Ewing sarcoma family of tumors: a pictorial educational review

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Authors: F. Moloney¹, M. Twomey², P. Nicholson¹, K. O'Regan¹; ¹Cork/IE, ²IE
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Learning objectives

To review the Ewing sarcoma family of tumors (ESFT) including their clinical presentation, typical radiological features, and management.

Background

The Ewing sarcoma family of tumors (ESFT) represents a family of morphologically similar small round-cell neoplasms.[i] on page

The family includes Ewing sarcoma of bone, extraosseus Ewing sarcoma, primitive neuroectodermal tumor (PNET), peripheral neuroepithelioma and Askin tumor (thoracopulmonary PNET).

Ewing sarcoma is poorly differentiated and can arise in bone or soft tissue. PNET shows neuroectodermal differentiation and arises in soft tissue. Each tumor arises from a common precursor cell and distinction is based on cellular differentiation or anatomic location or both. [ii] on page

Pathognomonic nonrandom translocations involving the EWS gene on chromosome 22 and one of several members of the ETS family of transcription factors on chromosome 11 are implicated in the majority of cases. The translocation t(11;22)(q24;q12) is the most common and leads to the formation of the EWS-FLI1 fusion protein, which contributes to ESFT pathogenesis by modulating the expression of target genes.[iii] on page

ESFT are the second most common type of bone cancer in children and adolescence. Clinical presentation is usually with localized bone pain with an associated soft tissue mass. The most significant prognostic factor for patients with ESFT is the presence of localized or distant metastatic disease.


Findings and procedure details

Ewing sarcoma (ES) is the second most common primary malignant bone cancer in children and young adults, after osteosarcoma. It is slightly more common in boys (55:45 male:female ratio). The most common age of diagnosis is the second decade of life, although approximately 20% of cases are diagnosed in patients over 18 years of age. [i] on page

Clinical presentation

Localized pain is the most common presenting symptom in patients with ES. Pain can be intermittent and variable in intensity and persist during the night. Pain is often accompanied by paresthesia. Patient's pain may then be followed by a palpable mass. Constitutional symptoms such as a low-grade fever or malaise may also accompany symptoms. Pain is often mistaken for bone growth or injuries resulting from sport or everyday activities. Pain without defined trauma adequate to explain the symptoms, lasting longer than a month, continuing at night, or with any other unusual features should prompt early investigation. [ii] on page

Most Ewing sarcomas occur in the flat bones of the axial skeleton and in the long bones, and unlike osteosarcomas, tend to arise in the diaphysis rather than the metaphysis. The most common sites of primary Ewing sarcoma are the pelvic bones, the long bones of the lower extremities, especially the femur and tibia, and the bones of the chest wall. Metastases, detectable in about 25% of patients at presentation, are most commonly to lung, bone, and bone marrow. Metastases to lymph nodes or other sites like the liver or central nervous system are rare.

Askin tumor (thoracopulmonary PNET) is the single most common presentation of extraskeletal ESFT. [iii] on page It typically presents as a large chest wall mass with intrathoracic extension. Tumors may displace the underlying lung or directly invade the pulmonary parenchyma or mediastinum and destroy adjacent ribs. MRI can be useful to delineate chest wall invasion. Pleural thickening and malignant effusion can also be seen. [iv] on page

Imaging

Initial investigation of ES is with a conventional radiograph. Tumor-related osteolysis, detachment of the periosteum from the bone (Codman triangle), and spiculae of calcification in a soft tissue mass are typically seen. A mixed sclerotic-lytic type lesion with a sclerotic component of 75% occurs in 40% of cases. A 50% sclerotic-
50% lytic type is seen in 20% of the cases. Only 11% present with a sclerotic component of 25%. An exclusively sclerotic lesion is infrequent (6%). Cortical permeation and destruction are present in 42%, whereas cortical thickening is rather uncommon (20%). A pathologic fracture is seen in 7.8% of cases. Osteomyelitis may present with a pattern similar to Ewing's sarcoma on a conventional radiograph.

The local extent of disease, including the intramedullary portion and the relation of the lesion to adjacent blood vessels and nerves, is best characterized with magnetic resonance imaging (MRI). Tumors are typically isointense or hypertense to muscle on T1-weighted images and hyperintense to muscle on T2-weighted images. MRI reveals skip metastases in 14% of patients.

MRI is highly accurate in the assessment of the intramedullary extent of tumor with excellent correlation between longitudinal T1-weighted images and identical pathological surgical specimens.

Axial turbo spin echo T2-weighted images best display the anatomical relationship between the tumor and adjacent soft tissues and neurovascular structures, allowing differentiation between intracompartmental and extracompartmental disease.

MRI is very sensitive, but less specific for the determination of epiphyseal involvement. It is also specific for excluding joint involvement although false-positive results can occur secondary to synovial inflammatory reactions.

Computed tomography (CT) can be useful for evaluating joint extension, periosteal reaction and matrix of the lesion. On CT, tumors are heterogeneous in attenuation and show variable enhancement following contrast administration. Central areas of low attenuation necrosis may be present but calcification is uncommon occurring in approximately 10%.

FDG-PET/CT has been shown to be a valuable tool in the management of ESFT with a reported sensitivity of 96% and a specificity of 92% for the staging and restaging of disease. FDG-PET/CT is also the most sensitive modality for therapeutic follow-up and surveillance following treatment, and can reveal early changes in tumor metabolism, which is an indicator of the therapeutic effect.

Management

Management of the ESFT is preferably conducted at a specialist center with a multi-disciplinary team. Treatment options include both local control with surgery, radiation or a combination of both, or systemic chemotherapy. Chemotherapy regimens
include cyclic combinations, incorporating vincristine, doxorubicin, cyclophosphamide, etoposide, ifosfamide and occasionally actinomycin D. Studies incorporating intensive therapy followed by stem cell infusion show no clear benefit. The results of new approaches include anti-angiogenic therapy, particularly since vascular endothelial growth factor is an apparent downstream target of the ews-fli1 oncogene, are awaited.  

**Prognosis**

Patients presenting with localized disease have an approximately two thirds chance of being cured while those with metastatic disease at presentation have a much worse outcome. Those with isolated pulmonary metastases experience an approximately 30% event-free survival rate, whereas those with more widespread disease, usually involving bone or bone marrow, have a less than 20% chance of cure with currently available therapy.  

[i] on page Ewing’s sarcoma family of tumors: current management.


**Images for this section:**

**Fig. 1:** 35-year old male patient who presented with left shoulder pain. A shoulder radiograph shows a destructive lesion with associated periosteal reaction at the inferior pole of the scapula.
**Fig. 2:** 28-year-old patient with right thigh swelling and night pain. T1-weighted coronal MRI shows a T1-hyperintense mass in the subcutaneous tissues of the medial thigh.
Fig. 3: 28-year-old patient with right thigh swelling and night pain. Gadolinium-enhanced coronal T1-weighted fat saturation image shows an enhancing mass lesion in the medial compartment of the thigh.
Fig. 4: 28-year-old patient with right thigh swelling and night pain. Gadolinium-enhanced axial T1-weighted fat saturation image shows an enhancing mass lesion in the medial compartment of the thigh. Pathology confirmed extra osseous ES.
**Fig. 5:** 18F-FDG PET-CT in the same patient shows a solitary metastatic deposit in the right lobe of the liver.
**Fig. 6:** 18F-FDG PET MIP in the same patient demonstrates pulmonary and hepatic metastatic disease.

**Fig. 7:** 21-year-old male patient with left shoulder pain and swelling. Technetium 99 m-methylene diphosphonate bone scan shows radiotracer uptake in the left scapula as well as in the skull vault.
**Fig. 8:** 21-year-old male patient with left shoulder pain and swelling. Contrast-enhanced axial CT image shows a soft tissue mass centered in the left scapula with involvement of the surrounding muscle.
**Fig. 9:** 18F-FDG PET MIP shows an FDG-avid mass at the inferior pole of the left scapula. Pathology confirmed ES.

**Fig. 10:** Gadolinium-enhanced axial T1-weighted image in the same patient demonstrates a metastatic deposit in the skull vault.
**Fig. 11:** 33-year-old male patient who presented with left shoulder pain, swelling and parasthesia. Axial contrast-enhanced CT shows a partially calcified low attenuation mass centered in the left deltoid muscle.
Fig. 12: 33-year-old male patient who presented with left shoulder pain, swelling and parasthesia. 18 F-FDG PET MIP shows FDG accumulation in the left shoulder mass.
Fig. 13: 33-year-old male patient who presented with left shoulder pain, swelling and parasthesia. Coronal oblique T2-weighted image demonstrates a large heterogenous T2-hyperintense mass lesion centered in the left deltoid muscle. Pathology confirmed Ewing sarcoma.

Fig. 14: 33-year-old male patient who presented with left shoulder pain, swelling and parasthesia. 18F-FDG PET-CT axial image demonstrates a large FDG-avid mass centered in the left deltoid muscle.
Fig. 15: 33-year-old male patient who presented with left shoulder pain, swelling and parasthesia. Gadolinium-enhanced coronal T1-weighted fat saturation image demonstrates a large enhancing mass lesion centered in the left deltoid muscle. Pathology confirmed extraosseous ES.
Conclusion

ES is a highly malignant bone tumor that predominantly occurs in young patients. The characteristic finding is a large soft tissue mass, which is best demonstrated on MRI. Seventy percent of these tumors arise in the pelvis or lower extremity in a diaphyseal location.

The ESFT, although rare, need to be considered in the differential diagnosis of any bone lesion in a child or adolescent. Knowledge of their typical radiological appearance will lead to early diagnosis and possibly better treatment outcomes.

Personal information

References


