Fortnightly Review

Paget's disease of bone: diagnosis and management

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Paget's disease may affect up to 10% of elderly people,¹ in a sex ratio of about three men to one woman; only about 5% will have symptoms. The disease is characterised by accelerated disorganised bone remodelling due to a primary abnormality of osteoclasts. Potent bisphosphonates, which inhibit osteoclastic bone resorption, offer the potential for long term control of the disease.

Clinical presentation

Symptoms are important in terms of the way that they present, their specificity for diagnosis, and their influence on management.

PAIN

Bone pain is the most common presenting symptom, but it is non-specific. When patients have symptoms, the severity of pain may vary considerably in different sites. Pain may arise from increased vascularity, from distortion of the periosteum due to disorganised remodelling, or from a focus of mechanical stress. Periarticular pain may be the presenting feature in 50% of cases² and is an important diagnostic problem because Paget's disease commonly affects bone around major joints such as the hip and knee, as well as those of the spine, with narrowing of the joint spaces and formation of osteophytes. Affected patients complain of a constant dull ache that is aggravated by weight bearing and may become particularly severe after movement. Assessing the relative contributions of bone and joint pain to a patient's disability, such as backache or hip pain, may be extremely difficult. Although symptoms are more likely with advanced degenerative changes, radiography does not reliably identify the sources of pain.³

DEFORMITY

Bowing of weight bearing bones is another common feature, most commonly in the femur, tibia, and forearm. Since deformity is usually acquired later in life and is often asymmetrical, it has relatively good diagnostic specificity. This type of deformity in the femur or tibia is often associated with stress fractures on the convex surface of the bowed bone. These may present as localised areas of bone pain or tenderness and may also extend to produce a complete transverse fracture. The radiographic appearances are diagnostic and are easily distinguished from other types of stress fracture such as the Looser's zones of osteomalacia. Symmetrical bowing deformity of the lower limbs may be confused with other metabolic bone diseases, such as the consequences of childhood rickets, but radiographs confirm the cause.

Summary points

- Paget's disease is a localised monostotic or polyostotic progressive bone disease of uncertain origin (it may be caused by a slow viral infection)
- It is characterised by increased bone remodelling, leading to pain, fractures, and deformities with the risk of skeletal, articular, or neurological complications
- Radiography, scintigraphy, and bone biochemistry are useful tools in achieving a positive diagnosis
- The primary aim of treatment is to reduce pain and the risk of developing long term complications
- Potent antiresorptive drugs are now available which control the increased bone remodelling and have led to a dramatic improvement in treatment

NEUROLOGICAL SYNDROMES

Neurological syndromes reflect the predilection for Paget's disease to affect mainly the axial skeleton. Skull deformity may result in enlargement of the vault, with a characteristic appearance particularly of the forehead (frontal bossing) or of the maxilla (leontiasis osseum). Basilar invagination is also common; it does not result in outwardly visible changes but is apparent radiologically and may cause symptoms due to internal hydrocephalus or long tract signs from brain stem compression. Cranial nerves may become compressed as they emerge from their foramina beside pagetic bone, and the auditory and ocular nerves seem particularly at risk. These changes usually occur in association with obvious radiological features of skull involvement and rarely pose a diagnostic problem.

Radiography and scintigraphy

Radiographs of painful or deformed bones are usually diagnostic, showing the characteristic mixed appearance of areas of lysis due to increased osteoclastic resorption with sclerosis from excessive osteoblastic bone formation. In the early stages of the disease the changes may be predominantly lytic with flame shaped resorption fronts in the long bones or osteoporosis circumscripta in the skull. A characteristic appearance that distinguishes Paget's disease from other conditions is the increased diameter of affected bones, particularly those of the spine or the shafts of long bones.

Severe deformity of the leg caused by Paget's disease

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Typical changes seen in Paget's disease: (left) stress fractures on lateral margin of cortex; (centre) resorption front; (right) mixed lytic and sclerotic lesion

Scintigraphy is a sensitive but non-specific method of detecting areas of skeletal abnormality and is a convenient way of assessing the distribution of Paget's disease. Although some sites may be asymptomatic it is important that they are identified because they may be susceptible to complications, such as fracture, which have a bearing on the choice of treatment.

Biochemistry

Paget's disease is characteristically associated with an increase in bone turnover but normal concentrations of serum calcium, phosphate, parathyroid hormone, and vitamin D metabolites.⁴ Traditionally, urinary hydroxyproline excretion (HYPRO) has been used as a marker of bone resorption and total serum alkaline phosphatase (TAP) has been taken to reflect the rate of bone formation.⁵ However, neither of these biochemical markers is entirely specific for bone since they receive a significant contribution from extra-skeletal sources. Over the past few years various additional markers of bone turnover have been introduced with the hope of increasing sensitivity and specificity.

Bone specific alkaline phosphatase (BAP) seems to have the best diagnostic accuracy as a measure of bone formation, with a sensitivity of 84% and a specificity of 100%.⁶ Considering its simplicity and low cost, total serum alkaline phosphatase concentration is still a credible alternative, with a sensitivity of 78% and a specificity of 100%. The main advantage for bone specific alkaline phosphatase over total serum alkaline phosphatase is in the assessment of localised or monostotic disease: bone specific, but not total, serum alkaline phosphatase concentration will often be raised and can be used to monitor the response to treatment. Bone specific alkaline phosphatase is also particularly useful when liver function tests are abnormal and the hepatic contribution to total serum alkaline phosphatase concentration is uncertain. This is less of a problem when turnover is very high but becomes progressively more important as activity approaches the normal range, when the liver component makes a proportionately greater contribution to the total.

Osteocalcin is a vitamin D dependent protein which binds calcium, has a strong affinity for hydroxyapatite, and comprises about 20% of the non-collagenous protein of bone. It is a reliable index of osteoblast function, but it may not be produced by cells at the same stage of differentiation as those which release alkaline phosphatase.⁷ Though it is a specific and sensitive marker of bone formation in osteoporosis,⁸ it has been disappointing in Paget's disease. Concentrations are less consistently raised than those of total serum alkaline phosphatase or bone specific alkaline phosphatase in untreated cases, and osteocalcin has limited value in monitoring the response to treatment.⁹

Type I collagen makes up 90% of the organic matrix

of bone and the carboxyterminal propeptide of type I procollagen (PICP) has been used as a marker of type I collagen synthesis and therefore of osteoblastic activity. Cross sectional histomorphometric and calcium kinetic studies seem to validate this assumption in a range of metabolic bone diseases,¹⁰ but type I procollagen has proved relatively insensitive in Paget's disease: only 45% of patients with active disease may have raised values.⁶ The reason for this discrepancy is uncertain, but the assay may not reflect the true rate of collagen synthesis or the radiometric assay may detect a different peptide from that which circulates naturally.

Among the resorption markers, excretion rates of pyridinoline (PYR) and urinary hydroxyproline have the best diagnostic accuracy, with sensitivities of 73% and 64% respectively.⁶ The main advantage of pyridinoline is in the assessment of limited disease, where its sensitivity detects a greater proportion of active cases. However, the lower cost and general availability of urinary hydroxyproline makes it an acceptable alternative for monitoring most other categories of Paget's disease.

Other resorption markers such as deoxypyridinoline (D-PYR), serum tartrate resistant acid phosphatase (TRAP), and the telopeptide carboxyterminal propeptide of type I collagen (1 CTP) seem to be less sensitive than pyridinoline and urinary hydroxyproline. The biochemical markers reflect the extent that the skeleton is affected by Paget's disease, so the less sensitive assays tend to provide normal values when disease is limited. In extensive and active disease, however, most markers of bone turnover will be abnormal and the choice of resorption marker can then be based on cost and availability.

Diagnosis

In most cases the diagnosis of Paget's disease can be made from the combination of symptoms, characteristic radiographic appearances, and raised concentrations of bone turnover markers. Difficulties with diagnosis tend to focus on a few specific problems.¹¹

A single sclerotic vertebra may cause uncertainty, and the differential diagnosis includes vertebral haemangioma, malignancy, and other infiltrations such as sarcoidosis, osteomyelitis, or vertebral compression fractures.

Vertebral haemangioma may show an increase in vertical trabeculation, but the end plates and neural arches are rarely affected, whereas they often are in Paget's disease. Vertebral size is usually normal but collapse may occur. Haemangiomas are usually solitary and other areas of abnormality—for example, on a bone scan—would make this diagnosis unlikely. Bone biochemistry may be unhelpful because it is usually normal in both haemangioma and in monostotic Paget's disease.

Collapsed osteoporotic vertebrae may appear mildly sclerotic and cause confusion with Paget's disease, although in Paget's disease the vertebra commonly expands in the anteroposterior or lateral directions. Osteoporosis is a generalised condition while Paget's disease is focal, and this is usually helpful in diagnosis. Bone scintigraphy may not be useful since a recently collapsed vertebra and Paget's disease both show increased uptake.

Malignancy, either primary or secondary, or infiltrations with sarcoidosis or infection may cause diagnostic difficulties, particularly if systemic features of the primary condition are absent or inconspicuous. In all these conditions isotope scanning is of limited value since increased uptake will generally be shown. Biochemical or haematological abnormalities, particularly hypercalcaemia, anaemia, raised sedimentation rate, or hypoalbuminaemia, may point to a

systemic illness; concentrations of bone markers may be raised and although non-specific may help exclude monostotic Paget's disease. Where doubt remains bone biopsy, if necessary with image intensifier control, is indicated.

Fibrous dysplasia may cause diagnostic problems,¹² but the polyostotic form is usually easy to distinguish from Paget's disease because it generally presents in childhood with fractures and long bone deformity, whereas Paget's disease is a condition of later life. Small solitary lesions of fibrous dysplasia may go unrecognised until early adult life, when they may cause diagnostic confusion with monostotic Paget's disease. The condition is usually asymptomatic unless a fracture occurs but, like Paget's disease, may be associated with increased uptake on isotope scans. Biopsy of the affected lesion may be needed when the clinical features are equivocal.

Aims of treatment and assessment of response

The first consideration is to identify which of the patients' symptoms are amenable to treatment and to select the best therapeutic option (box). Symptomatic polyostotic disease will almost invariably be associated with biochemical evidence of increased bone turnover, which should be measured three monthly to monitor the response to medical treatment. Pain usually responds to a reduction in disease activity and this tends to be more complete and prolonged if normal bone turnover is achieved.¹³⁻¹⁷ Symptoms due to degenerative joint disease rarely improve with antiresorptive treatment, and analgesics or joint replacement are preferred options. Pain localised to a stress fracture may respond to bed rest and low doses of bisphosphonate. Local bone remodelling tends to be in dynamic equilibrium and excessive deposition of bisphosphonate at the fracture site due to the high flow of blood to the bone may reduce remodelling to such an extent that the fracture is complete. An extending fracture requires surgical correction of the deformity, usually with internal fixation.

Monostotic disease may be present in up to a fifth of patients with symptoms¹⁸ and may present substantial problems in the evaluation of the response to treatment. Radiology may allow site specific monitoring of treatment but is useful only for assessing changes in resorption (infilling of intracortical lytic defects or regression of resorption fronts in long bones¹⁹). It is of no value in evaluating the response of mixed or sclerotic disease to treatment. Focal uptake measured with bone scintigraphy before and after treatment will also provide an objective assessment of focal response²⁰ but has limited repeatability because of exposure to radiation.

It is important to monitor the effects of treatment as objectively as possible as it may be associated with a 20-40% placebo response.^{21 22} The newer bone turnover

markers, such as bone specific alkaline phosphatase and pyridinoline, are particularly useful.

The rapid improvement in some neurological syndromes after treatment with antiresorptive agents is consistent with a vascular steal syndrome²³ and with the observation that myelographic evidence of improvement is often variable.²⁴ Some neurological syndromes may be the consequence of compression by expanded pagetic bone, and medical treatment will be expected to produce only slow improvement as the bone is remodelled to a more normal shape. Surgical decompression is indicated relatively early if medical management fails but is technically difficult because of the vascular bone and the nature of the deformity. Deafness may be found in up to 30% of patients whose skull is affected, but many of these elderly patients may be deaf for other reasons; as hearing loss changes only slowly, the response to medical treatment is difficult to evaluate.²⁵

Preoperative reduction in the flow of blood to bone has been advanced as an indication for antiresorptive therapy to reduce the risk of bleeding and improve the mechanical properties of bone. During total hip replacement, blood loss in patients with Paget's disease was double that of patients without the disease,²⁶ but an earlier study had found no evidence of increased blood loss, prolongation of operation time, or postoperative complications.²⁷ For elective surgery there seems to be no obstacle to controlling bone turnover with a bisphosphonate, but for emergency surgery calcitonin may have a more rapid suppressant effect on bone blood flow.²⁸

Prevention of deformity or degenerative joint disease is the most controversial indication for treatment, particularly if the patient has minimal or no symptoms. Given the long period of evolution of this type of complication it is almost impossible to establish objective evidence that antiresorptive therapy is beneficial. However, when these complications are found at an early stage then the potential of antiresorptive therapy to control the disease in the long term may be easier to support.

Treatment

The introduction of potent antiresorptive drugs has led to a dramatic improvement in the treatment of Paget's disease.^{29 30} The potency of the bisphosphonates and the sustained control of disease activity which they produce has resulted in them replacing calcitonin as the drug of first choice. Etidronate, pamidronate, and tiludronate are currently licensed for this indication in the United Kingdom, although alendronate (40 mg/day for up to six months)³¹ has recently been licensed in the United States.

Etidronate is given by mouth in a daily dose of 400 mg (approximately 5 mg/kg body weight) for six months and will reduce bone turnover by about 40-60%. Larger doses over shorter periods (10 mg/kg body weight for three months or 20 mg/kg body weight for one month) have also been shown to be effective, and bone turnover will be reduced in a dose dependent fashion. However, higher doses (>10 mg/kg body weight) may be associated with defective mineralisation and fractures.

Pamidronate is poorly absorbed and may have a local irritant effect on the upper gastrointestinal tract. Current recommendations are to give 30 mg weekly or 60 mg in alternate weeks, both doses diluted in 0.9% saline at an infusion rate of not more than 20 mg/h. Bone turnover will be reduced by 60-70%, with prolonged remission in those who achieve values within the lower half of the normal range after treatment.³²

Oral tiludronate is given as a 400 mg daily dose for

Therapeutic options in Paget's disease

Symptom	Aim of treatment	Treatment
Pagetic pain	Reduction of bone turnover	Bisphosphonates
Degenerative joint disease	Pain relief	Analgesics Joint replacement
Stress fractures	Pain relief	Bed rest and cautious use of bisphosphonates
	Prevent complete fracture	Surgical correction of deformity
Neurological syndromes	Reduction in bone turnover and blood flow	Bisphosphonates Calcitonin
	Reduction of compression	Surgery

Magnetic resonance image of lumbar spine of patient with Paget's disease, showing deformation of some of the vertebrae

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three months and reduces bone turnover by at least 50% in almost 60% of patients. Prolonged remission is achieved by those patients whose values of bone turnover after treatment are within the lower half of normal range. In clinical trials with tiludronate, mild gastrointestinal disturbances were no more common than among patients given placebo, and bone biopsy showed no evidence of defective mineralisation.³³

Calcitonin has been largely superseded by the bisphosphonates and has to be given either subcutaneously or by intranasal insufflation. It may occasionally be needed to reduce bone blood flow before operation.

Paget's disease is generally considered to be in remission until bone turnover has increased by more than 25% above the minimum achieved after treatment.¹⁶ Although bone turnover measurements after treatment may lie within the normal range for the population, they may nevertheless be greater than the value before the patient developed Paget's disease. The duration of remission achieved with bisphosphonates is considerably longer than that achieved by calcitonin.¹⁷

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ANY QUESTIONS

Could an Ethiopian with malaria infect North American mosquitos with chloroquine resistant parasites?

Vivax malaria was patchily endemic in rural areas of many of the southern states of the United States until the middle of this century. It had been systematically eradicated from Staten Island, New York, in 1905 and from the Mississippi Valley in the 1920s.¹ A resurgence followed the second world war, with many cases arising from transmission of infection imported by servicemen returning from the South Pacific. *Plasmodium vivax*, which in most endemic areas remains sensitive to chloroquine, is better adapted to survive the cold winters of much of the United States (because it can lie dormant in the human liver) than is *P. falciparum*, in which chloroquine resistance is now common. Travellers returning from the tropics infected with *P. falciparum* may give rise to small outbreaks of falciparum infection. Most travellers return to towns, and recent outbreaks have been in urban areas, notwith-

standing the comparative paucity of suitable vectors in towns.

In August 1993 three unacquainted people presented with *P. falciparum* infection in the Queens district of New York City.² In July and August of the following year 23 people presented with vivax malaria in the Houston area of Texas, with one case presenting in December of that year.³

Thus, while local transmission of chloroquine resistant *P. falciparum* is evidently possible, spread would be unlikely to continue for more than a few weeks of the summer or affect more than a handful of people.—C J ELLIS is a consultant physician in the department of infection and tropical medicine in Birmingham Heartlands Hospital

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