Extraosseous Ewing’s Sarcoma: Pictorial Review of Imaging Findings, Differential Diagnosis, and Pathologic Correlation

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Abstract
Extraosseous Ewing’s sarcoma (EES), first described in 1969, is a malignant mesenchymal tumor just like its intraosseous counterpart. Although Ewing’s sarcomas are common bone tumors in young children, EESs are rarer and more commonly found in older children/adults, often carrying a poorer prognosis. We discuss the multimodality imaging features of EES and the differential diagnosis of an aggressive appearing mass in proximity to skeletal structures, with pathologic correlates. This review highlights the need to recognize the variability of radiologic findings in EES such as the presence of hemorrhage, rich vascularity, and cystic or necrotic regions and its imaging similarity to other neoplasms that are closely related pathologically.

Introduction
Ewing’s sarcoma was first described in 1921 by James Ewing as an osteolytic bone tumor composed of malignant small round cells.¹² Extraosseous Ewing’s sarcoma (EES) was first described in 1969³; it is a malignant mesenchymal tumor much rarer than its intraosseous counterpart. The few case series and reports of EES that have been published in English literature in the last decade have been listed in → Table 1.⁴⁵ There are a few malignant and benign entities that may mimic an EES on imaging and therefore, it is essential that radiologists be familiar with this entity and its radiological aspects to help render an accurate diagnosis. This article depicts the imaging appearances and findings of five EESs in various anatomical sites, involving multiple modalities (→ Table 2). Pathologic features of EESs are discussed. This review is written with the intent to enhance the existing knowledge base/awareness among radiologists of this rare entity.

Discussion
Ewing’s sarcomas are common bone tumors in children.⁶ EES is rarer, more commonly found in older children/adults, and often carries a poorer prognosis.⁵¹⁰ EES has increasingly been reported from diverse sites whose origin has been attributed to ectopic neural and neuroectodermal proliferations. Genetic studies have suggested that EESs are in the same family as primitive neuroectodermal (PNET) tumors. Furthermore, genetic studies have demonstrated reciprocal
translocation of t(11; 22)(q24; q12) in approximately 95% of patients, with the remainder demonstrating t(21; 22) (q22; q12) translocation. Generally, these tumors are commonly seen in the paravertebral regions or in the deep soft tissues of the extremities, with lower extremities having a higher propensity than upper extremities. Patients with EES often note a rapidly growing soft-tissue mass, with about one-third being painful secondary to compression of adjacent structures. They often present in the second decade of life. There is a mild male predominance and predilection for Caucasians. There has not been any evidence of familial or environmental influence.

Radiographs may demonstrate a nonspecific soft-tissue mass in proximity to a bone without gross osseous involvement. Computed tomography (CT) usually shows a soft tissue mass with similar attenuation as skeletal muscle. Adjacent bone involvement is uncommon. Calcification is exceedingly rare and this feature was a consistent imaging appearance in our patients.

Sonographic findings are variable and nonspecific, and often demonstrate a hypoechoic, heterogeneous mass with internal vascularity. Cystic change and necrosis may be seen. Findings on magnetic resonance imaging (MRI) include a mass with signal intensity similar to skeletal muscle on T1-weighted imaging; internal areas of hemorrhage may be seen as high T1 signal. On T2-weighted images, the mass often demonstrates a heterogeneous intermediate to hyperintense signal. High T2 signal areas representing foci of cystic or necrotic changes are common. On postcontrast images, there is often heterogeneous enhancement. High-flow vascular channels or flow voids may also be seen (Fig. 5) which is extremely common, although not unique to EES. Some of
these masses may be quite complex, having undergone cystic degeneration/necrosis, and may contain internal septations. Fluid-fluid levels may also be observed. Histopathology confirms EES via monotonous proliferation of small blue round cells solidly packed with intracellular glycogen which may indent nuclei. Cystic/necrotic regions demonstrating rich vascularity, and areas of hemorrhage are often present. Membrane staining is almost always positive for CD99. Histologic staining for FLI1, demonstrating t(11; 22), will provide definitive diagnosis.

Treatment often involves neoadjuvant chemotherapy typically with ifosfamide and etoposide followed by a combination of surgical excision and radiation therapy. Increased tumor burden and distant metastasis at presentation are associated with a poor overall survival. The 5-year survival for patients with localized disease is around 60% and 40% for patients with metastatic disease.

Differential Diagnosis

Differential considerations of EES mainly include rhabdomyosarcoma and synovial sarcoma. Neuroblastoma and lymphoma are less common considerations. Benign entities such as a venous malformation, especially the microcystic type, soft-tissue abscesses, and hematomas can also mimic a soft tissue tumor. Rare tumors, such as extraosseous mesenchymal chondrosarcomas, may also be included in the differential for an EES.

Rhabdomyosarcoma is the most common soft tissue malignancy in children and may be painless though rapidly growing. CT will demonstrate a soft-tissue density with heterogeneous enhancement ± adjacent bony.
destruction.\textsuperscript{27} MRI demonstrates T1 isointensity to muscle ± areas of hemorrhage and T2 hyperintensity to muscle associated with avid enhancement.\textsuperscript{28} There may be prominent flow voids (in alveolar subtype). Embryonal, alveolar, and pleomorphic histologic subtypes, all show skeletal muscle differentiation which is key to histopathological diagnosis (\textsuperscript{27,28,29} Fig. 9).

Synovial sarcomas are the most common nonrhabdomyosarcomatous childhood malignancies of the lower extremities.\textsuperscript{30} These slow growing masses have predilection for juxta-articular regions.\textsuperscript{30,31} CT examination will demonstrate a heterogeneous soft-tissue mass with or without calcifications (\textsuperscript{29} Fig. 10). MRI demonstrates a mass, generally isointense to muscle on T1-weighted imaging, with heterogeneous and hyperintense T2 signal from necrosis, areas of hemorrhage, and bands of fibrosis. The combination of large cystic areas and prominent hemorrhagic foci often creates a "bowl of grapes appearance."\textsuperscript{30} Although the poorly differentiated subtype is histologically similar to EES, monophasic...
subtype reveals uniform atypical spindle cells, while biphasic subtypes have an epithelial element (►Fig. 10).32 “Synovial” is a misnomer, as these tumors are not derived from synovium. Cytogenetic studies show translocation of (x; 18).30-35

Outside of the adrenal gland, neuroblastomas (NBLs) are often paravertebral in location but in a younger demographic than EES.36,37 Laboratory assessment will commonly show elevated urinary catecholamine levels.36 Bony metastases are common and may be the presenting finding.36 On ultrasound, NBLs are heterogeneous solid lesions, mostly echogenic.36 The masses may appear heterogeneous from necrosis or hemorrhage, and calcifications are common.36 CT or MRI can accurately assess the location and the size of the primary tumor and identify vascular encasement which determines tumor resectability.36,37 Coarse, finely stippled, or curvilinear calcifications are seen in 85% of the neuroblastomas.36 MRI demonstrates high and low T1 and T2 signal, related to calcification, hemorrhage, and necrosis.36,38 Microscopic features include immature, undifferentiated sympathetic cells.39-42

Lymphomas are differentiated from EES via identification of lymph node involvement; EES rarely involves lymph nodes.43-45

Extraosseous mesenchymal chondrosarcomas are painless, slowly growing masses with chondroid matrix (►Fig. 11). The lesion is extremely rare in patients younger than 20 years of age. On CT, a soft tissue mass with similar attenuation to muscle is demonstrated with either central or eccentric mineralization.46,47 Necrosis may be present, and enhancement is heterogeneous. MRI findings include a soft-tissue mass containing variable low-signal mineralization with T2 hyperintensity and intense heterogeneous enhancement.46

Histopathologic features include a biomorphic appearance with well-differentiated cartilage surrounded by sheets of closely packed undifferentiated cells. Stains are positive for S100, neuron-specific

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Age (peak)</th>
<th>Sex</th>
<th>Location</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyosarcoma</td>
<td>First decade</td>
<td>Slight male predilection</td>
<td>Anywhere in the body. The alveolar and pleomorphic variants having a predilection for extremities</td>
<td>Heterogeneous magnetic resonance imaging (MRI) signal intensity and enhancement. Flow voids. Bone involvement in 25%</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>Third decade of life</td>
<td>Female predilection</td>
<td>Juxta-articular regions</td>
<td>“Bowl of grapes” and “triple sign” appearance on MRI from areas of necrosis and hemorrhage. Calcification in 30% of patients.</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>One</td>
<td>No sex predilection</td>
<td>Adrenal and paravertebral</td>
<td>Necrosis or hemorrhage, and calcifications are common. MRI demonstrates high and low T1 and T2 signal, related to calcification, hemorrhage, and necrosis.</td>
</tr>
<tr>
<td>Extraosseous mesenchymal chondrosarcoma</td>
<td>Second to third decade.</td>
<td>Female predilection</td>
<td>Head and neck</td>
<td>Central or eccentric mineralization. MRI variable low signal mineralization with T2 hyperintensity and intense heterogeneous enhancement</td>
</tr>
<tr>
<td>Venous malformation</td>
<td>Any age</td>
<td>No sex predilection</td>
<td>No site predilection</td>
<td>Highly vascular lesion with thrombus, or phlebolith, on imaging</td>
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Table 3  Differential diagnosis for Extraosseous Ewing’s sarcoma

Fig. 9 (A–C) Axial CT image (A) demonstrates a left axillary mass (white arrow). Hematoxylin and eosin magnification ×400 specimen (B) demonstrating skeletal muscle differentiation (black arrow). Rhabdomyoblasts highlighted by desmin stain (C). CT, computed tomography.

Fig. 10 (A, B) Axial CT (A) demonstrates a soft tissue mass (white arrow) in the anterior right upper thorax extending between the ribs. Hematoxylin and eosin magnification ×160 (B) shows short, uniform, moderately atypical spindle cells, consistent with monophasic synovial sarcoma. CT, computed tomography.
enolase, and Leu-7, and negative for actin, epithelial membrane antigen, and cytokeratin.47-51

Benign entities including venous malformations, soft-tissue abscesses, and hematoma can be distinguished based on several key features. Rapidly growing venous malformations can be distinguished by identifying a highly vascular lesion with thrombus or phlebolith on imaging. Soft-tissue abscesses are often thick rimmed, with irregular peripheral enhancement, and the patient usually has systemic and local symptoms of infection. Hematomas may show dark signal on susceptibility weighted sequences due to presence of blood products.52-56

Conclusion

EES should be considered in the differential diagnosis when a circumscribed, aggressive appearing mass is encountered in the lower extremities or paravertebral regions of an older child/adolescent. Features, like flow voids, T1 signal similar to muscle, proximity to bone without gross osseous involvement in the early stages, cystic changes/necrosis, and lack of calcification, are seen in EES and are helpful in narrowing the differential diagnosis.

Declaration of Patient Consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of Interest

None declared.

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