BACKGROUND Paget disease was first described in 1877 by Sir James Paget. It is a focal disorder of bone remodelling, involving increased bone resorption and formation. The aetiology is uncertain but both environmental and genetic factors are thought to be involved in pathogenesis.

OBJECTIVE This article outlines the clinical presentation, diagnosis and treatment of Paget disease.

DISCUSSION Paget disease is associated with musculoskeletal pain, significant disability and impaired quality of life. Complications include pathological fracture, arthritis in adjacent joints, hearing loss, other neurological complications, heart failure and, rarely, osteosarcoma. Recent clinical trial data has demonstrated histological and radiological improvements in bone of patients treated with bisphosphonates. There is little data evaluating the long term effect of therapy on the risk of complications, however, restoration of normal bony architecture offers the prospect that complications related to deformity and increased bone fragility might be reduced by effective therapy.

Case history
Mr HTC, a retired tiler/plasterer was referred in December 1991 because of pain, localised to the right lower leg. There was no other pain referable to the skeleton. He reported a past history of gout affecting the right ankle beginning in 1976, hypertension and gastro-oesophageal reflux. On examination, the right lower tibia was warm and there was some mild swelling at the right ankle but no obvious deformity. The remainder of the physical examination was unremarkable. A bone scan demonstrated increased uptake, consistent with Paget disease (PD) of bone in the right tibia (Figure 1). Serum alkaline phosphatase was 294 U/L (reference range 20–120 U/L) and urine hydroxyproline excretion was increased, 119 mmol/2 hour (reference range 0.40–1.92 mmol/2 hour). A plain radiograph of the right tibia showed bowing, cortical thickening and disruption of the normal trabecular pattern – typical of PD of bone (Figure 2a). The patient was lost to follow up when he moved interstate and remained untreated in spite of a recommendation to commence bisphosphonate therapy. In June 2003 he sustained a pathological fracture through the distal third of the right tibia (Figure 2b) after a fall from standing height and was treated with an intramedullary nail.

Comment
Treatment with a bisphosphonate would have been likely to improve Mr HTC’s symptoms, but whether his fracture could have been prevented by earlier treatment of PD is less clear. Caution with the use of oral bisphosphonates is required with a history of gastrooesophageal reflux. Treatment with intravenous disodium pamidronate would be an alternative. Open reduction and internal fixation of fractures associated with PD may be required because of the increased risk of delayed union.
Paget disease (PD) is a common, focal bone remodelling disorder involving both increased bone resorption and formation. The affected bone is enlarged, disorganised in structure, and weakened. Paget disease has an estimated prevalence of between 2–6% in the United Kingdom and a slight male predominance.\(^1,2\) Recent reports suggest that the incidence of PD may be decreasing.\(^3–6\)

### Aetiology

The aetiology of PD of bone remains unclear but geographical and familial clustering of PD suggests that common environmental or genetic factors may be involved in its pathogenesis.\(^1,3–9\) A viral aetiology has been proposed based on observations of virus-like nuclear inclusions in osteoclasts from pagetic bone, supported by immunohistochemistry and insitu hybridisation data.\(^11–13\) Transduction of normal osteoclast precursor cells with vectors expressing measles virus nucleocapsid and matrix genes can induce a paget phenotype in osteoclast-like cells.\(^14\)

In a recent case report, PD has been transferred from acetabulum to an unininvolved mid femur site as a result of autologous bone grafting during total hip arthroplasty.\(^15\) Familial clustering lends support to the genetic hypothesis with an autosomal dominant pattern of inheritance with variable penetrance being described.\(^16\) Among 128 first degree relatives of 35 index cases, 40% were affected,\(^17\) whereas 20% of patients registered in the New England Registry for Paget Disease of Bone (NERPDB) report having an effected sibling or parent.\(^7\) Linkage to a number of genetic loci suggest that PD is a genetically heterogeneous disorder, but several of the mutations reported affect the signalling pathway central to the regulation of osteoclastogenesis.\(^18\)

### Diagnosis

Paget disease should be considered in the differential diagnosis in any patient with unexplained musculoskeletal symptoms. Data from the UK General Practice Research Database (GPRD) suggests that only a small proportion of cases are coming to clinical diagnosis.\(^5\) Among 2465 general practice patients identified as suffering from PD, 66.7% reported bone pain and analgesics/nonsteroidal anti-inflammatory drug use was higher than controls in the year before diagnosis (5.2 vs 2.5 prescriptions per year). Bony deformity or swelling was present in 9.2% and 13.3% were asymptomatic.\(^5\) This contrasts with population based data suggesting that one-third of patients are asymptomatic at diagnosis.\(^8\)

In the GPRD, the diagnosis was most often made by X-rays (85%) and isotope scintigraphy was used in 17.5% of patients.\(^6\) A mixed appearance of areas of osteolysis and sclerosis is characteristic of pagetic bone. Lytic changes are prominent in early lesions with the occurrence of flame shaped resorption fronts in long bones or osteoporosis circumscripta in the skull. Bone volume may be increased, particularly in the spine and the shafts of long bones. Progression of disease within a radiologically involved site may occur but the involvement of new bony sites is uncommon.

Radionuclide bone scans should be performed at the time of diagnosis. They are a sensitive method for identifying affected bones and can increase detection of affected sites by 15–30%. Radionuclide uptake correlates with symptoms attributable to PD.\(^19\) By contrast, there appears to be little relationship between radiological changes in bone and symptoms.\(^20\) Among 170 patients with 863 pagetic sites only 30% of bones involved were associated with symptoms.\(^21\)

An increase in serum alkaline phosphatase is a valuable clue to diagnosis \(^22\) and the prevalence of ‘biochemical PD’ is reported to be comparable to that observed in a radiological survey.\(^5\) Approximately 95% of patients have raised serum alkaline phosphatase that correlates with the extent of skeletal involvement.\(^15,23\) Measurement of serum alkaline phosphatase in patients with unexplained musculoskeletal symptoms and among family members of patients with PD is likely to reveal additional cases.
Complications

Paget disease is associated with significant disability, impaired quality of life and a variety of complications (Table 1, Figure 3). Pathological fracture is common. Among 236 patients followed for a median 10.5 years, 14% of fractures were attributable to PD. In this cohort, 79% of tibia/fibula fractures and 62% of all fractures of the femur or tibial shaft involved pagetic bone. After the diagnosis of PD, the overall incidence of fractures was 8.6 per 100 person years and the incidence of fractures involving pagetic bone was 1.2 per 100 person years, resulting in a cumulative incidence of fracture through pagetic bone of 19% at 20 years. Fracture risk was significantly increased in men but not women. Neither baseline serum alkaline phosphatase nor number of sites of pagetic involvement predicted subsequent fracture. Patients with a family history of PD are more likely to report a history of fracture or deformity. Open reduction and internal fixation of fractures has been recommended because delayed union often complicates fracture healing.

In the NERPDB, 44% of patients reported reduced physical activity, 32% were taking chronic pain medication, and 25% were using a walking aide. Arthritis in joints adjacent to pagetic bone affects up to 50% of sufferers and deformity 36% of sufferers.

Neurological complications appear to be relatively uncommon in general practice settings although hearing loss affected approximately 20% of patients in the NERPDB. Heart failure risk is significantly increased, whereas the risk for ischaemic heart disease, hypertension and cerebrovascular events does not differ from controls. Osteosarcoma arising in affected bone is a rare complication, occurring in 0.3% of GPRD patients.

Treatment

Symptomatic disease and preparation for orthopaedic surgery are the established indications for treatment.

Symptom control

Bisphosphonates are the treatment of choice and there is evidence that treatment can improve symptoms, bone histology and radiology. Calcitonin therapy can also relieve bone pain and suppresses disease activity. In the GPRD, bisphosphonate therapy was prescribed for 26.9% of patients and calcitonin for 7.3%. Treatment for 3–6 months with the potent oral bisphosphonates, alendronate and risedronate, can normalise bone turnover in 50–60% of patients. The potent bisphosphonates suppress bone turnover for 1–2 years before biochemical markers begin to slowly increase above normal values. Continuous treatment with alendronate over a 2 year period has been reported to normalise the bone scan appearance in approximately one-third of patients. However, among patients with impaired swallowing, significant gastro-oesophageal reflux or oesophageal motility disorders, these medications should be avoided because of the risk of erosive oesophagitis and intravenous preparations such as disodium pamidronate can be used.

Does treatment reduce complications?

There is little data evaluating the long term effect of
Theme: Paget disease of bone - diagnosis and indications for treatment

these therapies on the risk of complications. High dose treatment with etidronate, the first bisphosphonate to enter clinical practice, was associated with mineralisation defects and fracture.31 Other, uncontrolled data suggest that etidronate therapy may reduce the incidence of fracture32 and Melton reported a nonsignificant reduction in fracture risk among the minority of patients receiving any antipagetic therapy.4 Recent clinical trial data has demonstrated histological and radiological improvements in bone of patients treated with bisphosphonates33 and offers the prospect that complications related to deformity and increased bone fragility might be reduced by effective therapy. Therapy may slow the progression of hearing loss33 and reverse neurological complications.34 An improvement in bony deformity in a patient with skull and facial involvement has been reported.35 Based on such limited data and the observation that 62% of patients develop new complications extended follow up,36 treatment of those regarded as being of high risk of complications has been advocated. Paget disease with extensive skull involvement, affecting weight bearing bones, vertebral bodies and areas adjacent to major joints, would represent an indication for therapy under this paradigm. Monitoring of bone turnover, usually by measurement of alkaline phosphatase at 4–6 monthly intervals, and re-treatment in those patients in whom normalisation has been achieved when levels increase to 20–25% above the upper limit of normal has been suggested. Among patients whose alkaline phosphatase fails to normalise re-treatment is suggested when values increase to 25% above the nadir.37

Conclusion

Paget disease may be asymptomatic but is frequently associated with impaired of quality of life and a variety of complications. Bisphosphonates suppress disease activity, improve bone histology and radiological appearance. The optimum treatment strategy may be to treat as early as possible with a view to halting disease progression. Restoration of normal bone architecture may be possible with effective suppressive therapy and offers the potential to reduce complications. However, whether prolonged suppression of disease activity with antiresorptive agents will reduce the occurrence of complications remains to be established.

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