Review Article

Paget's Disease - Current Concepts

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Abstract

Paget's disease of the bone remains the second commonest metabolic bone disease in adults. Early diagnosis and appropriate management is essential to reduce the risk of potentially debilitating consequences. Diagnosis can be challenging; with many patients initially asymptomatic. In the majority of cases it is a diagnosis made incidentally with either an unexplained alkaline phosphatase or radiographic abnormalities. In this review we focus on providing a clear understanding of the current concepts and theories regarding aetiology, pathophysiology, diagnosis and treatment of Paget's disease.

INTRODUCTION

Paget's disease (PD) of the bone was first described by Sir James Paget in 1877. Initially known as osteitis deformans, it was thought to be a consequence of chronic inflammation [1]. Further research later revealed that it is in fact a benign disorder of bone remodelling which is the second commonest metabolic bone disease in adults. Both genders are affected equally with the prevalence increasing with age. Approximately two percent over the age of 50 are affected. This rises to ten percent by 90 years [2,3]. Although PD has been described globally, it is predominantly a disease affecting those of white ancestry. The highest prevalence is observed in the UK, North America and Australasia; in comparison to Asia where it is rare [4-6].

There are two main subtypes of PD: monostotic, affecting a single bone, and polystotic where several skeletal sites are affected. The diagnosis is often made incidentally, either on plain radiographs or by an unexplained raised serum alkaline phosphatase (ALP). Most patients are asymptomatic at diagnosis. Those that do have symptoms usually complain of bone pain. Other presentations can include limb deformity, pathological fractures, and compressive symptoms as a sequelae of bone overgrowth. To date medical management remains the mainstay of treatment.

AETIOLOGY

Despite being first described in the late 1800s the aetiology of the disease remains poorly understood. Arguments exist for a combination of environmental and genetic factors. This is supported by epidemiological observations of familial aggregation, geographical variation, and decreasing incidence of the disease in the presence of external factors.

Genetics

The familial incidence of disease was first noted in 1883, with greatest risk, up to seven fold, in those with a first degree relative [7]. Studies have reported that in patients newly diagnosed there is a positive family history in approximately 15-40% [8,9]. Currently several susceptibility loci have been identified in patients suffering from classical Paget's disease.

Unfortunately there is n unifying single mutation present in all patients [10]. The most prevalent mutation is the SQSTM1 on chromosome 5. However this gene is still only mutated in approximately 40% of familial cases and 10% of sporadic cases [11-13]. Identification of a key gene may allow future disease prevention or a reduction in complications through prophylactic measures. A large trial, the ZiPP study, is currently underway to assess the merit of prophylactic treatment in preventing PD in SQSTM1 positive patients.

Environmental factors

Although there is a strong argument for genetics as the principle risk factor the variable penetrance supports the view of a potential environmental trigger. Many authors have hypothesised that persistent viral infection by the paramyxovirus infection triggers variations in osteoclast development and activity seen in PD [14]. This theory is based on the identification of microfilaments within the cytoplasm of osteoclasts, with the appearance of viral nucleocapsids [15,16]. In support of this, several authors have also demonstrated that through transfecting osteoclast precursors with canine distemper virus or measles virus they are able to trigger osteoclastogenesis with the creation of multinucleate osteoclast-like cells akin to those in PD [17-20]. Recent multi- centre studies performed by Helfirch et al and Ralston et al. have however failed to identify any trace of viral paramyxovirus RNA even in bone specimens of patients with active disease. This has cast doubt on this theory of a virus as a causative agent [21,22].

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PATHOPHYSIOLOGY

In affected bones focal areas of abnormal excessive accelerated bone remodelling are seen. This produces sites of poor quality expanded bone with a disorganised trabecular pattern. In the majority of patients, 70-80%, PD is a polyostoic asymmetrical pattern [23]. The spine, proximal femur and pelvis are the sites most commonly affected in 60-75% of patients. The tibia and skull are affected to a lesser degree, however any bone can be affected by the disease [4,24].

Three phases of disease have been described: (i) the osteolytic phase, (ii) mixed phase, (iii) quiescent phase. In polystotic PD although all affected sites are present from the outset of the disease the rate of progression can differ between skeletal areas [2].

Osteolytic phase

The initial lytic phase of disease sees recruitment of atypical osteoclasts, which are both larger and more highly nucleated than normal, resorb the bone. As cortical and trabecular bone is resorbed there is infiltration of vascular fibrocellular tissue to fill the void [25]. At the peak of disease, the rate of turnover can reach 20 times that of normal bone [26]. This focus of osteoclastic activity results in classic lytic, radiolucent, areas seen on plain radiographs, Figure 1. Patients may present at this stage either with symptoms of pain relating to enhanced turnover or with limb warmth and temperature gradients due to the increased vascularity.

Mixed phase

As part of this reparative phase osteoclastic activity starts to decline and there is a compensatory response from osteoblasts. Both lamellar and woven bone is deposited, often in a disorganised fashion. Histology of mature lesions in this stage reveal a mosaic, jigsaw type pattern which is pathognomonic of PD [27]. In comparison to normal bone turnover in which new bone forms around Haversian canals in PD the abnormal vascular channels disrupt formation. This results in sclerotic areas of new irregular thickened trabecular bone, which is characteristically denser than normal bone (Figure 2).

Quiescent phase

In the final phase of disease the process 'burns out' with osteoblastic activity diminishing. During this phase biochemical markers are often within normal limits [28-30].

DIAGNOSIS

At the time of diagnosis the majority of patients, 70%, are asymptomatic [31]. Diagnosis is commonly incidental during routine radiological or serological investigations. Radiographs taken for other reasons may reveal typical appearances or blood tests may show an unexplained elevated serum ALP in the absence liver disease. Calcium and phosphate are typically normal. Serum ALP can however lie within normal limits during the quiescent phase of disease. Typical radiographic findings of PD correspond with the histological stage. These typical appearances at several sites are described using specific terminology. These include: "osteoporosis circumscripta", "cotton wool appearance" and

Figure 1 Lateral radiograph of the proximal tibia during the lytic phase. There is a large lucent area which begins in the subchondral bone and extends to a sharp inferior margin (*arrows*). (Image reproduced with permission from Smith et al, RadioGraphics, 2002, Vol. 22, No. 5:1191-1216, copyright RSNA, 2002) [50].

Figure 2 Plain radiograph of the pelvis showing areas of lucent and sclerosis during the mixed phase. Radiographic evidence of Increased bone formation is seen as trabecular (*white arrows*) and cortical (*black arrows*) thickenings.
(Image reproduced with permission from Smith et al, RadioGraphics, 2002, Vol. 22, No.5:1191-1216, copyright RSNA, 2002) [50].

"Tam o'Shanter sign" in the skull; the "picture frame sign" in the spine and "candle flame sign" in long bones [32]. It is important not to confuse the normal linea aspera-pilaster complex, or "track sign", on femoral radiographs with the "candle flame sign" found in PD [33].

Once the diagnosis has been made patients routinely undergo skeletal surveying to identify all asymptomatic sites

of disease to guide management [20]. UK guidelines have previously recommended using bone scintigraphy to perform the skeletal survey in all patients with PD [34]. Bone scintigraphy is favoured over plain radiographs due to increased sensitivity. This was described as 95% versus 74% by one author [35]. This however carries implications not only in terms of cost and resource availability but also increased radiation exposure over conventional plain radiographs [36].

CLINICAL PRESENTATION AND COMPLICATIONS

Pain is the predominant feature in the cohort of patients presenting with symptoms. This usually originates from the pagetic lesion itself, however may result from local tissue destruction or compression, (Table 1). In late disease patients may present with limb deformity; most commonly bowing of the tibia (anteriorly), femur (laterally) or skull enlargement. When either the skull or vertebra are involved nerve compression is a major concern. Hearing loss has been reported in as great as 50% of patients with skull involvement [37]. Aside from local effects PD can present with systemic compromise. High output heart failure is a rare but serious complication. This can occur when disease is particularly widespread and active (>15% skeletal involvement) due to hypervascularization of the bone [38,39].

In rare cases a Paget's lesion can undergo malignant transformation to various types of sarcoma. This occurs in less than 1 % of patients and is more common in elderly patients. Sarcomatous change typically yields an osteosarcoma with the femur most commonly affected. Prognosis is poor, often fatal, with a mean survival of one year [6,40,41].

MANAGEMENT

The management of PD has three aims. The primary objective is to reduce bone pain which is caused by increased remodelling [42]. The secondary objective is to reduce osseous vascularity associated with hypercalcaemia, particularly in the preoperative setting. The final and most controversial treatment objective is to

decrease the likelihood of complications that could impact quality of life in asymptomatic patients, though there is no evidence to support this practice [43]. It is worth noting that a byproduct of the treatment of PD is normalisation of bone remodelling markers which can act as a surrogate for the monitoring of disease progression.

Calcitonin

Historically, calcitonin was the treatment of choice in PD. It is a hormone produced in the parafollicular cells of the thyroid gland. Its primary physiological role is to inhibit the effects of osteoclasts, by reducing their resorptive capacity and size, and consequently their action on bone. Secondary effects include increased excretion of phosphate and calcium in the urine. Due to acquired resistance, the effectiveness of calcitonin is short-lived [44]. Furthermore, it is only available as intramuscular or subcutaneous injection. For these reasons, calcitonin is now used as a second-line treatment.

Biophosphonates

Bisphosphonates are the primary treatment for PD. They are synthetic analogues of inorganic pyrophosphate [45]. Their chief mechanism of action is inhibition of osteoclast activity and therefore of bone resorption. They can be broadly sub divided into non-nitrogen-containing and nitrogen-containing types Nitrogen-containing bisphosphonates such as alendronate and zoledronic acid are more effective in reducing bone turnover [46]. They suppress protein prenylation by interfering with farnesyl diphosphate synthase [47]. This impairs osteoclast function. Non-nitrogen-containing bisphosphonates such as etidronate are taken up by osteoclasts during bone resorption and lead to the accumulation of toxic ATP analogues that are cytotoxic [44].

The main side-effects of oral bisphosphonate use are gastrointestinal upset whereas use of intravenous agents pamidronate and zoledronic acid is known to result in flu-like symptoms [43]. The main contraindication to bisphosphonate use is renal impairment, in which case oral preparations are preferred to intravenous [46].

Denosumab

This agent is a RANK ligand inhibitor. It has the potential to emerge as an alternative treatment for patients for whom bisphosphonates are contraindicated [48]. It has been shown to be an effective inhibitor of bone resorption [44].

Managing the consequences of PD

Analgesia is used as an adjunct to bisphosphonate treatment in managing bone pain. Furthermore, the consequences of PD (primarily osteoarthritis and secondary fractures) often require surgical intervention. As previously discussed, this can be complicated by the increased osseous vascularity. In case of cement less total hip arthroplasty one author found an average of 744ml blood loss in patients with PD compared to a institutional average of 200-450ml. In addition 28% of PD patients had losses of greater than 2000ml [49]. Vigilant preoperative planning should therefore be undertaken prior to surgical intervention, elective or emergency, in order to mitigate these complications. Current accepted measures include bisphosphonate therapy,

Table 1: Clinical manifestations of Paget's disease by site.	
All sites	Bone pain Warmth
Skull	Headaches Hearing loss Cranial nerve lesions Skull deformity (enlargement with frontal bossing) Hydrocephalus Poor fitting dentures
Spine	Vertebral collapse Spinal curvature Cord or nerve root compression
Limbs	Pathological fracture (including stress fractures) Deformity Degenerative changes (secondary osteoarthritis) Peripheral neuropathies
Micellaneous	High output cardiac failure
Neoplastic (<1%)	Sarcoma Giant cell tumour

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adequate cross match and cell salvage where possible. The use of preoperative embolisation may be considered when operating for malignant transformation.

SUMMARY

Paget's disease is a chronic benign disorder of bone remodelling. Despite the aetiology of the disease still remaining unresolved, it is clear that there is no single causative factor. Instead disease activation is a more likely a multifactorial progress that involves genetic susceptibility with environmental triggers. As we further understand the genetics involved in PD we may be able to focus treatment further improving outcomes.

Diagnosis in the early stages is difficult with many patients remaining asymptomatic or presenting with non-specific symptoms. Clinicians must therefore have a high index of suspicion of PD in all patients over 50 years with unexplained deranged alkaline phosphatase, abnormal radiographs or bone pain. Early accurate diagnosis provides an opportunity to quantify disease and plan treatment. Excluding neoplastic transformation in PD; neurological compression poses the most serious and irreversible complication. In view of this, accurate assessment of affected regions is essential to counsel patients and guide treatment. In our opinion we believe that where possible, bone scintigraphy should be performed to assess for extent of disease as this offers the greatest sensitivity. In particular to identify skull involvement that may be not appear on plain radiographs. Medical management can then be discussed with the patient, either symptomatic or asymptomatic, to manage symptoms, stem progression or prevent complications. The use of prophylactic treatment still remains highly controversial with limited supporting evidence. It is however worth considering when disease is active at sites where disease progression would be have detrimental effects. This concept requires more high quality research before it can universally adopted. In the interim pharmacological advancements with the advent of third generation bisphosphonates have been fundamental effective in managing pain, preventing deterioration and complications. This has improved the quality of life we can achieve for those suffering from PD.

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