

## Primary Ewing's Sarcoma of the Spine in Pediatric Patients: A Case Series Analysis and Literature Review

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### Abstract

Ewing's sarcoma is a common malignancy of the bone and soft tissues in pediatric patients. It mostly affects the long bones and pelvis, and less commonly the flat bones and vertebrae. Primary Ewing's sarcoma affecting the spine is very rare. The patient has non-specific symptoms for a prolonged period of time before the correct diagnosis is given. Patients can present with acute paraplegia due to spinal cord compression, which needs prompt surgical intervention. Early diagnosis and treatment is important for neurological recovery. The definitive management includes three main modalities: surgery, radiotherapy, and combination chemotherapy. Adequate surgical excision may not be feasible because of anatomical limitations and local control is mainly achieved by radiotherapy. Because of the low incidence of these tumors, a multitude of therapeutic strategies have been employed with varying success. Currently there are no clinical guidelines outlining optimal management. We present a series of six cases of primary Ewing's sarcoma of the spine, analysis of presenting complaints, examination findings, diagnostic investigations, treatment, outcome and review of relevant literature. Five out of the six patients had prolonged musculoskeletal symptoms before they were correctly diagnosed and three presented with acute paraplegia. All have received aggressive multimodality therapy with complete neurological recovery and are surviving.

**Keywords:** Ewing's sarcoma, Spine, Pediatric

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### Introduction

Ewing's sarcoma (ES) is the second most common primary bone tumor in pediatric patients, accounting for approximately 4% of pediatric malignancies. The incidence

peaks in the second decade of life.<sup>1</sup> The most commonly affected bones are the long bones of the extremities and pelvis; the vertebrae are affected in less than 5% of cases.<sup>2</sup> The patient presents with non-specific symptoms

such as low back pain, muscle aches and vague paresthesias which lead to diagnostic delays. During the later phase, spinal cord compression or intraspinal extension can produce neurological deficits that include rapidly progressing paraplegia.<sup>3</sup> Early diagnosis and prompt treatment can lead to recovery or preservation of neurological function, and aggressive multimodality treatment with chemotherapy, surgery and radiotherapy may translate into better outcome in these patients.

### Case Series

During the five-year period from 2009 to 2013, 64 pediatric patients (age <14 years) with ES were treated in our Pediatric Oncology Department, out of which 6 (9.3%) presented with primary ES of the spine. We performed retrospective analyses of case records from these patients and observations were deduced with respect to their age and gender, presenting complaints, clinical examination, investigations and metastatic status. The patients were followed through treatment and we assessed their overall responses and neurological outcomes (Table 1).

A total of 4 out of 6 patients were over 10 years of age. One child was 8 years old and the youngest was 5½ years old. This observation agreed with the general prevalence of ES in the second decade of life. Generally ES has a slightly higher predilection to affect boys, but in our study boys and girls were equally affected.

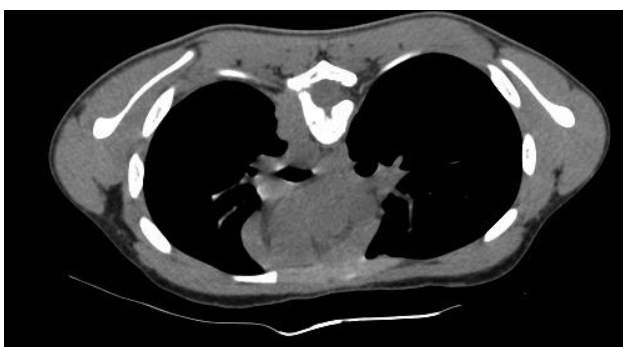
Most patients had prolonged onset of nonspecific symptoms. In our patients, five out of

six had an average duration of symptoms from 2-6 months; only one patient had a short history of 2 weeks duration. All patients had pain that affected the back, shoulders and legs, difficulty in walking and weakness of the lower limbs. All received symptomatic treatment for a variable duration prior to the final diagnosis. Interestingly, three out of six patients presented with acute paraplegia and urinary retention - a rarely reported presentation.

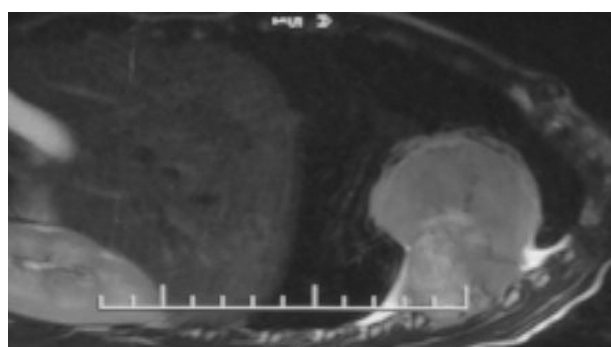
In three patients, computed tomography (CT) scans were performed and magnetic resonance imaging (MRI) of the spine was performed in the other three. Each of the six patients had evidence of a paraspinal mass lesion with intraspinal extension (Figures 1, 2). The lesion was located in the dorsal spine in all patients, except for one patient who had involvement of the lumbosacral spine. One patient had an intramedullary extradural spinal cord lesion that did not involve the vertebral body.

Two patients reported after tumor excision and their slides were reviewed. Biopsy was done in three patients, and CT-guided fine needle aspiration and cytology (FNAC) in one patient. Diagnosis was confirmed by histopathology and immunohistochemistry by demonstration of uniformly small round cells which were negative for cytokeratin, desmin and chromogranin, focally positive for synaptophysin and strongly positive for MIC2 and nonspecific esterase (NSE). (Figures 3, 4).

Staging chest radiographs, chest CT scans, bone scans and bone marrow biopsy were



**Figure 1.** D5 vertebra body altered signal with a large paravertebral mass lesion extending into the spinal canal; The spinal cord is displaced right anterolaterally and compressed.



**Figure 2.** Contrast CT image: Large heterogeneously enhancing mass lesion in right upper hemithorax with erosion of the thoracic vertebral body and intraspinal extension.

performed in all six patients. Metastatic work-up was negative in all patients, which also proved that the lesion diagnosed in all patients was the site of primary tumor and not metastatic disease.

All patients received aggressive neo-adjuvant chemotherapy with ifosfamide, etoposide, vincristine, adriamycin and cyclophosphamide. In three patients with acute paraplegia, steroids were given to relieve spinal cord compression. For local treatment, surgery was done in three patients - two patients underwent upfront tumor excision, whereas in one patient debulking was done after 12 weeks of chemotherapy. Surgery was not considered feasible in the other three. Radiation therapy was given to all six patients.

All patients completed treatment with no evidence of disease on re-evaluation at the end of therapy. All had complete neurological recovery after initiation of treatment. At present, all patients are surviving and on follow-up with no evidence of recurrence. However considering the very short duration since treatment, it is difficult to comment on final outcome.

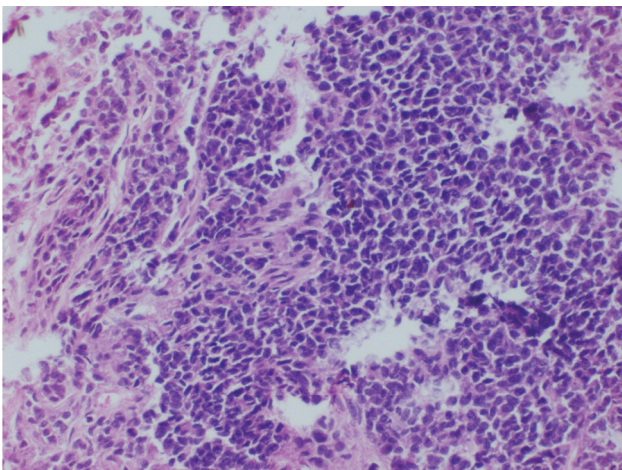
## Discussion

Ewing's sarcoma is a small, round cell tumor which commonly affects extremities, pelvis and flat bones, vertebrae and spine affected in less than 5% of cases.<sup>3,4,5</sup> Our series had a higher incidence of 9.3%.

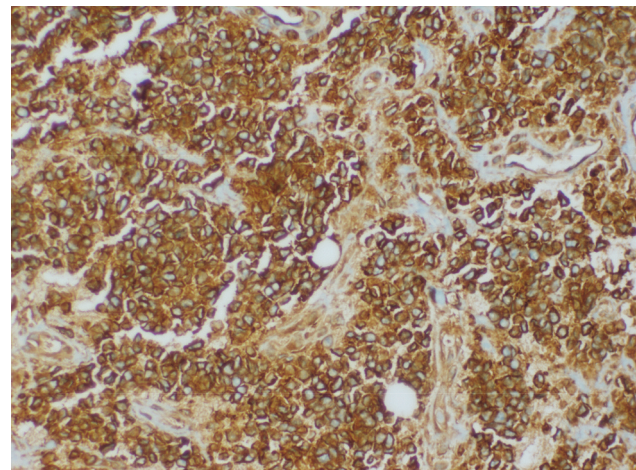
Primary ES of the spine arises from the epidural space or paravertebral soft tissue with secondary spinal involvement and rarely intradural extension

of the epidural tumor or intramedullary ES.<sup>6</sup> In a review by Tsutsumi et al., the thoracic spine was most frequently affected, followed by cervical, cervicothoracic, and thoracolumbar spine.<sup>7</sup> In our series, the dorsal spine was most commonly affected. Non-sacral spinal ES is not easily diagnosed because patients present with musculoskeletal symptoms and are initially treated for musculoskeletal disorders.<sup>3</sup> Only when neurological impairment occurs is spinal pathology suspected. This often occurs weeks after onset of initial symptoms. In some retrospective studies, a mean diagnostic delay of 8-12 weeks (range: 1-124 weeks) has been reported in primary ES of the spine.<sup>2</sup> In our series, the average diagnostic delay was 12.2 weeks. Presentation as acute onset paraplegia is extremely uncommon, as seen in cases 2,4 and 5 of the current series.

Definitive management of ES includes surgery, radiotherapy and chemotherapy. Given the low incidence of vertebral disease, there are no guidelines outlining optimal management. However a multitude of therapeutic strategies have been employed with varying success. Initial chemotherapy is administered before local treatment with the aim to shrink bulky and unresectable tumors and eradicate micrometastases. Initial chemotherapy is also administered for acute relief of epidural compression.<sup>8</sup> Chemotherapeutic agents used are ifosfamide, etoposide, vincristine, adriamycin, cyclophosphamide and actinomycin-D,<sup>5</sup> and the regimen is the same as



**Figure 3.** Sheets of uniform round cells (H&E, 200×).



**Figure 4.** CD99 stain shows diffuse membrane positivity (IHC, 200×).

**Table 1.** Details of six cases of paediatric primary ES of spine.

	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6
Age	10 years	13 years	5 ½ years	13 years	8 years	10 year old
Gender	male	male	male	female	female	female
Presenting complaints	Back pain, weakness of legs	progressively worsening back pain, acute paraplegia and urinary retention.	right shoulder pain and back pain, inability to walk and urinary retention	leg pains and paraesthesias over feet, difficulty in walking with weakness, acute paraplegia with urinary retention	difficulty in walking and back pain, acute paraplegia	back pain and pain in both legs, difficulty in walking and weakness of legs
Duration of symptoms	6 months	3 months	2 weeks	2 months	4 months	3 months
Clinical examination	paraspinal tenderness at D2-6, paraparesis with grade 2 power, no sensory loss.	paraparesis (grade 1 power) with sensory loss at D4 level.	paraparesis with Grade 3 power in both lower limbs, no sensory loss	paraplegia (Grade 0 power both lower limbs with exaggerated tendon reflexes), sensory loss below D2 level	paraplegia with Grade 0 power, no sensory loss or bladder involvement	Severe painful immobility of legs, Motor power Grade 3-4, tendon reflexes normal, no sensory loss or bladder involvement.
Investigations	CT scan	CT scan	CT scan	MRI spine	MRI spine	MRI spine
Tumour location	right hemithoracic paraspinal soft tissue mass lesion with destruction of D4 vertebra and intraspinal extension.	epidural mass with paraspinal soft tissue density at D4-D6 level with intraspinal extension	right hemithoracic paraspinal mass lesion with intraspinal extension at D4,5 levels	D1-D3 level paraspinal lesion with extradural cord compression and intraspinal extension at D1-D2 and D2-D3.	intradural extramedullary spinal lesion D4-D6 region without any vertebral body or posterior element involvement	large L5,S1,S2 vertebral lesion with extensive paraspinal soft tissue component and intraspinal extension.
Diagnostic procedure	ultrasound guided biopsy	CT guided biopsy from the paraspinal mass	Surgical slides review	CT-guided FNAC	Surgical slides review	Open biopsy
Metastatic work-up	negative	negative	negative	negative	negative	negative
Local therapy	debulking surgery at week 12 followed by RT(5400 cGy/30F)	RT (5400 cGy/30F)	thoracotomy and excision of right hemithoracic paraspinal tumour, IGRT (5400 cGy/30F)	RT (4500 cGy + 500 cGy boost)	D3-D5 aminectomy and excision of tumour, RT (4500 cGy)	RT (4500 cGy /25F + 1080 cGy boost)
Chemotherapy	I,E/V,A,C	I,E/V,A,C	I,E/V,A,C	I,E/V,A,C	I,E/V,A,C	I,E/V,A,C
Neurological outcome	Complete recovery	Complete recovery	Complete recovery	Complete recovery	Complete recovery	Complete recovery
Response and follow-up	Completed treatment, no disease at re-evaluation	Significant reduction of tumour, continuing chemotherapy	Continuing chemotherapy	Completed treatment, no disease at re-evaluation	Completed treatment, no disease at re-evaluation	Completed treatment, no disease at re-evaluation

I - Ifosfamide, E- etoposide, V-vincristine, A-adriamycin, C-Cyclophosphamide, D- dorsal, L- lumbar, S – sacral, CT – computed tomography, MRI – magnetic resonance imaging, RT – radiotherapy, FNAC- fine needle aspiration and cytology



for ES at any other site as data do not strengthen the need for a specific protocol for unusual site ES.<sup>4</sup>

Because of the anatomical constraints of the spine and neighbouring critical structures, and concerns about long term morbidity and functional loss in en bloc resection, spinal ES is often treated by intralesional excision or debulking.<sup>1</sup> In a series of 27 patients aggressively treated with surgery, Boriani et al. have reported that only en bloc resection with acceptable margins was associated with better local control and survival. Wherever tumor margins had to be compromised to preserve function, the outcome was not as good.<sup>1</sup> When there is epidural compression secondary to ES with rapidly progressing neurological symptoms or impending paralysis, prompt surgical intervention is the only primary alternative if an irreversible deficit is to be prevented.<sup>8</sup> Indelicato et al.<sup>9</sup> have reported in their review of 27 patients with spinal and paraspinal ES in which only 6 received both surgery and radiotherapy as local treatment; the majority received only radiation. In our series, surgery was possible in half of the patients without much operative morbidity. Radiation doses for spinal tumors should not exceed the limit of cord tolerance (45 Gy) to avoid the risk of radiation-induced myelopathy and secondary sarcomas. The lower survival rates reported with radiation therapy compared with surgery for local control might be related to residual nests of viable tumor within the radiated site, as potential sources of local recurrence or distant relapse.<sup>5</sup>

Multidrug chemotherapy combined with surgery and radiotherapy has now improved prognosis of ES of the spine. For non-metastatic spinal and paraspinal ES, Indelicato et al., in a review, have reported a five-year overall survival rate of 71%, cause-specific survival of 71%, and local control rate of 89%.<sup>9</sup> Data from the 30-year Surveillance, Epidemiology, and End Results Registry (SEER) has placed the 5-year and 10-year survival rates of spinal ES at 41% and 34%, respectively.<sup>10</sup> Despite recent advances in treatment, when compared to other sites of occurrence, prognosis of ES of the spine is

considered worse.<sup>1</sup> In one study of 43 cases of non-metastatic ES by Bacci et al., tumors primarily located in the sacrum had much poorer outcome than those located in the rest of the spine.<sup>5</sup>

Our case series is reported to bring to notice rare presentation of pediatric malignancy which may go undiagnosed because of misinterpretation of symptoms. A high index of suspicion is needed in children who present with prolonged musculoskeletal symptoms that have atypical features, especially signs of spinal cord compression. Early diagnosis is of tremendous importance in ES of the spine because prompt intervention is required to keep neurological damage to a minimum. The correct combination of surgery, multiagent chemotherapy and radiotherapy is required for long-term patient outcome and better quality of life.

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