In the past 30 years, more than 90% of children affected by the Ewing-Tumor have died, despite radiotherapy and local therapy. A combination of systematic chemotherapy and local therapy can be effective in treating the early formation of micrometastases.

Definition of Ewing’s Sarcoma

Ewing sarcoma is the second most commonly diagnosed malignant bone cancer among children and adolescents, after osteosarcoma. Represents 6% of all of childhood cancer (Uptodate 2018). The tumor is characterized by small, round, blue cells as well as by the translocation between tumor specific chromosomes, which fuses the EWS (Ewing’s Sarcoma) gene and another gene.

Epidemiology of Ewing’s Sarcoma

Spread of Ewing’s sarcoma

Over 80% of the patients are diagnosed with Ewing sarcoma before they are 20 years of age. The average age of diagnosis is 10 to 15 years. The incidence rate is 0.3 per 100,000 habitants and boys are 1.5 times more frequently affected than girls. Race-specific incidences indicate that the incidence among dark-skinned and Asian children is
significantly lower.

Studies show that Ewing sarcoma are more common in children who have umbilical hernias, but the mechanism underlying this possible association between hernias and Ewing sarcoma is unclear. Maybe a disruption in normal embryological development occurred.

Etiology of Ewing´s Sarcoma

Translocation in Ewing’s sarcoma

The malignant bone-tumor originates from the connecting tissues of the bone marrow structure and stems from the pluripotent cells of the neural tubes. Ewing sarcoma was the first solid tumor in which a balanced translocation was detected. The translocation involves the fusion of the EWS gene and the chromosome 22q12, mostly resulting in a translocation t (11;22) in 85 to 90 percent of cases. In 44 % of the cases, trisomy of chromosomes 1q, 2, 8, and 12 can be detected.

Ewing’s sarcoma usually arises in the diaphysis of long bones and flat bones such as scapula and the vertebra. In 2/3 of all cases, the tumor is localized in the section of the legs (especially the femur) and the pelvic region. The os illium is most commonly affected.

Note: In comparison to osteosarcoma, the flat bone of the axial skeleton is significantly more frequently affected in Ewing sarcoma cases. In case of tubular bones, the Ewing sarcoma is almost always diaphyseal and in the case of osteosarcoma, it is characteristically metaphyseal.

The metastases occur at early stage in the lungs and the bones. In 20 % of the patients, a metastasis can be detected at the time of the diagnosis.
Macroscopic view and histology

The tumor is greyish white and is either slimy or thick in consistency.

Image: “Macroscopic picture of a Ewing’s sarcoma” by Openi. License: CC BY 4.0

The tumor cells are unripe and roundish without distinguished cell boundaries. The PAS coloring in the glycogen deposits of the cells is visible. The examination must go beyond the immunohistochemical analysis in order to differentiate between the tumor cells from the lymphoma cells or the neuroblastoma. The expression of the product of the **MIC2 gene CD99** is characteristic. The expression of the mesenchymal marker, vimentin and the S100 Protein of the neuron specific enolase are frequently observed.

Image: “Ewing sarcoma cells” by Lance Liotta Laboratory. License: CC BY 2.5

On the basis of fine-tissue properties and the point of origin of the tumor, the tumor types within the Ewing sarcoma group are as follows:

Image: “Histopathological Image” by Ed Uthman. License:
Clinical Findings of Ewing’s Sarcoma

Symptoms of Ewing’s sarcoma

The symptoms mainly include a pain or a swelling of a weeks or months duration. The pain may appear to be a trivial trauma and is commonly misinterpreted as a pain arising out an injury or a growth-related pain. Often the pain is augmented by stress and persists through the night. Depending on the localization, the movements can be restricted. For example, the spinal column or the peripheral nerves are affected, the neurological failures like paralysis are more prominent.

In some cases, a tissue mass can be appreciated associated with other symptoms such as pain to palpation and erythema, fever, night sweats, fatigue and weight lost. These symptoms are present in 15 percent of all patients.

Note: With every case of suspected osteomyelitis, an Ewing’s sarcoma should be ruled out as similar symptoms like pain, swelling, redness, and fever and can be secondarily infected.

Diagnosis of Ewing’s Sarcoma

Radiological examination
Based on the diagnostic evidence, the radiological examination includes x-ray, CT or MRI. The x-ray displays images of moth-eaten pattern of bone deconstruction and typical onion-shaped periostal called the Codman triangle.

Next steps in the diagnosis

The gold standard in diagnosis is a biopsy with histopathological examination and immunohistochemistry.

For the staging, CT scan, bonescintigraphy or 18 flurodeoxyglucose PET and bone marrow must be conducted to rule out skeleton: bone marrow and pulmonary metastasis; being the pulmonary metastasis the most frequent site of spread.

Note: In 25 % of the patients, metastases are present at the point of diagnosis.
Laboratory studies include hemoglobin, serum chemistry with lactate dehydrogenase levels (LDH) because it is a prognostic factor correlated with the tumor weight and dissemination. However, there is no a specific tumoral marker for Ewing sarcoma.

**Therapy of Ewing’s Sarcoma**

**Combination therapy in Ewing’s sarcoma**

The therapy for Ewing sarcoma is a combination of **polychemotherapy, surgery and radiation**. After chemotherapy (with vincristine, actinomycin D, cyclophosphamide and doxorubicin) a total resection of tumor is carried. If the tumor grows along the medullary canal, the **entire affected bone** must be **operated** and radiated.

A prosthetic treatment or a rotationplasty is not necessary. Recovery of a bone metastasis is only possible through **stem cell transplantation**. Pulmonary metastases can be treated with bilateral pulmonary radiation.

**Note:** Ewing sarcoma must be treated as a systemic disease without metastatic evidence and normally requires chemotherapy.
Prognosis of Ewing´s Sarcoma

Survival rate of Ewing´s sarcoma

The prognosis of this bone tumor among other things is dependent on the tumor volumes and from the initial metastatic status. The overall **5-year survival rate** for Ewing’s sarcoma is **64 %**.

The prognosis of the initial extent of the spread of the tumor depends on the existence of the metastasis and its reaction to the cytostatic therapies.

Follow-Up Control and Care of Ewing´s Sarcoma

The chances of a relapse after the diagnosis are highest in the first three years and hence it is during this critical period that the regular findings of the lung metastasis based on X-ray and skeleton metastases from the scintigraphy are highly important.

Risks of developing a secondary malignant tumor

The development of **secondary malignancy** is a major risk after the chemo and radiotherapy. After 20 years, the risk of a secondary malignant tumor is approximately 5 %. The therapy associated with secondary malignancy comprises secondary myelodysplastic syndrome, acute myelogenous leukemia, and osteogenic sarcoma.

Furthermore, the long-term consequence of chemotherapy with alkylated substances is linked to **infertility**, especially among young men. In adolescent patients pretherapeutical sperm cryopreservation offer is important, it helps them plan ahead for their life and the quality of life.

Special Form of Ewing´s Sarcoma

**Extraosseous Ewing´s tumor**

Purely extraskeletal or extraosseous Ewing tumors are rare. Unlike the classic Ewing sarcoma of the bone, the incidences among young boys are not higher compared to adolescent girls. Mainly, the stem is affected. The guidelines for the diagnosis and therapy are the same.

**Note:** The molecular proof of the Ewing tumor specific EWS can be looked at as pathognomonic.

Review Questions

The answers can be found below the references.

1. **12-year-old adolescent visits his pediatrician, for the past two weeks he has had increasing swelling in the area under the right thigh. This pain increases at night and there is a presence of redness in the area. The mother says that the first time the swelling was seen when the child had a fall at a football game and she thought it was a sports injury. Further investigation with the child reveals that he also felt weak and slept a lot. Which of these findings from a conservative X-ray are typical for you to suspect Ewing Sarcoma?**
A. Greenstick fracture of the distal femur
B. Codman’s triangle
C. Stalked tumor of the metaphysis
D. Osteolytic tumor with central calcification
E. Heavily perfused nidus with the surrounding sclerosis

2. Which cell surface antigen do the cells in the Ewing sarcoma characteristically express?

A. CD2
B. CD8
C. CD31
D. CD60
E. CD99

3. Which localization is more typical for osteosarcoma than for Ewing sarcoma?

A. Scapula
B. The ribs
C. Metaphysis of the long hollow bone
D. Pelvic blade
E. Vertebral Body

References

Ludwig Gortner, Sascha Meyer, Friedrich Carl Sitzmann: Duale Reihe Pädiatrie, Thieme 2012

Correct answers: 1B, 2E, 3C

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