Soft tissue tumors: Ewing's tumors/Primitive neur ectodermal tumors (PNET)

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Identity

Note: Ewing tumours form a histologically heterogeneous family belonging to the group of small round-cell tumours and derived from neural crest cells.

Classification

Ewing's tumors cover several distinct histological types:
- Peripheral neuroepithelioma,
- Esthesioneuroblastoma,
- Askin's tumour,
- Ewing's sarcoma of bones and soft tissues.

Clinics and pathology

Epidemiology

Peripheral neuroepithelioma is a very rare tumour (1% of all sarcomas); Ewing's sarcoma represents 5 to 15% of malignant bone and soft tissue tumours; two thirds of cases of Ewing's tumours occur before age 35 years, with a median age of 20 years.

Clinics

Peripheral neuroepithelioma typically occurs in the extremities (buttock and upper thigh, shoulder and upper arm);
Esthesioneuroblastoma probably develops from the olfactory placode, in the nasal vault;
Ewing's sarcoma of bones affects preferentially long bones (especially the femur), the pelvis, and the ribs;
Extraskeletal Ewing's sarcoma occur in the paravertebral region and chest wall, often in association with vertebrae and ribs, and in lower extremities;
Askin's tumour is a pediatric tumour affecting mostly the chest wall and ribs.

Ewing's tumor: the tumor is composed of blastematous tissue with some differentiated glomerular structures associated with mesenchymal tissue and tubules. Courtesy Pierre Bedossa.
**Pathology**

Peripheral neuroepithelioma shows sheets or lobules of small round-cells with a scarce cytoplasm; cells are often arranged in rosettes with a neurofibrillar center (Homer-Wright rosettes).

Esthesioneuroblastoma is histologically very similar to neuroblastoma; rosettes may be present.

Askin’s tumour seems to be more related to neuroepithelioma than to Ewing’s sarcoma.

Ewing’s sarcoma forms sheets of uniform small round-cells, sometimes arranged in a lobular pattern; the cytoplasm is scanty, pale stained and often vacuolated (glycogen); Ewing’s sarcoma is considered as the less differentiated form of the Ewing’s tumours family.

**Treatment**

The treatment of Ewing’s tumours is generally based on combined therapy with adjuvant chemotherapy, surgical resection and radiotherapy.

**Prognosis**

Combined therapies have largely improved the prognosis of Ewing’s tumours in the recent years; the prognosis is mainly determined by the presence of metastases at the time of diagnosis (15 to 35% of the cases); the 5-year survival rate is 10-35% in patients with metastases, and 54-74% for patients with a localised disease at presentation.

**Cytogenetics**

**Cytogenetics, morphological**

About 90% of Ewing’s tumours, whatever their type, show a t(11;22)(q24;q12); the translocation results in the fusion of the EWS gene with the transcription factor gene FLI1, leading to a hybrid transcript and an oncogenic chimeric protein; in about 5% of the cases, the EWS gene is involved in variant translocations: t(21;22)(q12;q12) and t(7;22)(p22;q12), leading to fusions EWS-ERG and EWS-ETV1, respectively.

**Additional anomalies**

Additional anomalies in Ewing’s tumours 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**

**Genes**

**EWSR1**

Location: 22q12

Protein

RNA binding.

**FLI1**

Location: 11q24

**ERG**

Location: 21q21

**ETV1**

Location: 7p22

`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.
Result of the chromosomal anomaly

**Hybrid Gene**

**Description**
The 5’ EWSR1 is fused to parts of either FLI1, ERG, or ETV1.

**Fusion protein**

**Description**
N terminal domain of EWS protein with DNA binding domain of FLI1, ERG (ETS family genes).

**Oncogenesis**
Through transcription dysregulation.

**References**


Jeon IS, Davis JM, Braun BS, Sublett JE, Roussel MF, Denny CT, Shapiro DN. A variant Ewing's sarcoma translocation fuses the EWS gene to the ETS gene ETV1. Oncogene. 1995 Mar 16;10(6):1229-34.


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