Pediatric Extraosseous Ewing Sarcoma: Common Imaging Findings, Differential Diagnosis, and Pathologic Correlates; a Multi-Year Analysis at a Large Children's Hospital.

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Learning objectives

* Viewers will gain a visual understanding of the multi-modality imaging appearances and findings of extraosseous Ewing sarcomas in various anatomical sites.

* Additionally, viewers will be able to understand and recognize pathological correlates of extraosseous Ewing sarcomas.

* Finally, viewers will be able to include extraosseous Ewing sarcoma in the differential diagnosis along with other soft tissue masses.
**Background**

Ewing sarcoma was first described in 1921 by James Ewing as an osteolytic bone tumor composed of malignant, small round cells. Extraosseous Ewing sarcoma was first described in 1969; it is a rare, malignant mesenchymal tumor similar to its intraosseous counterpart. Although Ewing sarcomas are one of the most common bone tumors in children, extraosseous Ewing sarcoma is more commonly found in adults, and often carry a poorer prognosis [1].

This tumor has increasingly been reported from diverse sites whose origin has been attributed to ectopic neural and neuroectodermal proliferations. Genetic studies have suggested that extraosseous Ewing sarcomas are in the same family as primitive neuroectodermal (PNET) tumors. Furthermore, genetic studies have demonstrated reciprocal translocation of t(11;22)(q24;q12) in about 95% of patients, with a majority of the remainder demonstrating t(21;22)(q22;q12) [2,3].

Patients demonstrating extraosseous Ewing sarcomas often note a rapidly growing soft tissue mass, with about 1/3 being painful secondary to compression of adjacent structures. They often present in the second decade with a mild male predominance and predilection for caucasians. There has not been any evidence of familial or environmental influence [2,3,4].

Treatment often involves surgical excision and chemotherapy. Radiation therapy and stem cell reinfusion are considered as well, on a case-by-case and institutional basis [5,6].

There are a few malignant and benign entities that may mimick extraosseous Ewing sarcoma. Therefore, it is essential that radiologists be familiar with this entity and its radiological aspects to help generating an accurate differential diagnosis.
Findings and procedure details

The imaging findings of extraosseous Ewing sarcomas are variable in appearance and location, with a common theme. The imaging appearance is typically aggressive and complex. The lesions are large, solid, and heterogeneous, with some having cystic changes. Familiarity with the imaging appearance on various modalities is critical.

Generally, these tumors are commonly seen in the deep soft tissues of the extremities, with lower extremities having a higher propensity than upper extremities, though they can be found anywhere. Extraosseous Ewing sarcomas are often close to, though not originating from, bone. Often the masses are well circumscribed though can be infiltrative, and multilobulated. Radiographs may demonstrate a soft tissue mass [1-7].

Computed tomography (CT) findings usually show a soft tissue mass with similar attenuation compared to skeletal muscle (Figure 1). Adjacent bone involvement is uncommon, as is bony metastatic disease in early stages (Figure 2). Calcification is exceedingly rare (Figure 1).

Sonographic findings are variable and nonspecific, and often demonstrate a hypoechoic, heterogeneous mass with internal vascularity (Figure 3). Cystic change and necrosis may be seen (Figure 4).

Findings on magnetic resonance imaging (MRI) include a mass with signal similar to skeletal muscle on T1 weighted imaging, which may be mildly increased (Figure 5) or decreased (Figure 7). Areas of hemorrhage will demonstrate T1 hyperintensity. T2 weighted images often demonstrate heterogeneous intermediate to hyperintense signal. High signal areas representing foci of fluid or cysts are common (Figure 7). On contrast enhanced images, there is often heterogeneous enhancement (Figure 5 and 7). High flow vascular channels or flow voids may also be seen (Figure 5).

Some of these masses may be quite complex and have undergone cystic degeneration/necrosis with internal septations (Figure 9). CT evaluation of these complex masses demonstrate a heterogenous mass with mixed soft tissue and fluid density secondary to the cystic changes, with calcification almost never seen (Figure 9). MRI of these lesions will demonstrate multiple cysts, hyperintense on T2 weighted images, with enhancement of the soft tissue component, cysts, and septations (Figure 10). Fluid-fluid levels may also be observed [8,9].
On gross pathological specimen extraosseous Ewing sarcoma often appears gray-yellow or gray-tan with lobulations and a soft texture. Histopathology confirms extraosseous Ewing sarcoma via monotonous proliferation of small blue round cells solidly packed with intracellular glycogen which may indent nuclei (Figure 6, 8). Cystic/necrotic regions demonstrate rich vascularity, and areas of hemorrhage are often present. Membrane staining is almost always positive for CD99 (Figure 6, 8). Histologic staining for FLI1, demonstrating t(11;22), will provide definitive diagnosis (Figure 8).

Differential considerations of extraosseous Ewing sarcoma 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 extraosseous soft tissue sarcoma. Although metastatic disease to the soft tissues may mimic an extraosseous Ewing sarcoma, this is rarely seen in children.

Rhabdomyosarcomas are the most common soft tissue malignancy and may be painless though rapidly growing. CT will demonstrate a soft tissue density with heterogeneous enhancement +/- adjacent bony destruction. MRI demonstrates T1 isointensity to muscle +/- areas of hemorrhage, and T2 hyperintensity to muscle with avid enhancement. 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 (Figure 11) [10,11].

Synovial sarcomas are one of the most common childhood malignancies in the lower extremities. These slow growing masses have predilection for juxtaarticular regions. CT examination will demonstrate a heterogeneous soft tissue mass +/- calcifications. MRI demonstrates a mass generally T1 isointense to muscle with bands of fibrosis and variable enhancement. Although the poorly differentiated subtype is histologically similar to extraosseous Ewing sarcoma, monophasic subtype reveal uniform atypical spindle cells while biphasic subtypes have an epithelial element (Figure 12). "Synovial" is a misnomer, as these tumors are not derived from synovium. Cytogenetic studies show translocation of (x;18) [12].

Neuroblastomas are often paravertebral in location and in a younger demographic than extraosseous Ewing sarcoma. Laboratory assessment will commonly show elevated urinary catecholamine levels. Bony metastases are common and may be the presenting finding. Although the masses may appear heterogeneous from necrosis or hemorrhage, calcifications are common. MRI demonstrates high signal on T2 and low signal on T1 weighted imaging with heterogeneous signal related to calcification, hemorrhage and necrosis. Sonographic images will often show increased,
heterogeneous, echogenicity with shadowing from calcifications. Microscopic features include immature, undifferentiated sympathetic cells [13].

Lymphomas are differentiated from extraosseous Ewing sarcoma via identification of lymph node involvement; extraosseous Ewing sarcoma rarely involves lymph nodes.

Extraosseous mesenchymal chondrosarcomas are painless, slowly growing masses with chondroid matrix (Figure 13). On CT, a soft tissue mass with similar attenuation to muscle is demonstrated with either central or eccentric mineralization. Necrosis may be present, and enhancement is heterogeneous. MRI findings include a soft tissue mass containing variable low signal mineralization with isointensity (to muscle) on T1 weighted imaging and hyperintensity on T2 weighted imaging with intense heterogeneous enhancement (Figure 13). Histopathologic features include a bimorphic appearance with well-differentiated cartilage surrounded by sheets of closely packed undifferentiated cells. Stains are positive for S100, neuron-specific enolase, and Leu-7, and negative for actin, epithelial membrane antigen, and cytokeratin [14-16].

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 will commonly have systemic symptoms of infection. Hematomas often demonstrate fluid-fluid levels and lacks solid regions of enhancement [17-19].
Fig. 1: Initial axial (soft tissue and bone windows), coronal, and sagittal CT at diagnosis shows a circumscribed, non-calcified, slightly heterogeneous subcutaneous mass in the right occipital scalp associated with small soft tissue tail medially. There is thinning of the calvarium compared to left side without destruction or intracranial extension.

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**Fig. 2:** Initial staging bone scan from same patient (Figure 1) demonstrates no bony metastatic lesions.

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**Fig. 3:** Initial ultrasound of this patient shows a circumscribed solid mass with mild heterogeneous echotexture (predominately hypoechoic with areas of slight hyperechogenicity) with mild internal vascularity in the right posterior neck subcutaneous soft tissues just to the right of spinous process of C2 and C3. No sonographic evidence of internal calcifications are present.

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Fig. 4: Left thigh mass adjacent to hip demonstrating heterogeneous echogenicity appearing predominantly solid with some areas of cystic change/necrosis. The mass did contain some color Doppler flow.

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Fig. 5: (From left to right, top to bottom) Axial T1, T2, T2 fat sat and T1 fat sat with gadolinium, sagittal T1, T2, and T1 fat sat with gadolinium demonstrates, within the right anterior deltoid muscle, a mildly heterogeneous but predominantly of intermediate T1 (greater than muscle) and T2 signal solid mass that diffusely enhances and contains a few flow voids representing vessels.

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**Fig. 6:** Histopathological images from patient in Figure 5: (Top and bottom left) Low and high power views of the classic round blue cell look that is seen with neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and lymphoma. (Bottom right) Immunohistochemical stain for CD-99, which is a Beta 2 Microglobulin on the outside of the cell hence the brown outline. In a mass CD-99 is not specific for Ewing sarcoma but highly characteristic. *Special thanks to the Pathology Department of Akron Children’s Hospital for pathological images.*

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**Fig. 7:** Axial STIR, T1, T1 fat sat, and T1 fat sat post gadolinium with sagittal STIR and T1 with gadolinium demonstrates a mass within the left biceps muscle that is of heterogeneous increased T2 signal and intermediate T1 signal (same as muscle) that demonstrates heterogeneous enhancement with some areas of cystic change/necrosis. There is adjacent edema in the noninvolved biceps musculature.

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**Fig. 8:** Histopathological images from patient in Figure 7: (Top) High power view of the small round blue cell tumor. (Bottom left) The CD99 staining demonstrating a rim of brown around the cells, highly characteristic of, though not specific for, Ewing sarcoma. (Bottom right) The FLI1 is a new immunohistochemical that looks for the chromosome 11-22 translocation (EMS-FLI1) that is characteristic of Ewing sarcoma, thus it stains the nucleus brown as seen in this patient. *Special thanks to the Pathology Department of Akron Children's Hospital for pathological images.*

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Fig. 9: Sagittal and transverse sonographic images (top row) demonstrate a predominantly hyoechoic mass in the right groin with internal septations and areas of heterogenous increased echogenicity. Axial, coronal and sagittal CT demonstrate a heterogenous well circumscribed soft tissue mass with mixed density in the right groin without evidence of calcification.

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Fig. 10: (Same patient as Figure 7) Axial T1, T2, T2 fat sat and T1 fat sat post gadolinium with coronal T1, T2, and T1 fat sat post gadolinium demonstrate a complex mass, predominantly multicystic and septated with some solid tissue in the right proximal thigh quadriiceps muscles at the groin, with enhancement of the cysts, septations and solid tissue.

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Fig. 11: Axial CT demonstrates multiple left axillary and subpectoral masses. Pathologic specimen demonstrating skeletal muscle differentiation (arrow) (H&E, 400X). Rhabdomyoblasts highlighted by desmin stain (bottom) (Desmin, 400X). *Special thanks to Dr. Daniel Wasdahl for pathological images.*

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**Fig. 12:** Chest radiograph and coronal and axial CT with soft tissue and bone windows demonstrate a heterogeneous soft tissue mass in the anterior right upper thorax extending between ribs. Pathologic specimen demonstrating short, fairly uniform, moderately atypical spindle cells (H&E, 160X), consistent with monophasic synovial sarcoma. *Special thanks to Dr. Daniel Wasdahl for pathological images.*

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Fig. 13: Top left: AP and lateral (frog leg) radiographs of the left femur demonstrate an extraskeletal lesion with dense mineralization, adjacent to the medial aspect of the femur. Top right: Coronal T1 and Sagittal STIR images demonstrate the superior and inferior margins of the mass, again without evidence of signal abnormality in the adjacent femur to suggest bony invasion. Bottom: Axial MRI sequences (T1 Fat Sat, T2, and T1 Fat Sat post contrast) demonstrate a large mass centered in the adductor magnus of the left thigh with internal calcification and peripheral vascularity. The mass demonstrates intermediate T1 signal and increased heterogeneous T2 signal (black pepper sign) compared to background muscle. There are no signal abnormalities within the adjacent femur to suggest bony invasion.

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Conclusion

Extraosseous Ewing sarcoma should be considered when a circumscribed, solid, aggressive appearing mass is encountered in an older child/adolescent in the extremities or in close proximity to the skeletal structures.

Familiarity of the radiologist with its radiological appearance is essential in providing an accurate differential diagnosis. Features including flow voids, T1 signal similar to muscle, proximity to bone, cystic changes/necrosis and lack of calcification all help consider extraosseous Ewing sarcoma and narrow the differential diagnosis. While a predominantly cystic/necrotic mass with imaging features similar to what we have demonstrated favor extraosseous Ewing sarcoma, this entity should also be considered when a lesion presents as a predominantly solid mass, similar to rhabdomyosarcoma, or in close proximity to skeletal structures, similar to synovial sarcoma.

Knowledge of pathological correlates provides the radiologist with a foundation to better understand the variability of radiological findings, including the presence of rich vascularity in cystic or necrotic regions, and hemorrhage. Solidly packed blue round cells and CD99 positivity, along with FLI1 staining to recognize chromosome 11;22 translocation, help confirm the diagnosis.
References


