Ewing's sarcoma

Definition
A small round blue cell tumour of bone, first described by James Ewing in 1921 (he reported on a 14 year old girl with a lytic lesion of the ulna that responded well to chemotherapy).

Incidence
Second most common bone malignancy
0.6/million in England, 0.8/million in Sweden
51 in NSW between 1991-1995 i.e. about 10/year
M>F 1.6:1 … Mayo data suggest distinct male predilection
Most common 10-20, rare under 5 or over 30.
Almost unknown in blacks.

Aetiology
No known predisposing factors, although there may a link to increased levels of radium in the drinking water.

Site
Metadiaphysis of long bones
Femur most common, pelvis next most common
As patients get older there is a tendency for flat bones to be involved.
The fibula is another common site.
The spine is an uncommon site (3.5%) but is usually (58%) associated with neurological deficit.

Clinical
Pain in 90%
Swelling in 70%
Pathologic fracture in 5-10%
Neurological involvement is common (58%) if the spine is involved
Inflammatory like symptoms – this can be explained by the fact that the tumour characteristically outgrows its blood supply resulting in extensive degeneration and necrosis. 20% of patients present with a fever.
Early metastasis to the lungs.
Metastases to the bones are also common; in fact they are so common that it has been suggested that ES may be multicentric in origin.
Usually presents as a IIB lesion (high grade, extra-compartmental)

Investigations
Bloods
A. Increased WBC, around 20 000
B. Normochromic, normocytic anaemia
C. Increased LDH (bad sign)
D. Increased ESR

Radiology
Classic appearance is a lesion in the medullary portion of the midshaft with cortical destruction (giving a permeative effect) and multiple layers of periosteal new bone (onion skinning).
May be a sunburst appearance.
May be sclerosis suggesting an osteosarcoma
MRI: intermediate intensity on T1 and high intensity on T2, reflecting cellular nature.

Differential diagnosis - radiology
Infection – note the systemic features and increased WBC, ESR
Eosinophilic granuloma
Osteosarcoma

Gross pathology
Poorly demarcated, greyish white tumour tissue with areas of haemorrhage, cystic degeneration and necrosis. Can even look like pus.
The extent of bone destruction is greater than suggested on X-rays

Histology
Known to be of neuroectodermal origin.
Ewing's sarcoma and PNET form a spectrum with ES being less differentiated
Sheets of closely packed small round blue cells, 2-3 times larger than lymphocytes. Monotonous and remarkably cellular – there is little stroma.
Glycogen positive in 80%– helps distinguish between ES and NHL. Stain with PAS.
-On electron microscopy glycogen appears as round black structures lying in the cytoplasm.
Areas of degeneration
May be foci of reactive bone that may be confused with osteosarcoma
Pseudorosettes consist of 8-10 cells circling a centre that may be a capillary or a void.
Neural elements common to ES and PNET are neuron specific enolase and Leu 7.
How does one tell ES and PNET apart? PNET has:
1. Homer-Wright rosettes in a fibrillary background
2. A lobular arrangement of cells
3. Prominent organelles and neurosecretory granules.

Note: there is no difference in survival between patients with ES and PNET in whom histological criteria are used for diagnosis.

Differential diagnosis – histology
Osteomyelitis
Eosinophilic granuloma
Lymphoma
Leukaemia
Metastatic neuroblastoma
Small cell lung cancer
Embryonal cell rhabdomyosarcoma

Molecular biology
Translocation common to ES and PNET is t (11,22).
This produces a cell surface glycogen that can be targeted by monoclonal antibodies HBA-71 and MIC2.

Staging
CT and MRI
Bone scan shows involvement of other bones in 10% at presentation
Bone marrow aspirate and biopsy
Assessment of cardiac function (gated heart pool scan)

Biopsy
1. Best done percutaneously
2. Should be done at the tertiary referral centre because biopsy related complications are five times more common if the biopsy is done at the referring hospital
3. The soft tissues are biopsied if possible to avoid creating a stress riser.

Management
Two objectives:
1. Local control
2. Systemic control (chemotherapy)

Local control
This can be through surgery, or radiotherapy, or both. Historically radiotherapy was used but has now been supplanted by surgery.
Surgery has several advantages:
1. It allows assessment of the tumour responsiveness to adjuvant chemotherapy
2. Radiotherapy can cause secondary sarcomas, up to 35% at 10 years
3. Retrospective trials at the Mayo, Sloan Kettering and Mass. Gen have shown that surgery confers a survival advantage.

Limb sparing surgery – followed by radiotherapy if inadequate margins (defined as less than 1 cm) have been achieved.

Radiotherapy to an unresectable primary is with doses in the order of 54 to 60 Gy.
Recurrence after a satisfactory response to chemotherapy followed by definitive radiotherapy is around 15%.

Complications of radiotherapy include:
1. Limb length discrepancy
2. Joint contracture
3. Muscle atrophy
4. Pathological fracture
5. Late radiotherapy induced tumours (particularly if more than 60Gy is used)

Systemic control
Intense neoadjuvant therapy
One routine is vincristine, dactinomycin, cyclophosphamide plus doxirubicin alternating with ifosfamide and etoposide
High dose intermittent therapy is preferable to moderate dose continuous therapy.

Intense postoperative chemotherapy is then continued for at least one year, with the agents changed if the surgical specimen shows that the agents have been ineffective.
Patients with marrow involvement at outset may be offered marrow ablation with stem cell rescue.

Prognosis
Poor prognostic factors are:
1. Metastatic disease – 25% of patients present with gross metastatic disease, and these have only a 13% long term survival
2. Large tumours – greater than 8cm or 100mL
3. Pelvic sites
4. Older age
5. Increased LDH
6. Poor response to initial chemotherapy

Good prognostic factors are:
1. Distal tumour site
2. Rib primaries

The current 5-year survival rate for all patients is 70%.