

## Primary Non-metastatic Epithelioid Sarcoma of Lumbar Vertebra L3: Pediatric Case Report and Brief Review of the Literature

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### ABSTRACT

Epithelioid Sarcoma (ES) is a rare non-rhabdomyosarcoma soft tissue sarcoma. It is a high-grade malignancy that most commonly occurs in young adult males. These tumors are characterized for slow growing nodules with predilection for the extremities. A proximal form arising in the deep part of the pelvis, perineum, and genital tract and proximal extremities has been described. Only three cases with localization to the spine have been reported. We report the case of an 11-year old female with a primary ES of the lumbar spine, who presented with antalgic gait and evidence of L3 vertebral collapse on x-rays. She had upfront surgery for spine stabilization and biopsy. Treatment consisted of neoadjuvant chemotherapy with ifosfamide and doxorubicin, local control with radiation therapy, and second-look surgery with complete reconstruction of L3. She tolerated treatment well, without significant toxicities or complications. When this paper was submitted for publication, she had completed 6 months of follow up in first clinical remission without evidence of local or distant disease. This is the first case of ES diagnosed at our center,

likely the first pediatric case of ES diagnosed in the Dominican Republic; although a national cancer registry does not exist. Establishing the diagnosis would not have been possible without access to international experts in pediatric oncologic pathology thought existing institutional collaboration. This is not a novel case but a diagnostic challenge, issue exacerbated in developing countries. We are proud to have offered appropriate, timely treatment, with a similar integral quality as in a developed country.

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**Key words:** Epithelioid sarcoma; Non-rhabdomyosarcoma soft-tissue sarcoma; Vertebra; lumbar spine; Child; Pediatric

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### INTRODUCTION

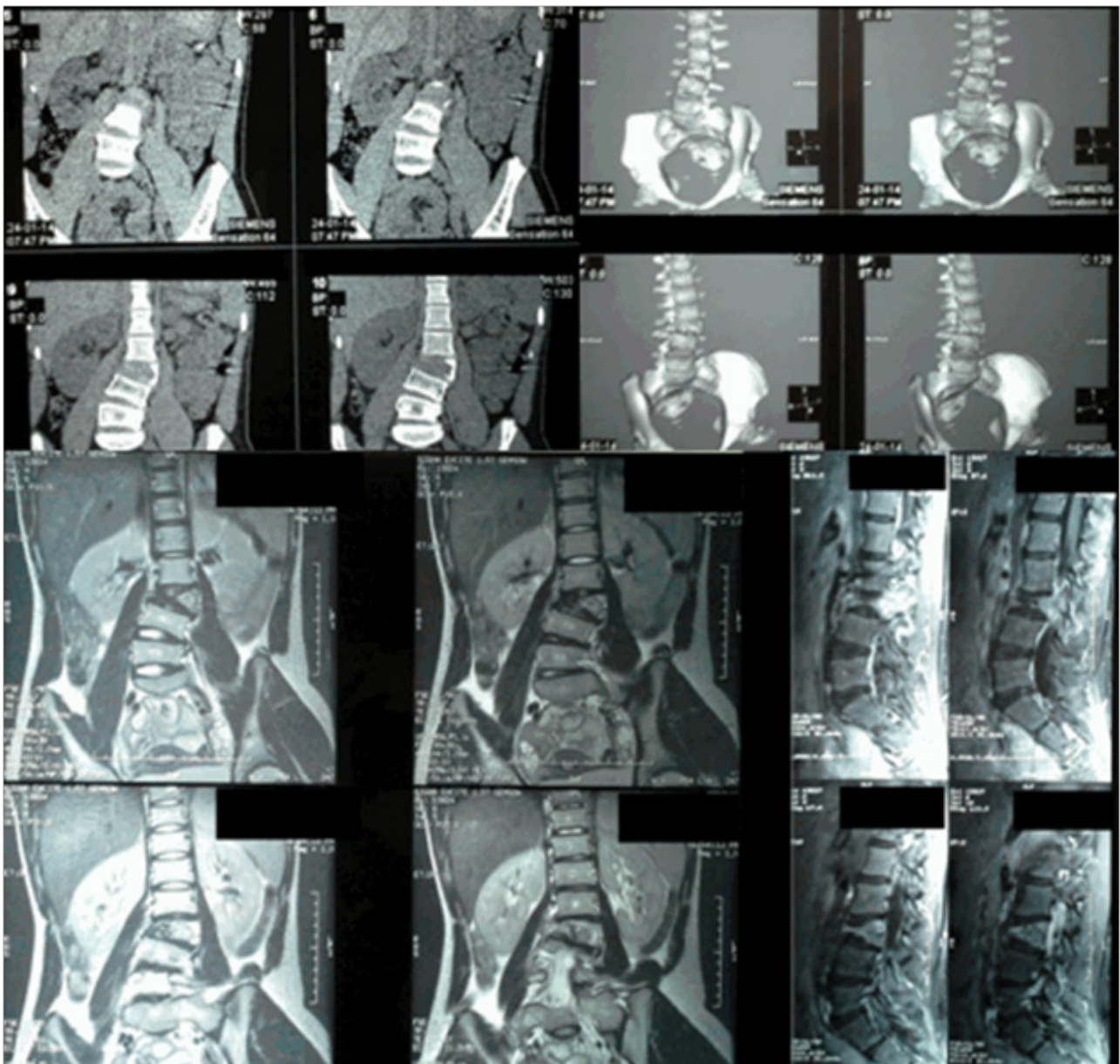
Epithelioid Sarcoma (ES) is a rare non-rhabdomyosarcoma soft tissue sarcoma. It typically occurs in the distal extremities of young male adults as a slow-growing nodule within the dermis, subcutis, or deeper soft tissues<sup>[1-3]</sup>. Due to its insidious presentation and histologic findings, its classic form can be mistaken with chronic inflammatory processes<sup>[2,3]</sup>. However, the clinical course is characterized by high frequency of nodal spread and relentless local and distal recurrences<sup>[1,2]</sup>. Three histologic variants have been described: epithelioid, spindle, and mixed, and lesions are usually positive for vimentin, keratin, and epithelial markers; highlighting the presence of a spectrum of cellular differentiation in these fibrohistiocytic tumors<sup>[3,4]</sup>. A proximal form arising in the deep part of

the pelvis, perineum, and genital tract and proximal extremities has been described and typically has an even more aggressive clinical course than distally located tumors<sup>[4,5]</sup>. In these cases, ES has distinct histologic features resembling carcinomas and rhabdoid tumors<sup>[4]</sup>. Interestingly, only three cases of ES localized to the spine have been reported in the literature (one thoracic, one lumbo-sacral, and one sacral)<sup>[6-8]</sup>. We report the case of an 11-year old female with a primary ES of the lumbar spine, who presented with antalgic gait and evidence of L3 vertebral collapse on x-rays. She had upfront surgery for spine stabilization and biopsy. Treatment consisted of neoadjuvant chemotherapy with ifosfamide and doxorubicin, local control with radiation therapy, and second-look surgery with complete reconstruction of L3. She tolerated treatment well, without significant toxicities or complications. When this paper was submitted for publication, she had completed 6 months of follow up in first clinical remission without evidence of local or distant disease.

## CASE REPORT

An 11-year old female with history of intermittent discomfort in the lower back presented for evaluation to her pediatrician. Symptoms had developed over the previous year and parents had been managing with oral analgesics and non-steroidal anti-inflammatory medications. Ultimately, pain increased in frequency and severity and parents noted spine deviation and antalgic gait, which prompted medical evaluation. The general pediatrician performed and X-ray which showed.

The general pediatrician performed and x-ray which showed marked scoliosis in the lumbar spine with destruction of L3 vertebra. The patient was then immediately referred to an orthopedist, who obtained further imaging. As seen in the upper panels of figure 1, computed tomography (CT) scan showed an expansive lytic lesion of neoplastic appearance on the L3 vertebral body. This prompted



**Figure 1** Preoperative coronal and sagittal MRI view where we can observe L3 destruction with the emerging mass and the spine deviation.



obtaining magnetic resonance imaging (MRI), which as seen in the lower panels of figure 1, showed extension of the neoplastic lesion into the right pedicle and right transverse process of the vertebra, with areas of calcification and causing marked scoliosis in the lumbar spine.

The surgical procedure revealed a mass emerging directly from the L3 vertebral body. The mass was invading the right posterior roots and was noted to be pushing, but macroscopically not infiltrating, the paraspinal muscles. Four screws and two orthopedic fixation hooks were placed to stabilize the spine and a biopsy was performed. Pathology reported “poorly differentiated malignant neoplasm, probably lymphoid vs. histiocytic origin”. Only one immunohistochemistry study was reported: cytokeratin; it was reported as positive.

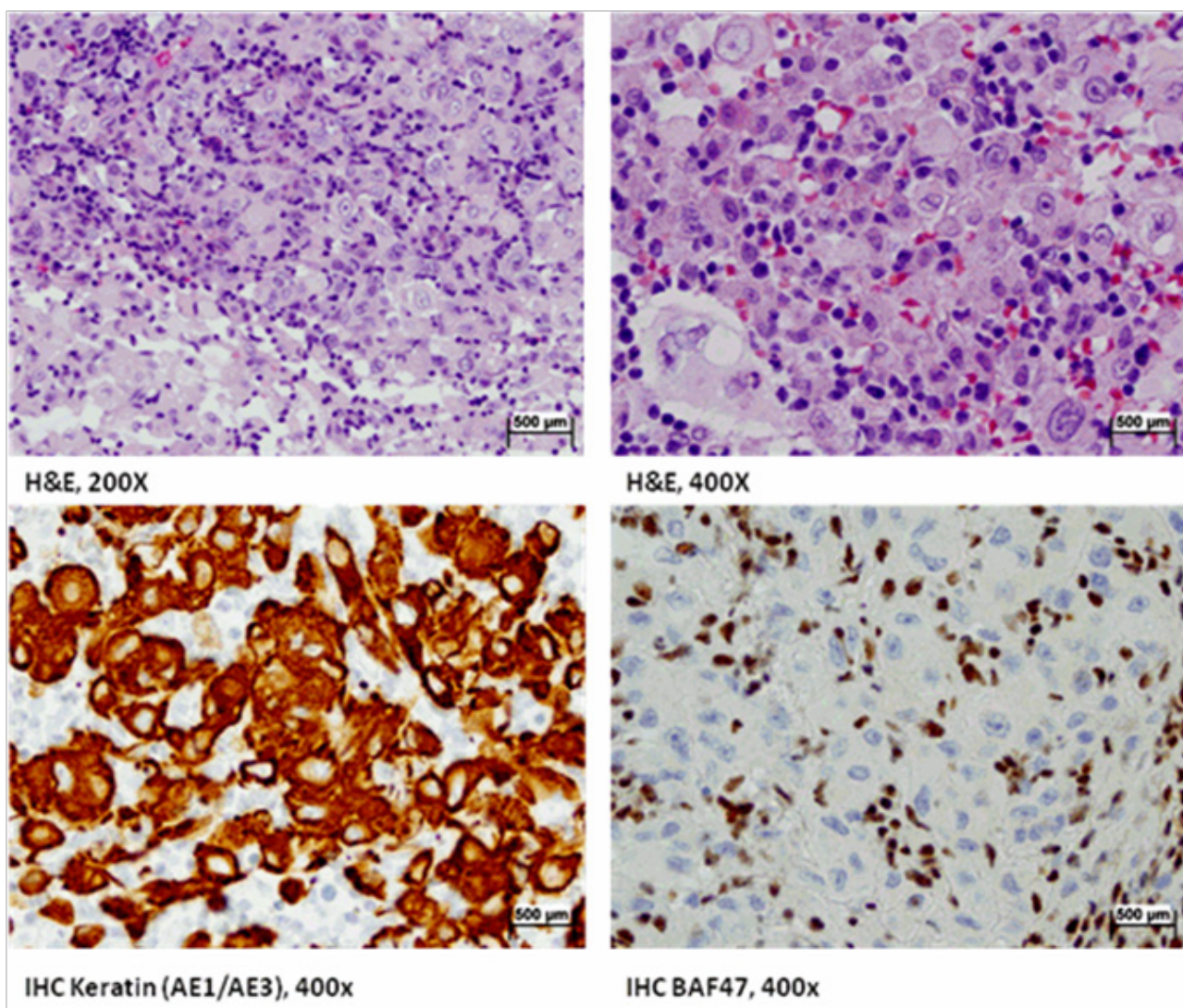
With this pathologic diagnosis, the patient was referred to the Department of Hematology and Oncology at Dr. Robert Reid Cabral Children’s Hospital in Santo Domingo, Dominican Republic. Further workup included chest X-ray, bone scan, CT angiography, and neck through pelvis CT. There was no evidence of neighboring solid organ invasion, neuro-vascular invasion, regional lymph node involvement,

or distant metastasis.

The original biopsy sample was reviewed at our institution and determined to be adequate. However, in the absence of a clear diagnosis, the biopsy was sent for second opinion to St. Jude Children’s Research Hospital. The report described: “The biopsy shows infiltrative sheets of epithelioid cells with large nuclei and abundant eosinophilic cytoplasm admixed with a prominent acute and chronic inflammatory infiltrate. Scattered cells display a rhabdoid appearance with eccentric nuclei and glassy cytoplasm. Immunohistochemistry revealed co-expression of vimentin, cytokeratin AE1-AE3 and epithelial membrane antigen, all this finds compatible with Epithelioid Sarcoma.” These findings are illustrated in figure 2.

**Treatment and evolution**

Based on clinical findings, the patient was determined to have a non-metastatic, bone-invasive, non-resected, malignant soft tissue sarcoma of size greater than 5cm. Using as a reference the most recently completed Children’s Oncology Group soft tissue sarcoma clinical trial<sup>[9]</sup>, which is used as standard of care in many pediatric



**Figure 2.** H+E histology staining and immunohistochemistry images. Figure: 3A, Diffusely arranged epithelioid cells infiltrating the bone and admixed with acute and chronic inflammatory cells (H&E, 200X); 3B, Some cells show eccentric nuclei, prominent nucleoli and eosinophilic cytoplasm (H&E, 400X); 3C, Tumor cells demonstrate strong cytoplasmic expression of cytokeratin AE1/AE3 (400X); 3D, Loss of expression of INI1 protein is noted in the tumor cells. The inflammatory cells and endothelial cells provide positive internal control for INI-1 immunostain (400X).

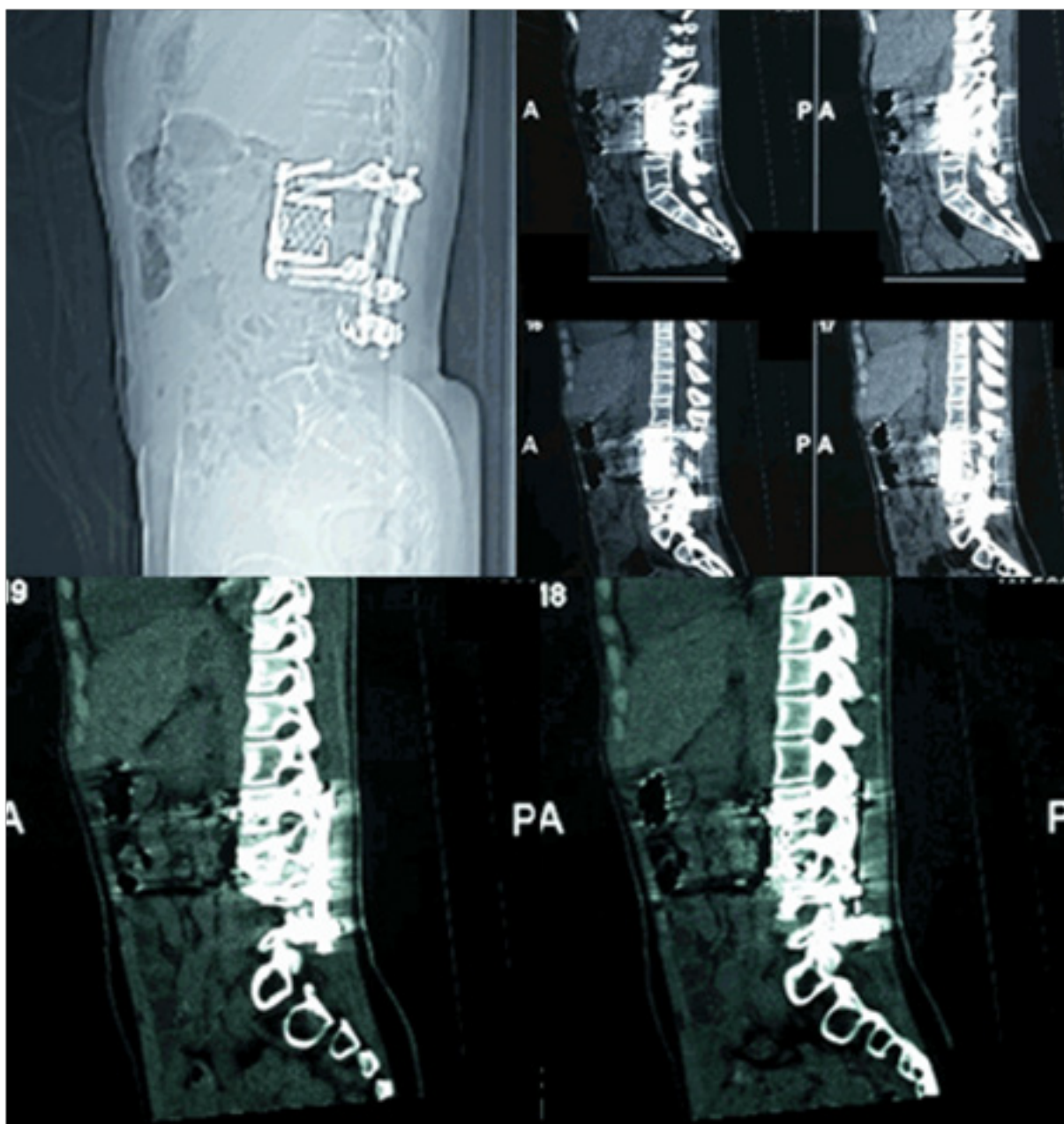
oncology institutions in North America, the patient proceeded to start treatment with one cycle of neoadjuvant chemotherapy and radiation therapy starting at week 4. In total, the patient received 7 cycles of chemotherapy. Four cycles included ifosfamide 9 gm/m<sup>2</sup> divided into three days and doxorubicin 75 mg/m<sup>2</sup> divided into two days. Two cycles included ifosfamide only and one cycle included doxorubicin with same reference dosing. The cumulative ifosfamide dose was therefore 36 gm/m<sup>2</sup> and the total doxorubicin dose 375 mg/m<sup>2</sup>. Bladder protection was provided with mesna and hyperhydration. Local control was provided starting at week 4 with 45Gy of radiation to the original tumor volume using intensity modulated radiation therapy (IMRT). The patient went for second look surgery and reconstruction of L3 vertebra at week 13 (Figure 3 for post-operative x-rays and CT). No tumor or residual mass was at the time of second-look surgery and the biopsies obtained were negative for presence of malignant cells. The patient tolerated treatment very well without significant toxicity.

## DISCUSSION

### Epithelioid Sarcoma

Epithelioid sarcoma (ES) is a high-grade malignancy. It was described by Laskowski and Enzinger, first in 1961 and later in 1970<sup>[1,2]</sup>. It typically occurs in the distal extremities of young adults as a slow-growing nodule within the dermis, subcutaneous tissue or in the deep soft tissues<sup>[1-3]</sup>. It can be mistaken with chronic inflammatory processes, necrotizing granulomas, and some fibrohistiocytic tumors, generally has an epithelial and mesenchymal differentiation<sup>[3]</sup>.

The conventional or distal form is composed of spindle-to-polygonal epithelioid cells arranged in nodules that commonly exhibit central necrosis<sup>[4]</sup>. In 1997, a proximal form arising in the deep part of the pelvis, perineum, and genital tract and proximal extremities was described<sup>[4,5]</sup>. As described by the authors<sup>[4]</sup>, it consists of large epithelioid carcinoma-like and/or rhabdoid cells, has a more aggressive clinical course than distally located tumors, and has a



**Figure 3** Post-operative CT at final follow up that shows complete remission of the mass and the orthopedic reconstruction.



possible link with malignant rhabdoid tumor. Local recurrence rate as high as 85% and 30-50% likelihood for metastases, predominately lymphatic or in the lungs, have been reported<sup>[8]</sup>.

To our knowledge, there are only three cases of ES reported in the literature with localization to the spine (lumbo-sacral junction, sacrum and thoracic)<sup>[6-8]</sup>. Distinctive histopathological features have not been reported for this location. This is the first case of ES diagnosed at our center and since we are the main referral center for pediatric oncology, likely the first pediatric case of ES diagnosed in the Dominican Republic; although a national cancer registry does not exist. Establishing the diagnosis would not have been possible without access to international experts in pediatric oncologic pathology thought existing institutional collaboration.

### Clinical Features

Epithelioid sarcomas occur most frequently in young adult males with usual median age in the mid-twenties<sup>[10]</sup>. Although less common in females, epithelioid sarcoma has a more favorable prognosis in this population<sup>[3]</sup>. These tumors are characterized for slow growing nodules, which may be single or multiple<sup>[11,12]</sup>. More superficial lesions can ulcerate, but in general only 20% of patients present with main complaint of pain at diagnosis<sup>[3]</sup>. About 13% of patients will present with multifocal tumors and about 13% of patients will present with metastatic disease<sup>[13]</sup>. Our patient did not fit the clinical features frequently reported. However, the only other pediatric case of spine ES reported in the literature presented did not present with classic findings either; it presented as a painless, bulging, cystic thoracic spine mass found incidentally in an obese 14-year old boy. Factors adversely affecting the survival rate include size of the tumor, infiltration into muscular, neural or vascular structures, primary location in the trunk, and presence of pulmonary metastasis<sup>[8]</sup>. The only adverse prognostic factor identified in our patient was size >5cm and axial (proximal) location, we therefore hope for a favorable prognosis.

### Pathology

In ES, the cytoplasm is acidophilic, well defined and contains arrays of rough endoplasmic reticulum, a prominent Golgi apparatus, and free ribosomes as well as occasional mitochondria, lysosomes, and droplets of osmophilic material. Intermediate filaments are a common and striking feature than often may be arranged as in myofibroblasts and from paranuclear masses or whorls, thing that give the striking epithelioid appearance and eosinophilia of the tumor cells<sup>[11,13,14]</sup>.

Immunohistochemistry studies are always positive for vimentin, but epithelial markers such as AE1/AE3 are also positive in up to 95% of the cases<sup>[3,14-16]</sup>. Loss of INI staining is also now considered characteristic and can be used to confirm the diagnosis as a complement to epithelial markers and CD34<sup>[4,16]</sup>. CD34 is positive in more than 50% of epithelioid sarcomas<sup>[16]</sup>, but is negative in carcinomas. S100 (commonly positive in malignant peripheral nerve sheath tumor), endothelial markers (positive in epithelioid angiosarcoma), and CK5/6 (positive in squamous cell carcinoma) are usually negative in ES. As described in the case and shown in figure 2, our patient's histologic and immunohistochemistry evaluation was fairly typical.

### Treatment

Adequate treatment for this very aggressive tumor requires early recognition, followed by thorough assessment of extent of disease. Regional lymph node dissection strongly considered because lymph node metastasis are common in ES. Surgical treatment requires early

radical excision or amputation and this is the primary treatment modality if the tumor is situated in the fingers or toes<sup>[1,10,12,13]</sup>. Radiotherapy has been used for marginal primary resection, local regional recurrence, or palliative care<sup>[13]</sup>. Chemotherapy has been use, particularly for initially unresectable tumors and non-metastatic disease<sup>[1,4,5,8,10,12,13]</sup>. Our patient was treated with neoadjuvant chemotherapy and radiation and had an excellent response.

Chemotherapy included two key active agents in non-rhabdomyosarcoma soft-tissue sarcomas, ifosfamide and doxorubicin. On second-look surgery no evidence of disease was identified.

### Prognosis

Factors adversely affecting survival for patients with ES include: age of the patient (older patient's worse prognosis), sex (better prognosis in females), depth of the tumor (infiltration into muscular, neural or vascular structures), size of the tumor (larger worse), localization of the tumor (proximal worse), and pathology features (hemorrhage, necrosis, vascular invasion worse) and presence of metastasis<sup>[1,4,8,13,14,16]</sup>. The 5-year and 10-year overall survival are approximately 50-70% and 42-55% respectively<sup>[3,4,7]</sup>. In other reported spine ES cases, relapse has occurred within 2 years<sup>[7,8]</sup>. The only adverse prognostic factors identified in our patient were size >5cm and axial (proximal) location. She is now 6 months in clinical remission, but she will need continuous observation over several years.

## CONCLUSION

Epithelioid sarcoma of the spine is an extremely rare entity. Because of its aggressive evolution, physicians and pathologists should be aware of this entity to avoid delayed diagnosis as well misdiagnosis. Multimodal therapy with a combination of surgery, chemotherapy and/or radiation is often needed to cure these patients.

This is not a novel case but a diagnostic challenge, particularly in developing countries, where pathologic expertise may be limited, case load is typically large for the number of available pathologists, and extensive immunohistochemistry panels are unaffordable. Furthermore, accurate pathologic diagnosis is only one of many challenges faced by pediatric oncology centers in developing countries to correctly diagnose, treat and cure children with cancer<sup>[17]</sup>. We will monitor this patient's course closely. In this case, we are proud to have offered appropriate, timely treatment, with a similar integral quality as in a developed country.

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## CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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