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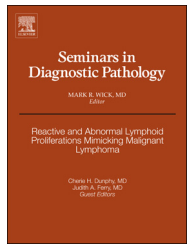

# Ewing sarcoma

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ABSTRACT

Classification of small round cell tumors of bone is often challenging due to overlapping clinicopathologic features. The purpose of this article is to review the clinical, radiological, histologic, and molecular features of Ewing sarcoma and to provide a discussion of the differential diagnosis of small round cell tumors of bone.



## Introduction

Skeletal Ewing sarcoma, extraosseous Ewing sarcoma, primitive neuroectodermal tumor (PNET), and Askin tumor (Ewing sarcoma arising in chest wall) are thought to represent a clinicopathologic spectrum of the same neoplastic entity, sometimes collectively called "Ewing family of tumors." Shared immunohistochemical and genetic features support this view. The purpose of this article is to provide an overview of the clinical, radiological, histologic, and molecular features of Ewing sarcoma and to review bone tumors in the histologic differential diagnosis.

## Ewing sarcoma

### *Epidemiology, clinical, and radiographic features*

Ewing sarcoma (ES) is the second most common primary malignant bone tumor in children and adolescents, following osteosarcoma. The highest incidence is in the second decade of life, with approximately 9–10 cases per million per year seen in patients aged 10–19 years compared to an overall incidence of three cases per million per year in the United States population.[1,2] It is uncommon in patients younger than 5 years or older than 30 years. ES occurs predominantly in Caucasians; it is infrequent in the African American population for reasons unknown.[3] A slight male predominance exists (M:F sex ratio = 1.5:1).[1,3]

The majority of ES arise in bone, and up to 30% in soft tissue.[4] Skeletal ES most frequently involves the diaphysis or metadiaphyseal region of long bones (lower > upper extremities). The pelvis, ribs, and spine are also commonly involved.[2,5] The histogenesis of ES remains debated but is thought to originate from either neural crest stem cells[6,7] or mesenchymal stem cells.[8]

Clinically, patients often present with localized pain and swelling. Patients may also present with a palpable mass, pathologic fracture, or constitutional symptoms such as fever, fatigue, weight loss, or anemia.[9]

Radiographically, ES is a permeative and predominantly osteolytic lesion that frequently extends through cortex into the periosteum and soft tissue. Intermittent activity of the tumor creates the classic "onion-skin" multilayered periosteal reaction. Erosion of outer cortex by periosteal tumor can result in a concave cortical defect called "saucerization." A "hair-on-end" vertical form of periosteal reaction and Codman triangles (Fig. 1) may also be seen in ES.[10] In the absence of cortical destruction, radiographic findings may be subtle and Ewing sarcoma may not be seen on plain radiographs.

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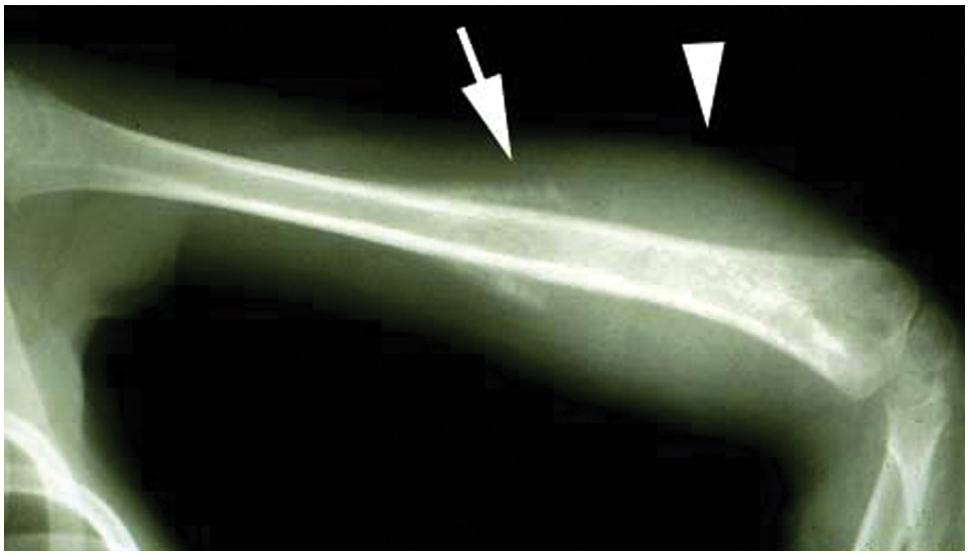

**Fig. 1 – Ewing sarcoma of bone in a child. Plain radiograph shows a mass in the metadiaphyseal region of the distal humerus. Codman triangles (arrow) and extension of tumor into surrounding soft tissue (arrowhead) are seen.**

Imaging modalities such as magnetic resonance imaging and computed tomography help determine the extent of bone and soft tissue tumor involvement.

### *Pathology*

Grossly, the mass is gray-tan with infiltrative borders. Areas of hemorrhage and necrosis are often present, resulting in soft or partially liquefied areas that may resemble purulent exudate.

Microscopically, ES is a histologically diverse group of tumors with varying degrees of neural differentiation. Traditionally, ES is divided into three major histologic subtypes: classical ES, primitive neuroectodermal tumor (PNET), and atypical ES. *Classical ES*, which constitutes the majority of cases, is comprised of solid sheets or vague lobules of uniform small cells with round or oval nuclei, smooth nuclear contours, fine chromatin, inconspicuous nucleoli, scant amount of lightly eosinophilic or clear cytoplasm, and indistinct cell borders (Fig. 2A). Cytoplasm clearing is due to accumulation of cytoplasmic glycogen, which can be highlighted by Periodic acid–Schiff (PAS) stain. Areas of necrosis and hemorrhage are common. Perivascular cuffing may be seen in areas of geographic necrosis (Fig. 2C). Mitotic count is typically low and extracellular matrix absent.

Tumors with evidence of neural differentiation (Fig. 2D) are classically termed *primitive neuroectodermal tumor* (*PNET*). Homer Wright rosettes (clusters of cells with a solid neurofibrillary core formed by tangled cytoplasmic processes) or immunohistochemical evidence of neural differentiation support a diagnosis of PNET. Various definitions have been proposed to define the minimal criteria for PNET,[11] but a widely accepted diagnostic criterion is not available.

*Atypical ES* (*large cell ES*) refers to tumors with features that deviate from those described in classical ES such as nuclear enlargement and pleomorphism, irregularity of nuclear membrane, vesicular or course chromatin texture, and prominent nucleoli (Fig. 3A).[12–14]

Other histologic patterns have been observed in genetically confirmed cases of ES such as extensive spindling (Fig. 3B), abundant hyaline sclerosis, hemagioendothelial features, and adamantinoma-like ES (Fig. 3C and D). More typical ES histomorphology is usually seen, at least focally, within these variants.[12,14,15] The adamantinoma-like ES is an interesting variant with a nested, epithelioid growth pattern. Histologic features that have been described include prominent desmoplasia, peripheral nuclear palisading, hyperchromatic nuclei, and dense eosinophilic matrix.[12,16] Adamantinoma-like ES usually has strong cytokeratin staining. Suspected ES cases with unusual histologic features require ancillary studies to confirm the diagnosis.

While knowledge of histologic heterogeneity is important for recognizing ES, determination of exact histologic subtypes may not be critical given shared genetic abnormalities that characterize the Ewing family of tumors.

### *Immunophenotype*

CD99 is a highly sensitive and useful immunohistochemical marker for ES, usually showing a diffuse, strong, membranous pattern of distribution (Fig. 2B).[12,14] In tumors that are CD99 negative or have unusual staining pattern, further workup with cytogenetic or molecular studies should be done to confirm ES. Although sensitive, CD99 is not specific for ES. Many other neoplasms with small round cell morphology can be positive for CD99 including lymphomas, mesenchymal chondrosarcoma, small cell osteosarcoma, synovial sarcoma, and desmoplastic small round cell tumor (DSRCT).[17–22] Markers of neural differentiation (e.g., NSE, S-100 protein, and CD57) may be expressed even in the absence of histologic evidence of neural differentiation.[11,23]

FLI1 is touted as a sensitive marker for ES, with positive cases showing nuclear staining. FLI1, however, is not specific for ES and has been observed in other neoplasms including lymphoblastic lymphomas (LBL), DSRCT, Merkel cell carcinoma, and synovial sarcoma. Background endothelial cells