Paget's disease

Paget's disease of bone becomes increasingly more common with age with a prevalence of 10% at the age of 70 years. The diagnosis may be missed unless the clinician is vigilant, recognises the presenting features, and investigates further. This article reviews the presenting features, investigation and treatment of what can be a painful and debilitating disease.

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In 1877 Sir James Paget described a patient with abnormalities of the axial skeleton and enlargement of the skull, with signs of cardiac failure and osteosarcoma of the humerus. He coined the term osteitis deformans and postulated that bone resorption initiated by chronic inflammation led to bone deformity, pain and associated features of the disease.[1] Later the presence of multi-nucleated osteoclasts were recognised as the key pathological feature of the disease.[2]

Paget's disease of bone (Paget's) is a disease of ancient times evidenced microscopically by signs of disease in pre-historic skeletons.[2] There is a high predisposition to Paget's in Western Europe with an incidence of 3–4% in middle aged people, increasing to 10% in the elderly. The mean age of presentation is 59 years plus or minus 14 years with a higher prevalence in men than women.[3]

Under the age of 40, appendicular, monostotic lesions and thoracolumbar spine involvement are common, as are pain and symptomatic pathologic fractures. Malignant transformation such as osteosarcoma is less common (0.3%).[4] There is a trend towards more axial involvement in older people.[5]

Clinical presentation

The classical advanced features of multiple bone pain, increased size, osteosarcoma and heart failure as described by Paget on his first patient are relatively rare at presentation.[1] In most instances the diagnosis is made incidentally based on radiographs or investigation of a raised serum alkaline phosphatase (ALP).[6–8] (Figure 1) There now exist evidence-based recommendations for diagnosis of Paget's which is primarily made on radiographs of at least one skeletal area.[7] It is recommended that any additional painful areas are X-rayed and the requirement for a complete skeletal survey is unnecessary. Isotope bone scintigraphy has a place in the assessment of extent of disease involvement.

ALP is a useful parameter for monitoring Paget's because the level increases and decreases in line with changes in bone turnover. In patients who have a normal ALP or deranged liver function tests due to liver disease, bone-specific alkaline phosphatase should be monitored.[7]

Symptoms and complications

The commonest symptom reported is bone pain.[9,10] Micro-fractures of remodelled bone on weight-bearing is one of the postulated mechanisms of pain, but the causes of pain may be multi-factorial; from the disease itself, secondary osteoarthritis,

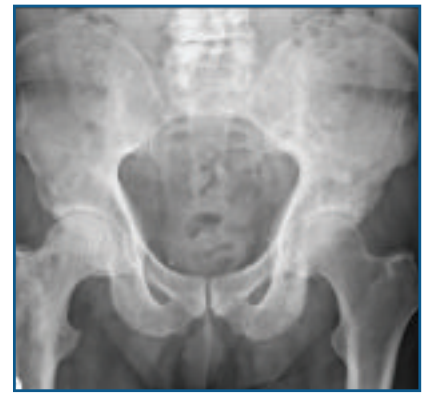

Figure 1. Plain radiograph showing Paget's affecting the right head and neck of femur and left ilium.

Box 1: Complicating features of Paget's disease of bone

Bone
Pain
Deformity
Pathological fractures
Pagetic arthritis
Deafness
Malignant osteosarcoma

Neurological
Cranial nerve palsies
Spinal stenosis

Cardiovascular
Heart failure

nerve impingement in spine disease or from osteosarcomatous transformation.[10,11] The common sites of bone involvement are the axial skeleton, skull, pelvis and lumbar spine, tibia and femur.[9,10] (Figures 2 and 3)

Investigations and diagnosis

Laboratory

Serum alkaline phosphatase is the most sensitive and widely used biochemical marker of disease in Paget's. It is elevated due to the action of increased osteoblastic activity. Serum levels of ALP might not, however, correlate with symptoms of the patient.[6]

Radiography

Radiological features of Paget's are described as porotic bone in the early stages and subsequently replaced by osteosclerotic bone.[8] (Figure 4). Classically the bone trabecula is thickened and cortical bone porous, giving a cotton wool appearance on radiographs due to the decreased density of the bone. Bowing of long bones is also a feature due to non-fusion of diseased periosteum with cortical bone.[2] 85% of Paget's diagnoses are made by plain radiography.[10] If the diagnosis is unclear, more advanced investigations may be required. Plain radiographs also help demonstrate associated diseases such as osteoarthritis and complications such as pathological fractures.[9,12]

Isotope bone scintigraphy

Paget's is characterised by increased activity of metabolically active bone and isotope bone scintigraphy will detect these areas by uptake of tracer (Figure 5). This provides a sensitive method of detecting Paget's, particularly when there is multifocal involvement. Isotope bone scintigraphy is limited by its inability to discriminate between other metabolic bone disorders and Paget's.[6, 7,13]

Complicating features

Paget's may have complicating features broadly divided into bone, neurological and cardiovascular.[6] (Box 1).

Pain

One of most common symptoms in Paget's is pain. The pain can be divided into pain directly from osteoclastic resorption of bone or from compression of nerves by deformed bone.

Deformity

Paget's may present to surgeons as a cosmetic complaint in terms of deformity or as pathological fractures which usually occur

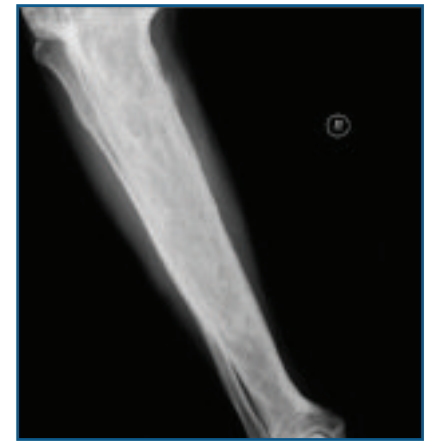

Figure 2. Paget's affecting the entire length of the tibia.

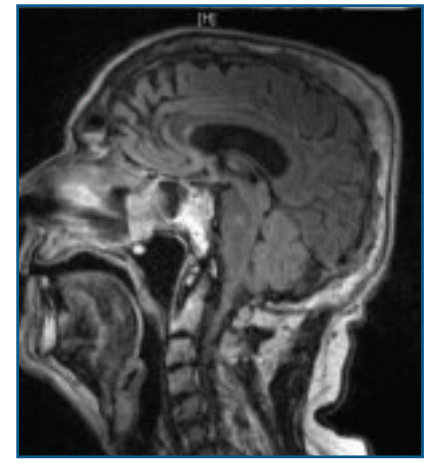

Figure 3. Skull MRI showing thickened skull secondary to Paget's.

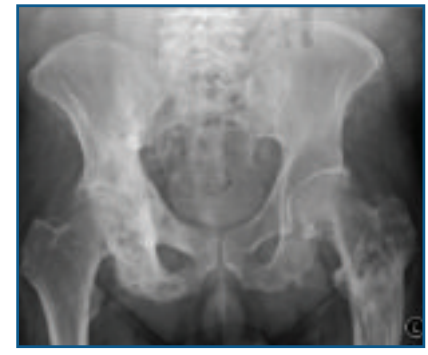

Figure 4. Thickened porous right inferior pubic ramus. There is also involvement of the left neck and shaft of femur.

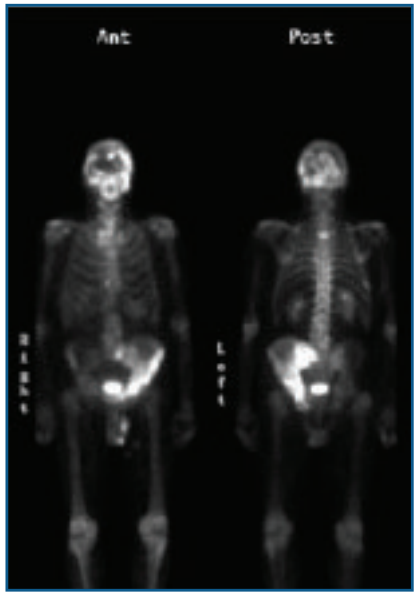

Figure 5. Isotope bone scintigraph demonstrating Paget's affecting the left hemi-pelvis and skull.

as a result of mechanically weakened bone from repetitive bone resorption and ineffective bone formation.[11] (Figure 6). Mal-union of bone is the dreaded and common complication in both the conservative and surgical management of fractures in Paget's. Rates for non-union may be as high as 40% in internal fixation of neck of femur fractures.[11-14]

Arthropathy

Secondary osteoarthritis (OA), calcific peri-arthritis and crystal arthropathies are associated with Paget's. It is thought that the ineffective remodelling in Paget's causes abnormal bone enlargement close to the joint, contributing to abnormal joint biomechanics and cartilage support.[15] (Figure 7).

Due to the excessive bone remodelling in Paget's, it is thought that in about 20–40% of patients, hyperuricaemia is present due to a surplus of nuclei acid. This therefore contributes to calcific peri-arthritis and gout.[15]

Neurological

Deafness is a well recognised complication in patients with Paget's. Studies revealed that the deafness is mostly likely caused by cochlear capsule dysfunction secondary to bone mineral density loss and not by auditory nerve dysfunction.[16,17] The characteristic finding in Paget's associated deafness is sensorineural hearing impairment at high frequency and an air-bone gap at lower tones.

Neurological symptoms in Paget's may manifest depending on the location of the lesion. These can range from individual cranial nerve compression such as first cranial nerve involvement presenting as anosmia; to cerebellar signs in cervico-medullary junction compression, and upper motor neurone signs, sensory deficit and weakness in spinal cord compression.[18] The suggested mechanisms for neurological symptoms are direct compression on nerves by remodelled bone, alteration in the weight bearing capacity of the bone, sarcomatous change causing local nerve involvement, and vascular ischaemia of nerves.

Malignancy

Sarcomatous change affects around 1% of patients with Paget's.[6,19] The commonest type is osteosarcoma (70–80%) followed by fibrous histiosarcoma (approximately 20%), chondrosarcoma (5–10%) and angiosarcoma (1%).[20-22] The prognosis following sarcomatous change is very poor with a five year survival rate of 10% and mean survival time of four months.[19,22]

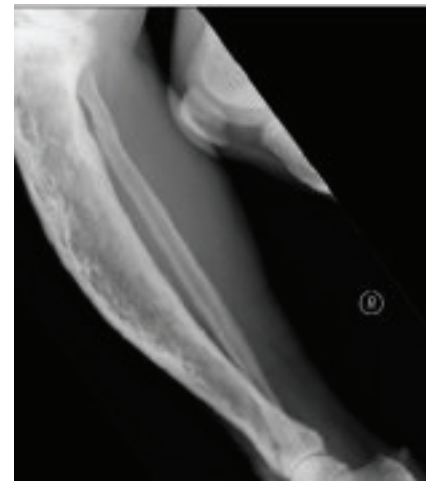

Figure 6. Bowed, enlarged, Paget's-affected tibia with fracture of the non-diseased fibula.

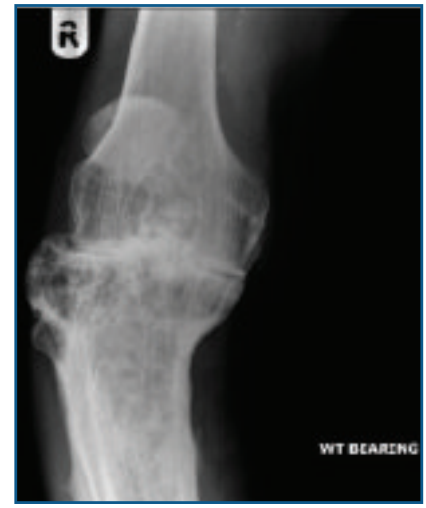

Figure 7. Paget's affecting the tibia causing genu varum and secondary knee osteoarthritis.

Heart failure

People with Paget's disease are at an increased risk of developing heart failure with figures of 3–4%.[9,23] Factors involved in the development of heart failure in include increased vascularity to diseased bones, increased atherosclerosis, spine deformity causing reduced movement of the thorax and anaemia in severe cases.[24]

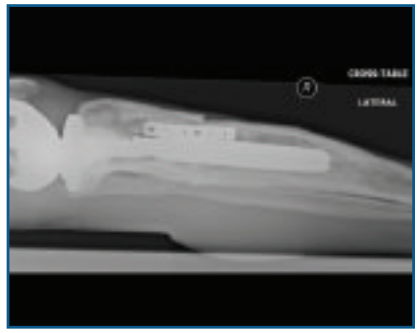

Figure 8. Total knee replacement in the presence of tibia-affected Paget's. Note the iatrogenic fracture to straighten the bowed tibia and the long shaft of the prosthesis.

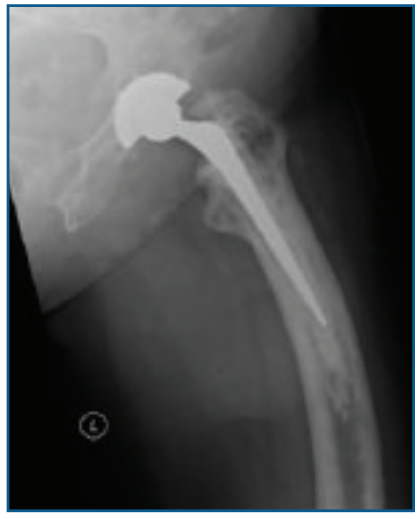

Figure 9. Hip replacement in a Pagetic femur. Note the bowed proximal femur and the affected trochanter.

Older patients

In older patients, the diagnosis may be overlooked. The majority of cases present with pain due to Paget's disease itself. Others may present with deformity, reduced mobility and hearing impairment. These features are often misinterpreted as part of the ageing process.[25]

Spinal stenosis

Spinal involvement is frequent. As bone is a dynamic organ and the spine is involved in weight-bearing, the extent of repair tends to exceed resorption. Vertebral end-plates are affected by this phenomenon, resulting in convex masses that project beyond them. The vertebral bodies themselves become flattened and widened due to bone softening caused by the remodelling. The effect of these changes is spinal canal narrowing that could potentially compress the cord and the nerve roots.[18]

Aetiology of Paget's

The exact aetiology still remains inconclusive although several studies have postulated paramyxo viruses as the putative causative agents. Measles virus and canine distemper viruses have been found in bone biopsies and postulated as possible aetiologies for Paget's. Further theoretical support originates from studies that demonstrate infection of osteoclasts with canine distemper virus increases osteoclastogenesis.[26] Consumption of bovine brain and meat and being in contact with cattle were shown to be possible environmental factors involved for Paget's.[27]

Genetic

Paget's may be inherited in an autosomal dominant fashion.[24] Genetic mutations in the sequestosome 1 gene (SQSTM1) on the PDB3 locus on chromosome 5q are thought to cause familial and sporadic Paget's.[28–30]

Management of Paget's

Although there are no published NICE guidelines on the management of Paget's, there exist evidence-based guidelines published by The Bone and Tooth Society and the National Association for the Relief of Paget's Disease.[12]

The main aim of treatment is symptom control and prevention of complications of the disease although in practice this only applies to pain and osteolytic lesions. Treatment can be broadly divided into pharmacological, non-pharmacological and surgical.

Pharmacological treatments can be used for bone turnover pain by preventing osteoclastic resorption by the use of bisphosphonates.

Bisphosphonates bind to the bone hydroxyapatite matrix and act through cellular signalling to inhibit osteoclastic activity and also trigger cell apoptosis.

Etidronate (Didronel), pamidronate (Aredia), risedronate (Actonel), tiludronate (Skelid) and zolendronate (Zometa) are the only bisphosphonates licensed in the UK for treating Paget's. They vary in side effect profile and effectiveness. The newer bisphosphonates are preferred to etidronate, which is one of the older agents, because of their better effectiveness and side-effect profile. Measurement of ALP is a cheap and easy marker of response, the aim being to suppress levels to the normal range.[14]

Common analgesics such as paracetamol, non-steroidal anti-inflammatories, opiates and low dose tricyclic anti-depressants are used for symptomatic control of pain.

Non-pharmacological

treatments involve physiotherapy, use of TENS and use of walking sticks to aid gait stability.

Surgery is usually reserved for patients who have fractures or deformity, or do not respond to medical therapy (Figure 8, 9)

While it is appropriate to treat patients with spinal cord compression, hearing loss, hypercalcaemia and pre-surgery with bisphosphonates, there is weak evidence for using these agents for prevention of fractures or deformity in Paget's.

Conflict of interest: none declared

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