Pagetâ s Disease of Bone: Progress Towards Remission and Prevention

Abstract:

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Abstract

Pagetâ s disease of bone is a focal disorder of bone remodelling leading to areas of enlarged weakened bone manifesting with chronic pain, bone deformity, and fracture. Predominantly a disease of older adults, its prevalence is strongly linked to European ancestry. Pre-disposing factors include exposure to viruses such as measles and mutations in the SQSTM1 gene. PDB is diagnosed on plain radiograph, the extent of disease is delineated by radionuclide bone imaging, the degree of activity is quantified biochemically, and it is treated with a nitrogen-containing bisphosphonate, most effectively by a single intravenous infusion of zoledronate 5mg. Lifelong specialist follow-up is advocated because some patients require repeated infusions. Current clinical research is focusing on genetic factors in order to identify patients suitable for prevention.

Introduction

Pagetâ s disease of bone (PDB), an eponym after Sir James Paget who described the condition in the nineteenth century, is a chronic metabolic disorder of bone remodeling at a focal level. It may affect one bone (monostotic) or many bones (polyostotic)[1]. It is often diagnosed incidentally, but otherwise presents late, with slowly progressive, non-specific and common symptoms that challenge a physicianâ s acumen. We present a review of epidemiology, diagnosis and management of this condition and look to the future of disease prevention.

Aetiopathogenesis of PDB

PDB is a disease of older adults (rare before 40), most commonly of European heritage, with highest prevalence found in Britain, Ireland and mainland Europe. Its prevalence varies widely throughout the world from 0.7% to 4.6%[2]. This has led to the theory that PDB originated in Britain and has spread with migration. The true prevalence is unknown, because patients frequently have minimal or no symptoms. Recent data suggests a reduction in the incidence globally, with some groups reporting that the age at diagnosis is increasing, while the level of serum total alkaline phosphatase (ALP) at the time of diagnosis is reducing. The reasons behind this reduction in occurrence are not understood but unknown environmental factors are believed to be responsible. The normal adult skeleton undergoes remodelling in multicellular units with about 10% of the skeleton being replaced yearly. Remodelling balance may be positive, negative or neutral depending on the degree of bone resorption with respect to the degree of formation. In PDB, bone remodelling is chaotic, leading to woven bone, which is weaker than lamellar bone. The axial skeleton including skull, spine (lumbar more than thoracic more than cervical), pelvis and long bones of the extremities are the most frequently affected. These foci of abnormal weakened bone result in pain and associated complications. This tends to be slowly progressive, and has the potential to cause significant disability.

Abnormal osteoclastic activity is thought to be responsible for the development of PDB[2]. The disease can be divided into three pathological phases, all of which may be present simultaneously in the same bone. The initial osteolytic stage is characterized by abnormal osteoclastic bone resorption, and is typically followed by a period of compensatory disorganized osteoblastic bone formation (mixed osteoclastic-osteoblastic stage) while the bone marrow is replaced by connective tissue. A burnt-out osteosclerotic stage eventuates with greatly expanded but weakened and deformed bone. Genetic and environmental factors are believed to play important roles in PDB development. Among many possible predisposing genes, SQSTM1 influences osteoclast activation and is thought to be strongly associated with developing PDB but is also a risk factor for disease progression and severity[2]. Exposure to infection such as paramyxoviruses are thought to be key factors in the development of abnormal bone remodelling and subsequent PDB[2]. The declining incidence of PDB in recent decades also supports the theory that infections are causative or contributory to PDB development, since vaccination programs have expanded and certain infections are better controlled.

Diagnosis

PDB often goes undiagnosed for years, because symptoms can be absent or mild. Commonly, the diagnosis is made incidentally following blood or radiological tests for other reasons. The most preeminent symptom is pain, usually localized to the affected bone. Secondary complications such as hearing loss, osteoarthritis or neuropathy can occur as a result of bone expansion. Rare complications include osteosarcoma, hypercalcaemia (in patients who are immobilised), high output cardiac failure, paraparesis and basilar invagination with brainstem compression[2]. Imaging is critically important in diagnosing PDB. On plain film, enlarged bones with cortical thickening and coarse trabecular pattern are commonly seen[3]. Each of the osteolytic, mixed and osteosclerotic stages have distinct features, the earliest being a local radiolucency indicative of osteolysis. While plain imaging is often sufficient for diagnosis in the appropriate clinical setting, radionuclide bone scanning has a higher sensitivity and has the advantage of identifying the total extent of disease. However, radionuclide imaging may fail to identify the osteosclerotic phase of disease, as a consequence of low remodelling activity. Computed tomography and MRI are helpful if there is concern about metastases, pathological fracture, osteosarcoma or neurological complications[2].

Monostotic disease is more difficult to diagnose radiologically. Historically, this has led to a higher rate of bone biopsies to confirm diagnosis. MRI is of particular use in this area and is usually able to exclude disorders that may mimic PDB, such as metastatic bone disease, hyperostosis frontalis, fibrous dysplasia and pustulotic arthrosteititis[4]. A characteristic feature of PDB on MRI is the presence of prominent islands of preserved fatty (yellow) marrow in the involved bone[5] (Figure 1). In metastatic bone disease the yellow marrow is replaced by metastases. Laboratory testing should include measurement of calcium, phosphorus, total ALP, parathyroid hormone and 25-hydroxyvitamin D (25OHD). Depending on clinical suspicion and indication, liver dysfunction or underlying malignancy will need to be excluded. Bone turnover markers of resorption (serum C-terminal telopeptide of type I collagen) and formation (serum pro-collagen type I N pro-peptide) are readily available and should be measured at diagnosis, especially in cases of liver dysfunction when interpretation of total ALP as a bone marker is not possible[2]. It is important to have a baseline measure of bone remodelling activity, because this has a role in assessing the response to treatment. Of note, osteocalcin, which is a marker of the late phase of normal bone formation, is usually within the reference range, in keeping with the absence of normal mineralization in the woven bone of PDB.

Treatment

The treatment of PDB has advanced immeasurably following the introduction of nitrogen-containing bisphosphonates (N-BP), in particular intravenous zoledronate[2,6]. They produce a sustained reduction in bone remodelling at active sites, which usually results in improvement in pain, although the long term clinical benefits of this therapy have not yet been established[2]. Biochemically there is a rapid and prolonged drop in ALP to the reference range. Nothing emulates the degree and durability of the response in total ALP that is seen with zoledronate[7]. Assuming that there is no contraindication, the patient should be treated with a single 5 mg dose of intravenous zoledronate. The goal of treatment is to achieve remission, which is defined as achieving bone turnover below the midpoint of the reference range for the chosen bone turnover marker[7]. We aim to achieve and maintain a total ALP below 75 IU/L. Clinical review with measurement of total ALP should be at 6-monthly intervals. The need for subsequent infusions depends on clinical judgment based on appraisal of symptoms and total ALP response. In our experience about 25% of patients need repeat infusion of zoledronate[8]. There are two clinical considerations at the time of the infusion: risk of hypocalcaemia, and the acute phase reaction. The former is called the â hungry boneâ ; where shutting off bone resorption in the setting of a high bone turnover state like PDB with ongoing high bone formation leads to net transfer of circulating calcium into bone resulting in hypocalcaemia, which may be severe and prolonged[9,10]. The acute phase response is a non-specific physiologic immune-driven reaction to a challenge; patients are apt to develop flu-like symptoms with

fever and myalgia within 1-2 days following the infusion, most commonly after the first infusion[11]. This response may be prevented by ensuring adequate vitamin D status[11,12]. So, for both these reasons, prior to zoledronate infusion we favour pre-treating our patients for at least 3 months with an oral bisphosphonate (alendronate 70mg weekly, or risedronate 35mg weekly) and supplementation with calcium (1000mg daily) and vitamin D (20µg daily). Also, at the time of the first zoledronate infusion, we prescribe paracetamol 1000mg and advise patients to repeat this dose about 8-hourly until symptoms settle.

By the time that PDB is diagnosed, it is already at an advanced stage with bone enlargement and deformity; therefore, we are currently participating is a randomised controlled trial of genetic testing and targeted zoledronate therapy to prevent SQSTM1-mediated Paget's disease[13]. The main aim of this trial is to determine if targeted intervention with zoledronate can prevent the development of raised bone turnover or focal bone lesions in subjects who carry mutations in SQSTM1.

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