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Solid Tumour Section

Review

Bone and Soft Tissue: Ewing sarcoma

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Abstract

Ewing sarcoma is a bone or soft tissue sarcoma most commonly diagnosed in adolescents and young adults. It is one of the pediatric small, round, blue cell tumors and a fusion gene-driven cancer.

Keywords
Ewing sarcoma; EWS; EWSR1; FLI1; EWSR1/FLI1; bone sarcoma; soft tissue sarcoma; AYA cancer

Identity

Other names
Previous nomenclature: peripheral primitive neuroectodermal tumor, Askin's tumor. As of WHO 2013, these histologic classifications are no longer used and these entities are now all referred to as Ewing tumors.
Additionally, there is now an entity of tumors deemed "Ewing-like" sarcomas (defined by fusion type, see separate entry on Ewing-like sarcomas).

Note
Ewing sarcoma is defined by the presence of a fusion gene, most commonly EWSR1/FLI1.

Phylum
Soft Tissues: Ewing sarcoma

Classification

Ewing sarcoma is a tumor of the bone (most commonly) or soft tissue and is defined by the presence of the fusion gene EWSR1/FLI1 or other less common FET/ETS family fusions.

Clinics and pathology

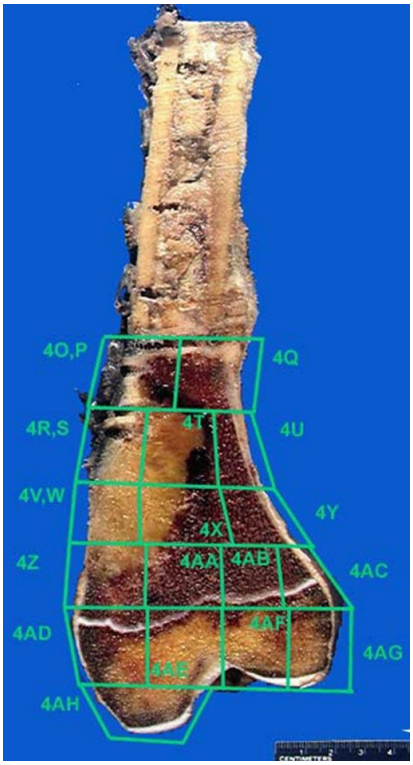

Figure 1. Gross dissection map of a treated, resected Ewing sarcoma of the femur. Image courtesy of Sarangarajan Ranganathan.

Phenotype / cell stem origin

Thought to be derived from a neural crest or mesenchymal cell of origin, although the exact cell of origin is still a source of debate.

Etiology

Ewing tumors arise most commonly from a translocation of chromosomes 11 and 22, resulting in the generation of the fusion gene EWSR1/FLI1. Recent evidence has demonstrated that ~40% of Ewing tumors FET/ETS fusions arise from chromoplexy.

Epidemiology

Ewing sarcoma is a rare subtype of sarcoma. It is the second most common primary bone sarcoma in pediatric patients and can also occur in the soft tissue.

In the United States, there are 200-250 newly diagnosed cases annually. Ewing sarcoma most commonly occurs in the AYA (adolescent and young adult) patient population, with a peak incidence at 15 years of age. This tumor can also less commonly occur in older adults, with a second smaller peek in incidence in patients older than 35 years. There are no known environmental exposures known to cause Ewing sarcoma.

Clinics

Ewing sarcoma can arise in the bone or soft tissue. Bone lesions are the most common and occur most often in the pelvis or femur. Common locations for soft tissue Ewing sarcoma include the buttock, thigh and chest wall. Many other bone and soft tissue primary locations for Ewing tumors have been reported but are less common.

70-75% of Ewing tumors present as a single, localized mass. The remaining ~25% of patients present with upfront metastatic disease in the lung or bone/bone marrow, as noted on imaging (PET and CT scans) and bilateral bone marrow biopsies obtained for disease staging.

Pathology

Uniform sheets of small, round blue cells, often (95%) CD99+ and (100%) Tdt- by immunohistochemistry staining. EWSR1 break-apart FISH probes are commonly used diagnostically to detect the presence of the EWS-containing fusion (most commonly EWSR1/FLI1). FISH probes are not as reliable for detecting EWSR1/ERG or non-EWSR1 FET/ETS fusions. Tumor sequencing is thus also used to more precisely define the fusion present in FISH "negative" cases.

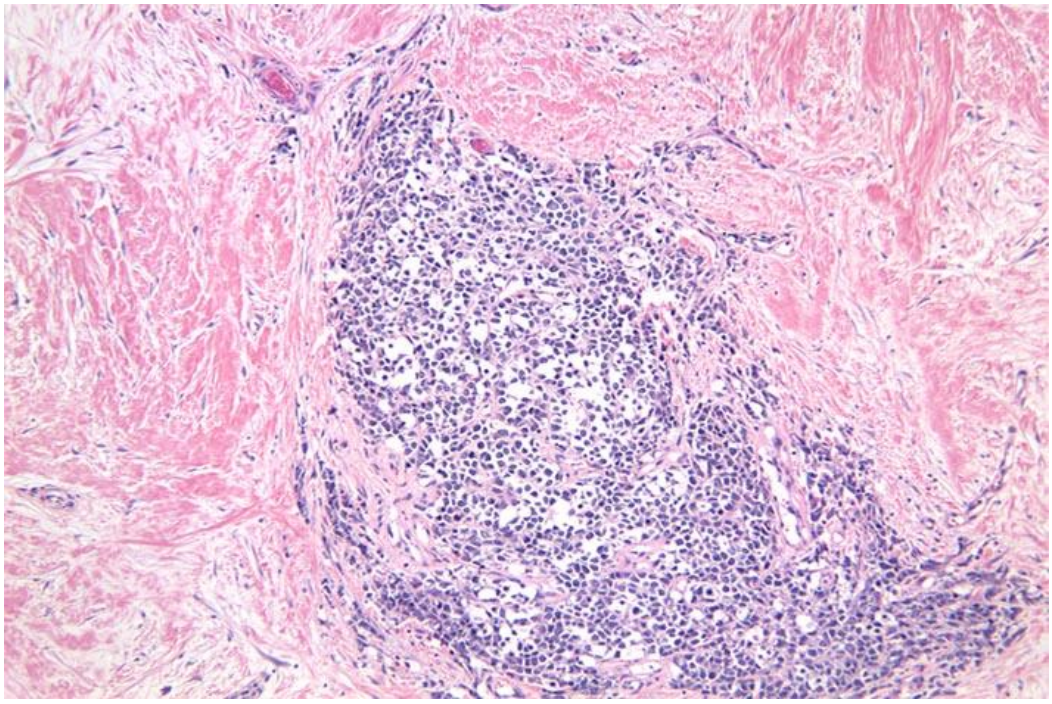

Figure 2. A small isolated focus of Ewing tumor cells in the bone marrow. Image courtesy of Sarangarajan Ranganathan

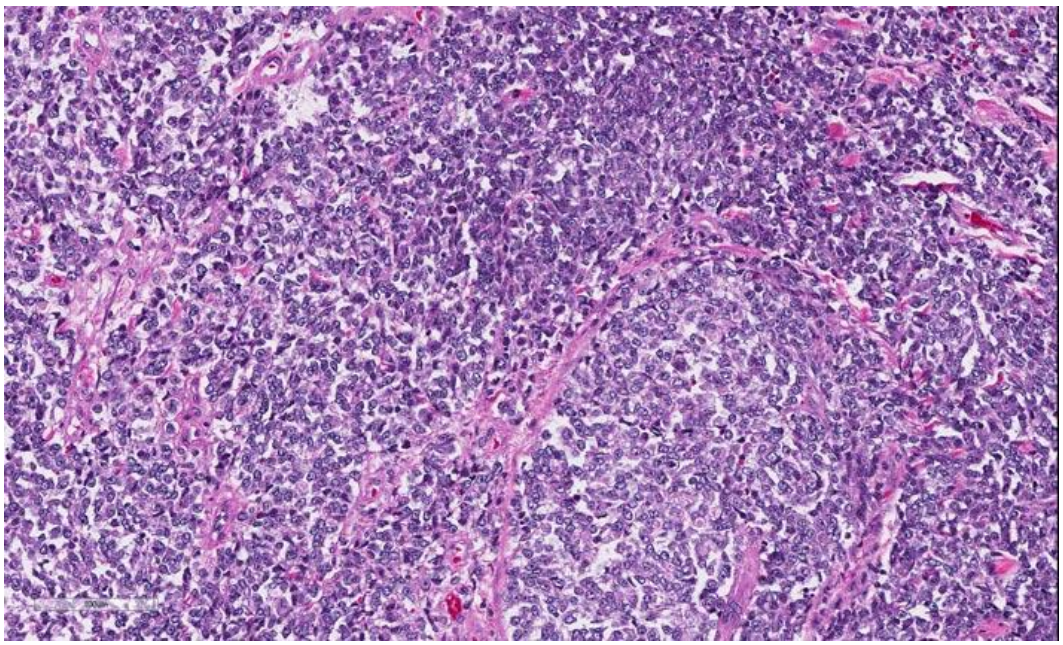

Figure 3. H&E section showing sheets of a small blue cell tumor with closely packed cells with indistinct cell borders and inconspicuous nucleoli. Note the cytoplasmic clearing. Thin fibrovascular septa are seen in between. (H&E x 200)

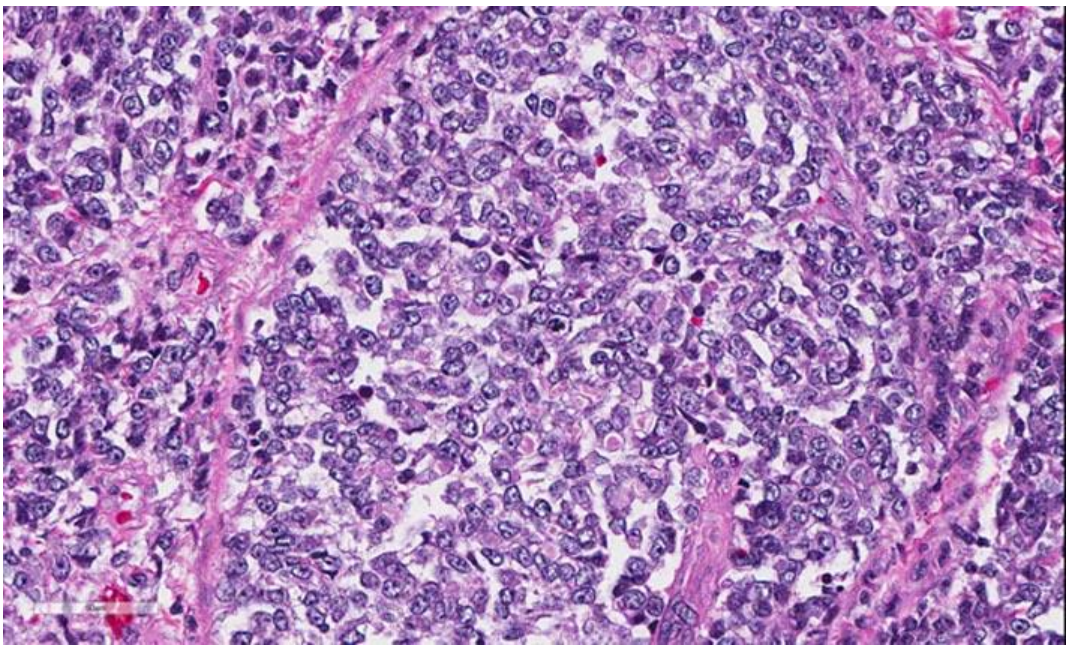

Figure 4. Higher magnification showing the individual tumor cells that are monomorphic and in sheets with no nucleoli and frequent mitoses. Note occasional cells with cytoplasmic eosinophilic staining. A break-apart FISH probe showed EWR1 rearrangement. (HE x 400) Image courtesy of Sarangarajan Ranganathan

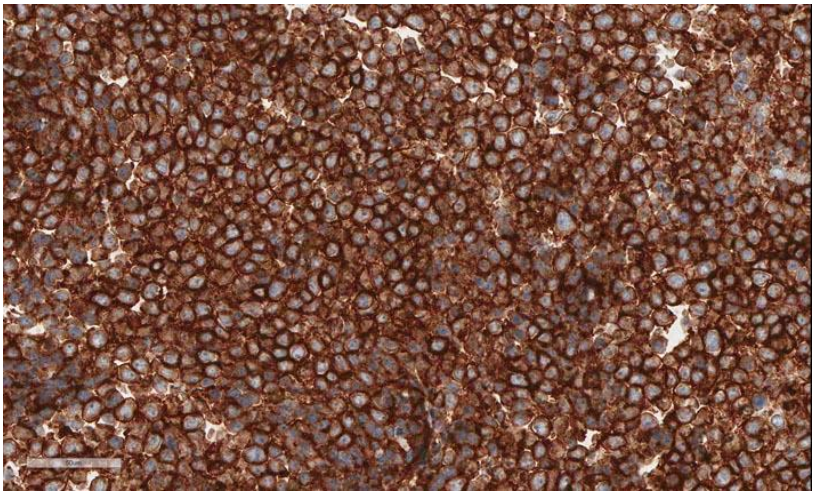

Figure 5. A CD99 stain showing strong and diffuse membranous staining of tumor cells (CD99 x 400). Image courtesy of Sarangarajan Ranganathan

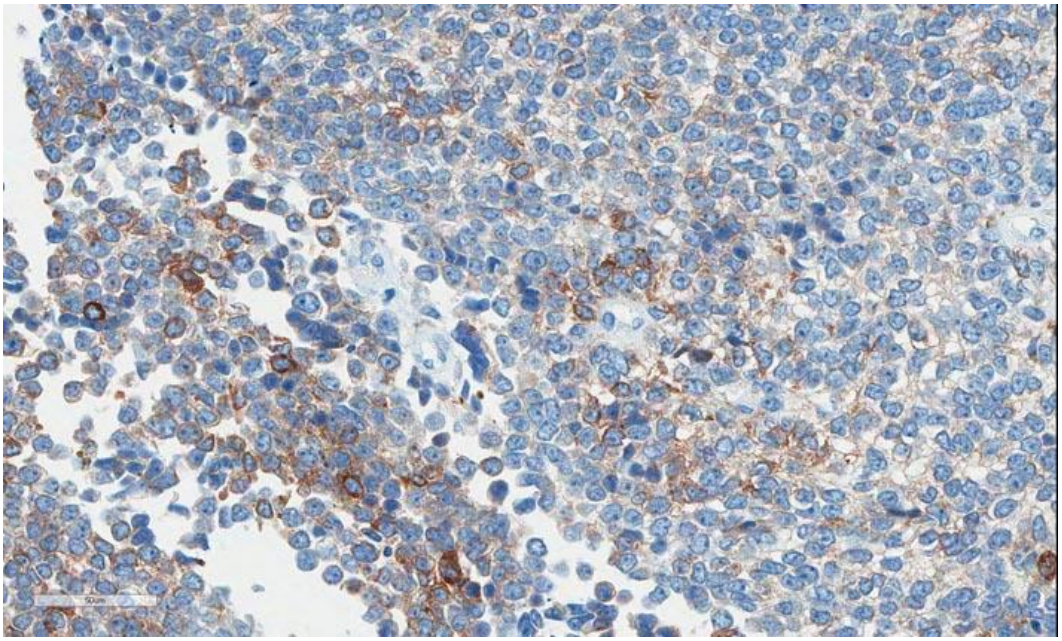

Figure 6. A synaptophysin stain showing scattered brown staining in cytoplasm of the tumor cells (Synaptophysin x 400). Image courtesy of Sarangarajan Ranganathan

Genes

Additionally, mutations in the following genes have been described in subsets of Ewing tumors: STAG2, TP53, EZH2, and deletions inCDKN2A.

Treatment

Localized Ewing sarcoma is currently treated with alternating, compressed cycles of multi-agent chemotherapy, such as VDC/IE (vincristine, doxorubicin, cyclophosphamide/ifosfamide, etoposide). Ewing tumors are sensitive to radiation and local control is achieved by surgery and/or radiation therapy.

Ongoing clinical trials aim to improve the outcomes for patients with upfront metastatic and relapsed Ewing sarcoma. These trials include international efforts to determine the most effective chemotherapy backbone for patients with relapsed
Ewing sarcoma.

Novel single agents include those attempting to target the EWSR1/FLI1 fusion itself.

Prognosis

Current survival estimates for patients with primary, localized Ewing sarcoma is ~70%. Survival for patients with upfront metastatic or relapsed Ewing sarcoma is only 10-30%.

Genetics

Germline Mutations

~13% of patients with Ewing sarcoma have been found to have germline mutations. These germline

mutations are enriched in genes associated with DNA damage repair.
The pathogenicity of such mutations remains a subject of ongoing investigation

Cytogenetics

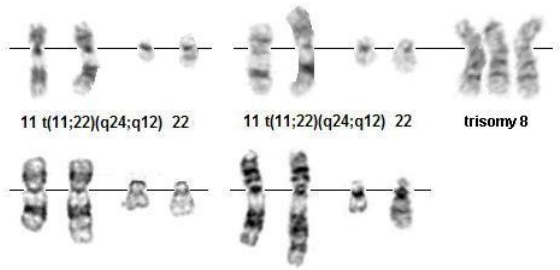

Figure 7. t(11;22)(q24;q12) in Ewing sarcoma, G- banding - top: courtesy Jean Luc Lai (with trisomy 8 on the right); - bottom: courtesy G. Reza Hafez, Eric B.Johnson, and Sara Morrison-Delap, UW Cytogenetic Services

Cytogenetics Morphological

About 85% of Ewing tumors show a t(11;22)(q24;q12); the translocation results in the fusion of the EWSR1 gene with the transcription factor gene FLI1, leading to a hybrid transcript and an oncogenic chimeric protein. Other more rare FET-ETS family member fusions have been described, such as: t(21;22)(q12;q12) and t(7;22)(p22;q12), leading to the fusions EWSR1/ERG and EWSR1/ETV1, respectively.

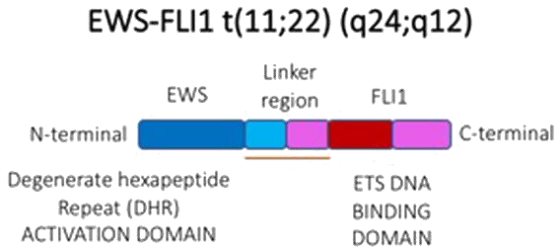

Figure 8. Schematic of the t(11;22)(q24;q12) EWSR1/FLI1 translocation demonstrating the 5' EWSR1 activation domain and the 3' FLI1 ETS DNA binding domain joined by a variable length linker region (denoted by the orange bar).

Additional anomalies

Additional anomalies in Ewing's tumors mainly consist in chromosome gains: +8 (45% of the cases) and, with a much lower frequency, trisomies 2, 5, 7, 9, 12 (between 10 and 15% of the cases); trisomy 1q, through unbalanced t(1q;16q), is observed in about 25% of the cases

Genes involved and proteins

The following genes have been identified as involved FET or ETS family members comprising various FET-ETS fusions: EWSR1, FLI1, ERG, ETV1, ETV4, FEV, FUS

EWSR1 (Ewing sarcoma breakpoint region 1)

Location 22q12.2

Protein
Contains both a transcriptional activation domain and an RNA-binding domain.

FLI1 (Friend leukemia virus integration 1)

Location 11q24.3

Protein
Member of the ETS family of transcription factors.

ERG (v-ets erythroblastosis virus E26 oncogene like (avian))

Location 21q22.2

Protein
Member of the ETS family of transcription factors.

ETV1 (Ets variant 1)

Location 7p21.2

Protein
Member of the ETS family of transcription factors.

ETV4 (Ets variant 4)

Location 17q21.31

Protein
ETV4 serves as a transcriptional activator.

FEV (fifth ewing variant)

Location 2q35

Protein
Member of the ETS family of transcription factors.

FUS (fused in sarcoma)

Location 16p11.2

Protein
The FUS protein binds to DNA and participates in transcription.

Result of the chromosomal anomaly

Hybrid Gene

Description
The 5' portion of FET family members are fused to the 3' portion of ETS family members to generate a FET-ETS fusion oncogene, most commonly (85%) EWSR1/FLI1.

Fusion Protein

Description
The resulting fusion protein results in an N-terminal FET family member with an activation domain bound to the C-terminal portion of an ETS family protein with DNA binding capabilities.

EWSR1/FLI1 t(11;22)
EWSR1/ERG t(21;22)
EWSR1/ETV1 t(7;22)
EWSR1/ETV4 t(17;22)
EWSR1/FEV t(2;22)
FUSR1/FEV t(2;16)
FUSR1/ERG t(16;21)

Oncogenesis

The resulting fusion oncoprotein participates in transcriptional dysregulation both through activating and repressing expression of hundreds of genes. EWSR1/FLI1 can interact with promoters to enhance gene expression by binding to GGAA enriched regions. NROB1 is a classic example of a protein upregulated in Ewing sarcoma.

TGFBR2 (TGF-beta receptor II) expression is one example of a gene/protein classically repressed by EWS-R1/FLI1.

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