)
4 (4)	18/F	L5	N/A	CT, RT	DOD (7)
5 (5)	18/M	L1	Complete	CT, RT	NED (16)
6 (5)	27/F	T6	Complete	CT, RT	NED (120)
7 (6)	23/M	L5-S1	Partial	CT, RT	DOD (12)
8 (7)	19/M	L2-3	Partial	CT, RT	NED (6)
9 (8)	12/M	L3	N/A	CT, RT	NED (15)
10 (9)	10/M	L4-S2	Partial	CT, RT	DOD (16)
11 (10)	17/M	L3	Partial	CT, RT	DOD (8)
12 (11)	18/M	T11	Partial	CT, RT	DOD (42)
13 (12)	4/M	L1	Complete	None	DOD (5)
14 (13)	7/M	T12-L1	Partial	CT	NED (40)
15 (14)	15/F	T12-L3	N/A	N/A	N/A
16 (15)	22/F	C7-T1	Partial	CT	NED (48)
17 (15)	38/M	C5-7	Partial	CT	AWD (5)
18 (16)	24/M	C1-5	Partial	CT, RT	NED (25)
19 (17)	29/F	C3-5	Partial	CT, RT	NED (30)
20 (17)	18/M	T8	Partial	CT, RT	AWD (18)
21 (17)	22/M	L5-S1	Partial	CT, RT	NED (15)
22 (17)	31/M	L3-4	Partial	CT, RT	NED (32)
23 (17)	13/M	C3-5	Partial	CT, RT	NED (11)
24 (18)	33/M	T4-7	Complete	CT, RT	NED (3)
25 (19)	12/F	T1-3	Partial	CT (PBSCT), RT	DOD (32)
26 (20)	7/F	C2-4	Complete	CT (PBSCT), RT	NED (60)
27 (21)	15/F	C3-7	Partial	N/A	N/A
28 (22)	13/M	T9	Partial	CT, RT	AWD (9)
29 (23)	18/M	C6-T1	Complete	CT	NED (13)
30 (this case)	37/F	T8-9	Partial	CT, RT	DOD (22)

M, male; F, female; C, cervical; T, thoracic; L, lumbar; CT, chemotherapy; RT, radiotherapy; PBSCT, peripheral blood stem cell transplantation; DOD, dead of disease; NED, no evidence of disease; AWD, alive with disease; N/A, not available.

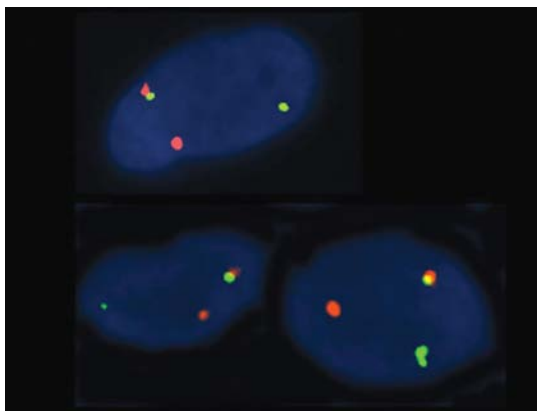


Figure 5. FISH analysis with the EWSR1 breakpoint flanking probe set (proximal portion, orange; distal portion, green) shows splitting of the orange and green signals, indicating disruption of EWS.

assessed in 200 interphase nuclei with strong, well-delineated signals by two different individuals. Tumor samples showed break-apart signals in 83 and 93% of cells, respectively (Fig. 5).

## Discussion

Ewing's sarcomas arising from soft tissues are referred to as EES. Most EES patients are between 10 and 30 years of age, with a peak incidence at ~20 years of age (3). The most common sites are the chest wall, extremities, buttocks, and retroperitoneal space. However, a number of cases have been reported to arise in various locations, such as the small intestine, vagina, kidney, skin, larynx, esophagus, and paravertebral region (3). Only 30 cases of EES arising in the spinal epidural space, including our case, have been reported in the English literature (Table I). The mean age at presentation was 18.8 years (range: 4-38 years),

with 73% of the patients being between 10 and 20 years old. Male patients predominated (66%). The male-female ratio of 1.5:1 in spinal epidural EES resembles that in Ewing's sarcoma of bone.

MRI is the most useful tool for early diagnosis to determine the extent of the tumor. The differential diagnosis of a spinal epidural mass is broad. Most epidural masses are metastatic malignancies associated with lung cancer, breast cancer, and lymphoma (13). Although primary epidural tumors are rare, primary epidural masses include schwannoma, meningioma, and primary bone tumor. Schwannoma was ruled out due to the lack of an intradural lesion. Meningioma was considered a distinct possibility. Epidural EES is particularly unusual, and it was not initially considered in the differential diagnosis. There are 10 cases documenting the MRI features of EES (14-18,20-23), with a limited case series, and they showed so-called dumbbell-shaped tumors that extended from an intraspinal origin with foraminal widening. In three cases, scalloping of bone was seen (15,23). The present case showed a dumbbell-type tumor without bone change.

Histopathologically, EES is classed as a small round cell tumor because of the uniform small round cell microscopic appearance. Such small round cell tumors may be misdiagnosed as lymphoma, small cell metastatic carcinoma from lung, and poorly differentiated synovial sarcoma. Therefore, immunohistochemical analysis is needed for further tumor classification. Approximately 95% of EESs show membranous immunoreactivity for CD99 (MIC2), but this is not specific (27,28). Most lymphomas are positive for LCA. Since only ~50% of poorly differentiated synovial sarcomas express cytokeratins, and many show CD99 immunoreactivity, the immunohistochemical differentiation of poorly differentiated synovial sarcoma from EES is difficult in some cases (3). Finally, this case was diagnosed as EES based on identifying, in the majority of aberrant interphase cells examined, the presence of a rearranged *EWS* gene locus. The t(11;22)(q24;q12) translocation, a chromosomal abnormality specific to the Ewing's sarcoma, is detected in ~90% of cases (29). This translocation results in the formation of the *EWS-FLII* fusion gene (30). Another 10% of cases have a variant translocation fusing *EWS* to closely related *EWS* genes such as *ERG*, *ETV1*, *EIAF*, and *FEV*. The ability to identify tumor-specific chromosomal translocations and associated fusion gene transcripts using interphase reverse transcriptase-polymerase chain reaction (RT-PCR) (29,31,32) and FISH (26,32) can be useful. In the present case, limited paraffin-embedded material from a resected specimen was available for FISH studies, and epidural EES was diagnosed.

The results of treatment for epidural EES are very poor, even if both chemotherapy and radiotherapy are given. To date, the 5-year survival rate of EES has been reported as being between 38% (33) and 67% (34). However, the 5-year survival rate in EES around the spinal canal was reported to be between 0 and 37.5% (13) (Table I). Of 28 cases for whom follow-up data were available, 11 cases died after an average of 19 months, and 17 cases lived for an average of 27 months (range: 3-120 months). A diagnosis of EES tends to be late due to its rarity and the tumor being found after becoming massive (19). Furthermore, 20 of 26 cases (77%) were only partially resected due to infiltration of the surrounding nerve tissues.

Ten of these cases died after an average of 20 months. Five of the six cases that were completely resected lived an average of 42 months. Therefore, the poor prognosis of epidural EES may result from the diagnostic difficulty and the high rate of only partial resection of the tumors.

In conclusion, a rare case of epidural EES without evidence of systemic disease or chronic illness was reported. Imaging features may not distinguish it from other tumors, such as metastatic tumor or lymphoma. Some form of biopsy or partial resection was needed in all reported cases to confirm the diagnosis allowing appropriate management.

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