Ewing's sarcoma

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Ewing sarcoma is a malignant round-cell tumour. It is a rare disease in which cancer cells are found in the bone or in soft tissue. The most common areas in which it occurs are the pelvis, the femur, the humerus, the ribs and clavicle.

Because a common genetic locus is responsible for a large percentage of Ewing sarcoma and primitive neuroectodermal tumors, these are sometimes grouped together in a category known as the Ewing family of tumors.[1] The diseases are, however, considered to be different: peripheral primitive neuroectodermal tumours are generally not associated with bones, while Ewing sarcomas are most commonly related to bone.

Ewing sarcoma occurs most frequently in male teenagers, with a male/female ratio of 1.6:1.[2]

Although usually classified as a bone tumour, Ewing sarcoma can have characteristics of both mesodermal and ectodermal origin, making it difficult to classify.[3]

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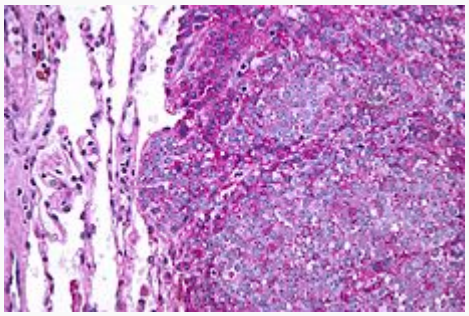


Micrograph of metastatic Ewing sarcoma (right of image) in normal lung (left of image). PAS stain.

ICD-9	170.9 (http://www.icd9data.com/getICD9Code.ashx?icd9=170.9)
ICD-O:	M9260/3 (http://www.progenetix.net/progenetix/I92603/)
OMIM	133450 (http://omim.org/entry/133450)
DiseasesDB	4604 (http://www.diseasesdatabase.com/ddb4604.htm)
MedlinePlus	001302 (http://www.nlm.nih.gov/medlineplus/ency/article/001302.htm)
eMedicine	ped/2589 (http://www.emedicine.com/ped/topic2589.htm)
MeSH	D012512 (http://www.nlm.nih.gov/cgi/mesh/2011/MB_cgi?field=uid&term=D012512)

Eponym

James Ewing (1866–1943) first described the tumour, establishing that the disease was separate from lymphoma and other types of cancer known at that time.[4][5]

Causes

Genetic exchange between chromosomes can cause cells to become cancerous. Ewing sarcoma is the result of a translocation between chromosomes 11 and 22, which fuses the EWS gene of chromosome 22 to the FLI1 gene of chromosome 11.

EWS/FLI functions as the master regulator.[6]

Other translocations are at t(21;22)[7] and t(7;22).[8]

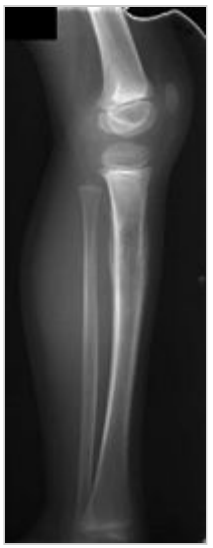
Clinical findings

Ewing sarcoma is more common in males and usually presents in childhood or early adulthood, with a peak between 10 and 20 years of age. It can occur anywhere in the body, but most commonly in the pelvis and proximal long tubular bones, especially around the growth plates. The diaphyses of the femur are the most common sites, followed by the tibia and the humerus. Thirty percent are overtly metastatic at presentation. Patients usually experience extreme bone pain.

It is positive for CD99 and negative for CD45.[9]

Imaging findings

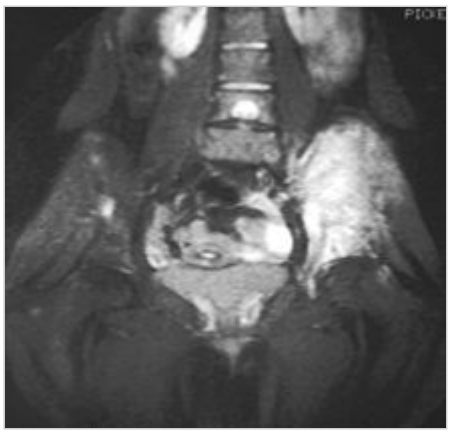
On conventional radiographs, the most common osseous presentation is a permeative lytic lesion with periosteal reaction. The classic description of lamellated or "onion skin" type periosteal reaction is often associated with this lesion. Plain films add valuable information in the initial evaluation or screening. The wide zone of transition (e.g. permeative) is the most useful plain film characteristic in differentiation of benign versus aggressive or malignant lytic lesions.



X-Ray of a child with Ewing sarcoma of the tibia.

MRI should be routinely used in the work-up of malignant tumours. MRI will show the full bony and soft tissue extent and relate the tumour to other nearby anatomic structures (e.g. vessels). Gadolinium contrast is not necessary as it does not give additional information over noncontrast studies, though some current researchers argue that dynamic, contrast enhanced MRI may help determine the amount of necrosis within the tumour, thus help in determining response to treatment prior to surgery.

CT can also be used to define the extraosseous extent of the tumour, especially in the skull, spine, ribs and pelvis. Both CT and MRI can be used to follow response to radiation and/or chemotherapy.



Magnetic resonance imaging slice showing Ewing's sarcoma of the left hip (white area shown right).

Bone scintigraphy can also be used to follow tumour response to therapy.

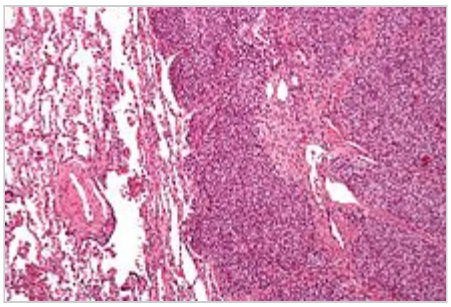
In the group of malignant small round cell tumours which include Ewing's sarcoma, bone lymphoma and small cell osteosarcoma, the cortex may appear almost normal radiographically, while there is permeative growth throughout the Haversian channels. These tumours may be accompanied by a large soft tissue mass while there is almost no visible bone destruction. The radiographs frequently do not shown any signs of cortical destruction.

Clinical differential diagnosis

Other entities that may have a similar clinical presentation include osteomyelitis, osteosarcoma (especially telangiectatic osteosarcoma) and eosinophilic granuloma. Soft tissue neoplasms such as pleomorphic undifferentiated sarcoma (malignant fibrous histiocytoma) that erode into adjacent bone may also have a similar appearance.

Diagnosis

The definitive diagnosis is based on histomorphologic findings, immunohistochemistry and molecular pathology.



Micrograph of a metastatic Ewing sarcoma with the characteristic cytoplasmic clearing on H&E staining, which was showing to be PAS positive.

Ewing sarcoma is a small round cell tumor, that typically has a clear cytoplasm on H&E staining, due to glycogen. The presence of the glycogen can be demonstrated with positive PAS staining and negative PAS diastase staining. The characteristic immunostain is CD99 which diffusely marks the cell membrane. Morphologic and immunohistochemical findings are corroborated with an associated chromosomal translocation, of which there are several. The most common translocation, present in approximately 90% of Ewing sarcoma cases, is t(11;22)(q24;q12).[10][11]

The pathologic differential diagnosis is the grouping of small round cell tumors, which includes lymphoma, alveolar rhabdomyosarcoma and desmoplastic small round cell tumor, among others.

Epidemiology

The frequency in the United States depends on the patient's age, with a rate of 0.3 case per 1,000,000 children in those younger than 3 years of age to as high as 4.6 cases per 1,000,000 in adolescents aged 15–19 years. Internationally the annual incidence rate averages less than 2 cases per 1,000,000 children.[12] In the United Kingdom an average of six children per year are diagnosed, mainly males in early stages of puberty. Due to the prevalence of diagnosis during teenage years, there may possibly be a link between the onset of puberty and the early stages of this disease, although no research is currently being conducted to confirm this hypothesis.

Treatment

Because almost all patients with apparently localized disease at diagnosis have occult metastatic disease, multidrug chemotherapy (often including ifosfamide and etoposide)[13] as well as local disease control with surgery and/or radiation is indicated in the treatment of all patients.[14]

Treatment often consists of neo-adjuvant chemotherapy generally followed by a limb salvage or an amputation and may also include radiotherapy. Complete excision at the time of biopsy may be performed if malignancy is confirmed at the time it is examined. Treatment lengths

vary depending on location and stage of the disease at diagnosis. Radical chemotherapy may be as short as 6 treatments at 3 week cycles, however most patients will undergo chemotherapy for 6–12 months and radiation therapy for 5–8 weeks.

Antisense oligodeoxynucleotides have been proposed as possible treatment by down-regulating the expression of the oncogenic fusion protein associated with the development of Ewing sarcoma resulting from the EWS-ETS gene translocation.[15][16] In addition, the synthetic retinoid derivative fenretinide (4-hydroxy(phenyl)retinamide) has been reported to induce high levels of cell death in Ewing sarcoma cell lines *in vitro* and to delay growth of Ewing sarcoma xenografts *in vivo* mouse models.[17][18]

Fertility preservation

In women, chemotherapy may damage the ovaries and cause infertility. To avail for future pregnancies, the woman may preserve oocytes or ovarian tissue by oocyte cryopreservation or ovarian tissue cryopreservation prior to starting chemotherapy. However, the latter may reseeding the cancer upon reinsertion of the ovarian tissue.[19] If it is performed, the ovarian tissue should be examined for traces of malignancy at both the pathological and molecular levels prior to the grafting of the cryopreserved tissue.[19]

Prognosis

Staging attempts to distinguish patients with localized from those with metastatic disease.[20] Most commonly, metastases occur in the chest, bone and/or bone marrow. Less common sites include the central nervous system and lymph nodes.

Five-year survival for localized disease is 70% to 80% when treated with chemotherapy.[21] Long term survival for metastatic disease can be less than 10% but some sources state it is 25-30%.[22]

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External links

- Cancer.Net: Ewing Family of Tumors, Childhood (http://www.cancer.net/patient/Cancer+Types/Ewings+Family+of+Tumors+-+Childhood)
- Ewing family of tumors (http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=322134) entry in the public domain NCI Dictionary of Cancer Terms