Classic diseases revisited

Paget's disease of bone

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Summary

Paget's disease of bone is a relatively common condition in the UK affecting up to 5% of the population over the age of 55 years with particularly high prevalence in the North West of England. The majority of those affected are asymptomatic. Its precise cause remains unknown, and until recently, choice of treatment of this sometimes painful and debilitating disease has been limited. In this article, we review various aspects of this disease, concentrating particularly on recent advances in our understanding of its aetiology and its treatment.

Keywords: Paget's disease, bone

Sir James Paget (1814–1899)

- born Norfolk, England
- trained at St. Bartholomew's Hospital, London
- past President, Royal College of Surgeons of England, Fellow of the Royal Society and Surgeon to the Queen
- described Paget's disease of bone in 1877, also described Paget's disease of the nipple and Paget's disease of the penis

Box 1

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Paget's disease of bone (osteitis deformans), named after Sir James Paget (box 1), an eminent 19th century surgeon, has been with man through the centuries. Its characteristic bone changes have been noted in Anglo-Saxon remains from around 950 AD¹ and in mediaeval remains from 15th century England.² Paget's clinical description of the disease as a slowly evolving, often benign, deforming disease of bone,³ remains accurate today. More than a century later, we perhaps understand the disease better and have the ability to diagnose and treat it more effectively, but many questions remain unanswered.

Paget's disease is a focal disorder of bone turnover characterised by excessive bone resorption coupled with bone formation which, while vigorous, often results in bone which is abnormal architecturally and is mechanically weaker. It may be monostotic (17%), but is more frequently multi focal, with a predilection for the axial skeleton (the spine, pelvis, femur, sacrum and skull, in descending order of frequency) although any bone may be affected (box 2).⁴

Epidemiology

Patients are usually over the age of 40 and the disease is mostly confined to Western Europe and parts of the world to which migration occurred from Europe. There is a particularly high prevalence of the disease (up to 8% of hospital patients over 55 years old) in the North West of England, but overall UK prevalence is around 5% in patients over 55 years old, with a slight male preponderance.⁵ Indirect evidence from mortality and primary bone tumour statistics hints at a gradual fall in frequency over the past century. With its late presentation and generally benign course, most patients are elderly and the prevalence in the over 90s rises to 10%.

In up to 14% of patients there is a positive family history with the cumulative risk of Paget's disease at its highest (around 20%) if the affected family member has both early age of diagnosis and bone deformity.⁶ Pedigree studies have led to speculation of the existence of a 'susceptibility gene' inherited in an autosomal dominant fashion, linked to the histocompatibility locus on chromosome 6⁷ with reported increased prevalence of HLA-DQW1, DR1, DR2, DRW6⁸ and HLA-DPW4⁹ in population surveys. Recently, two independent groups have described evidence of a susceptibility locus on chromosome 18q in kindreds affected by Paget's disease.^{58,59}

Histology

In the early phase of the disease, bone resorption predominates with abnormally large osteoclasts containing multiple pleomorphic nuclei and microfilamentous inclusion bodies.¹⁰ Following this initial osteolytic phase there is a mixed osteolytic–osteoblastic phase with an abundance of osteoblasts forming new matrix in the form of woven bone.¹¹ Mineralisation during these waves of activity is ineffective, resulting in a characteristic mosaic appearance due to persisting osteoid seams. Macroscopically, the bones are thickened and enlarged with reduced medullary spaces and the marrow is replaced by highly vascularised fibrous tissue.

Eventually, bone formation predominates but the osteosclerotic bone is thickened, architecturally disorganised and less able to withstand stress. There is a corresponding reduction in vascular fibrous tissue and haemopoietic function returns to the marrow cavity with no abnormality seen in haematological indices.

Radiological findings

The radiographic changes reflect the histological changes observed in many patients. Initially, lytic lesions predominate as seen with the characteristic skull X-ray picture of osteitis circumscripta and a progressive advancing lytic front in affected shafts of long bones. The osteosclerotic phase produces chaotic

Skeletal distribution of Paget's disease (% of patients with bone affected, from⁴)

- cervical spine (14%)
- femur (55%)
- humerus (31%)
- lumbar spine (58%)
- pelvis (72%)
- sacrum (43%)
- scapula (23%)
- skull (42%)
- thoracic spine (45%)
- tibia (35%)

Box 2

Figure 1 X-ray showing Paget's disease affecting upper femur with bowing, pseudo-fractures on the convex margin (arrow) and coarse trabecular pattern.

Figure 2 MRI scan showing spinal stenosis in Paget's disease affecting L1 (arrowhead) and resulting in spinal cord compression (arrows).

crisscross patterns with thickened cortical and trabecular bone sometimes accompanied by pseudofracture lines on the convex margins of long bones (figure 1). Plain radiographs are also useful in assessing the degree of deformity, and in the diagnosis of secondary arthritis and bone tumour.

Bone scintiscanning is useful in assessing the distribution of Pagetic lesions and, in addition, may reveal activity not seen on plain X-ray examination. Increased uptake often persists even in the presence of normal biochemistry, and differentiation from other pathology requires comparison with plain radiographs. It is worth noting that up to 9% of plain radiographs may appear normal despite scintigraphic evidence of Pagetic activity.⁴ Serial observations do not show spread of the disease from bone to bone, and changes only occur in preexisting sites.

Quantitative scintiscans are available, though not widely used, and can be used to assess treatment response. Magnetic resonance imaging also has a role to play in basilar invagination and spinal stenosis, allowing visualisation of soft tissue impingement (figure 2).

Laboratory investigations

Biochemical markers of bone turnover¹² reflect increased osteoclast activity, with an increase observed in concentrations of urinary hydroxyproline, pyridinoline, deoxypyridinoline, amino- and carboxy-terminal nonhelical (telopeptides) parts of type 1 collagen, all of which are produced during skeletal collagen degradation (box 3). The coupled increase in osteoblastic activity also results in elevated serum bone alkaline phosphatase, osteocalcin and procollagen extension peptides. Osteoblasts produce osteocalcin which is incorporated into the organic matrix of bone with a small proportion detectable in serum, and procollagen extension peptides are produced following the cleavage of procollagen to collagen.

Urinary hydroxyproline, pyridinoline and deoxypyridinoline can be measured in both 24-hour and fasting (early morning) second voided urine collections. 24-Hour measurements eliminate diurnal influence, and fasting samples avoid fluctuations caused by dietary intake of collagen. A urine sample collected after an overnight fast at a standard time, approximately two hours after the first passage of urine that morning (second voided specimen), will eliminate both dietary and diurnal influences. Differences in lean body mass can be corrected by using the ratio to urinary creatinine (which is dependent on lean body mass). In most hospital outpatient clinics, total alkaline phosphatase remains the simplest and most sensitive marker of disease activity. In our centre, however, urinary markers are also used as early evidence of both response to treatment, and relapse. A total alkaline phosphatase level within the normal range may also be misleading, as many patients continue to complain of pain and have continuing activity on bone scintiscans. This is likely to be due to the fact that, despite a rise in their bone alkaline phosphatase level, total alkaline phosphatase (comprising bone, liver and gut isoenzymes) remains within the normal population range.

Other biochemical changes include hypercalcaemia during immobilisation and occasional secondary hyperparathyroidism which has been attributed to a net excess in bone formation during the mixed osteolytic-osteosclerotic phase.¹³ The usual age range of patients with Paget's disease does, however, mean that primary hyperparathyroidism is often detected. Haematological indices are not disturbed and as a reflection of its focal nature, Paget's disease of bone does not result in increased erythrocyte sedimentation rates or C-reactive protein concentrations.

Clinical features

Indirect evidence suggests that at least 70% of patients are asymptomatic and diagnosis is often made on the basis of incidental radiographs or elevated alkaline phosphatase concentrations on enzyme profiles. Paget's disease can, however, present in a variety of ways with skeletal, neurological and cardiovascular signs and symptoms (box 4).

A common form of presentation is local bone pain, sometimes with obvious deformity, and local skin warmth due to increased bone microvasculature. The latter has been shown to be as much as six times that of normal bone.¹⁴ The pain experienced is often continuous with increased severity on resting and at night, but in practice may be difficult to distinguish from osteoarthritic pain.

Skeletal complications include osteoarthritis, deafness, fractures and sarcomatous change. Osteoarthritis of weight-bearing joints (especially knees, hips and spine) is extremely common but it is difficult to delineate the role of

Biochemical markers of bone turnover
<i>Osteoclast/bone resorption</i> <ul style="list-style-type: none">● hydroxyproline (urine)● pyridinoline (urine)● deoxypyridinoline (urine)● terminal collagen telopeptides (urine)
<i>Osteoblast/bone formation</i> <ul style="list-style-type: none">● bone alkaline phosphatase (serum)● osteocalcin (plasma)● procollagen extension peptides (serum)

Box 3

Summary of major clinical features
<i>Skeletal</i> <ul style="list-style-type: none">● bone pain● deformity● fracture● secondary osteoarthritis● dental complications● primary bone tumours
<i>Skeletal/neurological</i> <ul style="list-style-type: none">● deafness
<i>Neurological</i> <ul style="list-style-type: none">● cranial nerve palsies● spinal stenosis● hydrocephalus
<i>Others</i> <ul style="list-style-type: none">● vascular steal syndromes● high output cardiac failure● immobilisation hypercalcaemia● cardiac valvular calcification

Box 4

Figure 3 Pre- (A) and post- (B) treatment bone scintiscans in a patient treated with intravenous bisphosphonate

abnormal load bearing due to Pagetic deformity relative to the contribution of age-related degenerative changes. Fractures are estimated to occur in between 6-7% of patients,¹⁵ mostly affecting weight-bearing limb bones. An estimated 13% of patients suffer deafness,¹⁶ caused by ossicular involvement,¹⁷ auditory nerve and direct cochlea compression¹⁸ and possible changes in bone density and hence in the acoustic properties of bone.¹⁹ Not surprisingly, some also present with tinnitus and vertigo. Dental complications such as malocclusion, loosening and hypercementosis are common in patients with involvement of the mandible and maxilla.

Sarcomatous change fortunately occurs in less than 1% of patients,²⁰ the most common type being osteosarcoma, followed by fibrous histiocytoma, fibrosarcoma, chondrosarcoma, giant cell sarcoma and other rarer histological types. Commonest sites are the pelvis, humerus, femur, and skull, with tumours often presenting as pathological fractures and increasing bone pain unrelieved by treatment and with rising levels of alkaline phosphatase. The prognosis is poor with no effective treatment available.

Neurological complications include cranial nerve compression, noncommunicating hydrocephalus due to skull platybasia, spinal stenosis (figure 3) and vascular steal syndromes effecting spinal cord and cerebral blood supply.

Vascular steal from calf muscles is also blamed for intermittent claudication and a higher frequency of cardiac aortic valve calcification has been reported.²¹ In active and extensive Paget's disease the increased bone vascularity may rarely precipitate high output cardiac failure.

Aetiology

The description of viral-like inclusions in Pagetic osteoclasts by Rebel and coworkers in 1974⁶⁰ and the similarity of these inclusions to those found in cells infected with paramyxoviruses, has led to much work to isolate a causative virus. This is based on the theory that Paget's disease is caused by a slow viral infection with similarities to subacute sclerosing panencephalitis. In this progressive, dementing, ultimately fatal condition, measles virus (a paramyxovirus) is linked with multinucleated brain cells with similar microcylindrical inclusions which correspond to the viral nucleocapsid. In Pagetic osteoclasts the inclusions appear as tight nuclear aggregations of microcylindrical structures about 16-20 nm in diameter, and are degraded by trypsin, protease and RNase.²² An important feature of paramyxoviral infection is cell fusion which is in keeping with the abnormally large multinucleated osteoclasts in Paget's disease, some containing more than 100 nuclei.

An environmental agent would help explain the geographical distribution of the disease and the influence of emigration from the UK on lifetime risk, which decreases following migration and subsequently matches the incidence of the native population in the next generation.⁵ The hypothesis is not incompatible with evidence for genetic susceptibility either, as the HLA loci play a major role in the recognition of, and reaction to, infection.

Which virus then ? As yet, no one has isolated a complete virus and a number of candidates are available. Evidence for the presence of measles virus and respiratory syncytial virus has been found in Pagetic osteoclasts and multinucleated cells in marrow cultures from patients with Paget's disease. These cells express measles virus and respiratory syncytial virus antigens, as detected by polyclonal antisera²³ and monoclonal antibodies.²⁴ Measles virus RNA has also been detected by *in situ* hybridisation in Pagetic bone²⁵ but recent work attempting to sequence viral RNA with the sensitive reverse transcriptase/polymerase chain reaction have failed to detect paramyxoviral RNA.^{26,27}

Other workers have published evidence pointing to canine distemper virus as a possible candidate, and have localised canine distemper virus RNA in Pagetic osteoclasts by *in situ* hybridisation with labelled riboprobes. They have also sequenced canine distemper virus RNA from affected osteoclasts and noted a number of base pair changes, concluding that the persistent nature of the virus is due to viral mutation,²⁸ perhaps explaining why some workers have failed to detect canine distemper virus RNA by polymerase chain reaction.^{26,27} A number of studies have shown an association between previous pet ownership and Paget's disease²⁹ although this is not supported by all reports³⁰ and there is no evidence that there is a higher prevalence of Paget's disease in older veterinary surgeons. Parainfluenza type 3 and simian virus 5 antigens have been localised in Pagetic osteoclasts with mononuclear antibodies but this has not been confirmed by more recent and sensitive methods.²⁶

Attention has turned to the regulators of cell activity within the Pagetic osteoclast. Hoyland and co-workers have detected increased expression of interleukin-6 (IL-6)³¹ and c-fos oncogene³² directly in Pagetic bone by *in-situ*

hybridisation. Roodman *et al* have previously shown increased concentrations of IL-6 in conditioned media from long-term Pagetic bone marrow culture compared with conditioned media from normal bone marrow cultures.³³ Addition of Pagetic conditioned media to normal marrow cultures is also reported to stimulate the formation of ‘osteoclast-like’ multinucleated cells. However, reverse transcriptase/polymerase chain reaction analysis for cytokines and growth factor mRNA in bone biopsies³⁴ and in cultured bone cells³⁵ have shown no difference in expression of IL-6 and other cytokines between Pagetic and normal bone tissue.

An attractive hypothesis is that a paramyxoviral infection of bone leads to overproduction of cytokines, resulting in the clinical syndrome of Paget’s disease. Inherited abnormalities in immune response or in genes regulating bone activity would increase the susceptibility of the individual to developing the disease.

Treatment

While the cause of Paget’s disease remains unknown, no definitive cure is possible, although there are a number of available therapies which have been successfully used to suppress the abnormal osteoclast activity. In doing so these treatments alleviate the pain experienced and allow bone formation and mineralisation to proceed at a more normal pace, with the development of relatively normal new bone. Auditory symptoms are reported to improve with calcitonin³⁶ and bisphosphonate treatment,³⁷ although more extensive studies are required.

Calcitonin (box 5) acts via specific receptors on osteoclasts which results in suppression of bone resorption, and on pain-relieving central neural pathways. Efficacy is quick, with pain improving within weeks and with a detectable decrease in bone resorption markers in three hours. There is a more gradual reduction in alkaline phosphatase concentrations over weeks but the response is usually only sustained while the treatment continues, with relapse occurring within a few weeks of cessation of therapy. Human, eel, and salmon calcitonins are available and all require daily or alternate day subcutaneous injections. Flushing, nausea and diarrhoea are side-effects common to all calcitonins, with the development of neutralising antibodies to the non-human preparations sometimes resulting in a fall in efficacy.³⁸ More acceptable forms of administration of calcitonin and its analogues, ie, oral, intranasal and rectal routes, are currently under development. The results are promising and early data on nasal calcitonin show good efficacy and a better side-effect profile than injected calcitonin.³⁹

The bisphosphonate class of drugs is now the mainstay of treatment in Paget’s disease and offers sustained response and greater acceptability than calcitonin. Etidronate is the oldest licensed preparation in the UK and intravenous pamidronate and oral tiludronate have recently received their licences for use in Paget’s disease. Other bisphosphonates, such as clodronate and alendronate, have completed clinical trials and will hopefully receive licences in the near future.

Etidronate (box 6) has a relatively low therapeutic threshold on prolonged use, with the danger of mineralisation defects. Fracture rates seem increased in high-dose regimes⁴⁰ but are normal with lower doses.¹⁵ Etidronate should be used in doses of between 5-10 mg/kg daily (400 mg daily recommended) and in cycles of six months. Gastrointestinal absorption is poor and is in the order of 1-6%, further reduced in the presence of food. Disease remission can be in the order of years, with longer periods of remission seen with lower initial alkaline phosphatase levels and with greater responses (percentage reduction in alkaline phosphatase) early in the treatment course.⁴¹

Pamidronate (box 7) has recently been licensed for intravenous use in Paget’s disease of bone at a recommended total dose of 180 mg administered in six weekly 30-mg doses or three 60-mg doses at two-week intervals. This regime may be repeated at six-monthly intervals. Pamidronate therapy can normalise alkaline phosphatase levels in up to 90% of patients with subsequent remissions lasting at least two years in 50%.⁴² Pamidronate is more effective in patients with lower pretreatment alkaline phosphatase concentrations and normal levels are not always achieved in those with initial values above 240 U/l, despite additional treatment (although significant symptomatic improvement is still reported).⁴³ A transient reaction with pyrexia, myalgia and mild lymphopenia is seen in 10-20% of first infusions with pamidronate⁴⁴ and there have been a number of reports of pamidronate-associated uveitis.⁴⁵ Mineralisation defects⁴⁶ of debatable significance⁴⁷ and without clinical effect have been described in patients receiving intravenous pamidronate. Some physicians advocate the

Calcitonin
<ul style="list-style-type: none">• recommended regimes : 50 units three times weekly, increasing to 100 units five out of seven days, and to 100 units daily in single or divided doses• intramuscular or subcutaneous• three- to six-month course• test dose of 25 units useful – occasional severe reaction with hypotension, flushing and sweating• may need community nursing support• expensive

Box 5

Etidronate
<ul style="list-style-type: none">• 200 - 400 mg po daily for up to six months• requires at least two-hour fast before ingestion (overnight preferable) and no food, drugs or drink except water for 2 hours after ingestion• higher doses sometimes needed in shorter courses

Box 6

Pamidronate
<ul style="list-style-type: none">• 30 mg iv weekly for six weeks or 60 mg iv fortnightly for three weeks• repeatable every six months• requires day patient facilities

Box 7

Tiludronate

- 400 mg orally for 3 months
- repeatable every 6 months
- requires 1-h fast before and after ingestion
- gastrointestinal side-effects may limit acceptability

Box 8

concurrent use of vitamin D supplements with bisphosphonates to prevent possible osteomalacia, but there is little consensus on this point. In our clinic, all patients have their calcium balance assessed, as they are normally in the age range in which prevention of osteoporosis is also an important consideration.

The new oral formulation of tiludronate (box 8) is efficient in reducing Pagetic activity with up to 58% reduction of pretreatment alkaline phosphatase levels at six months, on a daily dose of 400 mg for six months.⁴⁸ A recent dose-ranging study has established that a three-month course of tiludronate 400 mg daily results in the best therapeutic/side-effect profile.⁴⁹ About 30% of patients experience adverse events which are mostly gastrointestinal in nature.⁴⁹

Good results are seen with oral and intravenous clodronate therapy with maximum suppression of alkaline phosphatase of up to 80% at six months, and remissions lasting for up to 12 months.⁵⁰ An oral course of 1600 mg daily for three months can induce remissions of up to 12 months in 69% of patients.⁵¹ Some studies have used five daily doses of 300 mg intravenously with good reductions in alkaline phosphatase after three months, and we are currently evaluating a course of four intravenous infusions, each of 1200 mg, at three-monthly intervals. Clodronate does not seem to interfere with bone mineralisation and its side-effect profile is excellent. Reported side-effects include gastrointestinal disturbances (in up to 10% with oral clodronate) transient asymptomatic hypocalcaemia, mild proteinuria and raised creatinine concentrations.⁵⁰

Intravenous alendronate is effective in reducing alkaline phosphatase concentrations to 35% of pretreatment values with maximum suppression after three months.⁵² Five consecutive infusions of alendronate (5-10 mg daily) can induce remissions of more than 12 months,⁵² the main side-effects being transient fever and arthromyalgia, with a transient fall in white cell count. Oral alendronate is also effective but can cause significant gastrointestinal discomfort.⁵³

Plicamycin is an antimitotic which inhibits RNA synthesis with selectivity for osteoclasts but is rarely used due to its toxicity, although there is good biochemical and symptomatic response.⁵⁴ Gallium nitrate also has anti-osteoclast activity although the effect is not cytotoxic. A recent randomised, dose-ranging trial of low-dose subcutaneous gallium nitrate has shown good efficacy at the higher doses tested.⁵⁵ The main side-effect of note was a mild reduction in haemoglobin concentrations.

Due attention should also be paid to simple analgesia and nonsteroidal anti-inflammatory drugs for symptom relief. Physiotherapy and simple aids and adjustments are useful adjuncts for some, and those with marked degenerative joint disease may benefit from surgical correction of deformities and arthroplasty.

Not all patients require treatment. Asymptomatic patients probably do not need much more than regular review appointments unless there is active disease at sites which may lead to complications. Lytic lesions at weight-bearing sites such as the vertebrae and lower limb bones require treatment to avoid fracture and/or deformity, and active disease adjacent to joints should also be treated in an attempt to prevent the development of secondary osteoarthritis. Asymptomatic patients may be safely reviewed at six-monthly or yearly intervals with serum total alkaline phosphatase and urinary pyridinolines as biochemical markers. The risk of sarcomatous transformation increases with disease length and, in theory, follow-up should be for life.

As in any other disease, the aim of treatment is to relieve symptoms already present and to prevent the development of future complications. It is often difficult to distinguish Pagetic pain from osteoarthritic pain and symptoms are often attributed wholly to Paget's disease. Expectations are hence often too high, and some effort must be made to distinguish the various sources of symptoms and to tailor patients' expectations accordingly. Biochemical and radiographic improvement may well be seen without symptomatic improvement and patients should be encouraged by the fact that future complications may be avoided.

Conclusions

While its incidence is probably decreasing, Paget's disease continues to afflict a large number of the UK's elderly population and presents considerable management problems in those effected by pain and its other complications. Bisphosphonate drugs have revolutionised the treatment of Paget's disease but an effective cure is unlikely to be found until the questions regarding its cause are answered. Some patients continue to be resistant to bisphosphonates and further work on newer anti-resorptive agents continues.

The absence of canine distemper, measles and respiratory syncytial virus RNA in recent reverse transcriptase/polymerase chain reaction studies, and the observation that similar inclusion bodies have been found in cells from giant cell tumours, primary oxalosis, osteopetrosis and other bone diseases,^{56,57} does not allow us to draw firm conclusions on the role of viral infection in the pathogenesis of Paget's disease. Studies of abnormal cytokine expression are similarly inconclusive. Current research should clarify the picture and provide further information on the basic physiology and biology of bone.

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