Paget's Disease of Bone: Progress Towards Remission and Prevention

Abstract

Paget's disease of bone is a focal disorder of bone remodelling leading to areas of enlarged weakened bone mainly affecting the proximal femur, spine, ribs, and skull. Nonetheless, it is not rare, affecting 1-2% of the population in the UK and Ireland. The prevalence varies widely throughout the world from 0.7% to 4.6%. 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 the incidence in Britain increasing, while the prevalence of serum alkaline phosphatase (ALP) at the time of diagnosis is reducing. The reasons behind this reduction in occurrence are not understood, and unknown environmental factors are believed to be responsible. The normal adult skeleton undergoes bone 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 characterised by increased bone formation, which is wider 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 classic sites, although bone remodelling can occur in any bone of the body. Disorganized bone formation (mixed osteoclastic-osteoblastic stage) while the bone marrow is replaced by connective tissue. A burnt-out osteoclastic 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, SOST gene mutations result in osteosclerosis and are strongly linked to European ancestry. Pre-disposing factors include exposure to viruses such as measles and mumps, and vitamin D. The disease can be divided into three pathological phases, 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 osteoclastic stage eventuates with greatly expanded and weakened and deformed bone. Genetic and environmental factors are believed to play important roles in PDB development. Among many possible predisposing genes, SOST gene mutations result in osteosclerosis and are strongly linked to European ancestry. Pre-disposing factors include exposure to viruses such as measles and mumps, and vitamin D.

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 common symptom is pain, usually located in the targeted bone. Severe pain occurs in some patients as hearing loss or knee pain. This can occur as a result of bone expansion. Rare complications include osteosarcoma, hypercalcemia (in patients who are not on bisphosphonate or denosumab therapy), and surgical intervention. Pain becomes critically important in diagnosing PDB. On plain film, enlarged bones with cortical thickening and coarse trabecular pattern are commonly seen. Each of the osteolytic, mixed and osteosclerotic stages have distinct features, the earliest being the osteolytic radiological pattern which can be best visualized by MRI (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 marrow markers of remodelling (serum C-terminal telopeptide of type I collagen) and formation (serum procollagen 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. It is important to have a baseline measurement of bone turnover markers. This has a role in assessing the disease activity of the patient. 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-BPs). These drugs are used to reduce bone turnover and hypertrophy, producing a sustained decrease in bone turnover markers, which usually results in improvement in pain, although the long term clinical benefits of this therapy have not yet been established. Biochemically there is a rapid and prolonged drop in ALP to the reference range. Nothing enhances bone turnover more than treatment with N-BP that is stopped, because there is a notion that there is no contradiction, 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. 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 judgement and response. PDB can be divided on aps of symptoms and total ALP response. In our experience about 25% of patients need repeat infusion of zoledronate. There are two clinical considerations at the time of the infusion: risk of hypocalcaemia, and the acute phase reaction. The former is called the hungry bone; where shutting off bone remodelling 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. The acute phase response is a non-specific physiologic immune-driven reaction to a challenge; patients are apt to develop flu-like symptoms with

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fever and myalgia within 1–2 days following the infusion, most commonly after the first infusion. This response may be prevented by ensuring adequate vitamin D status. 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 risendronate 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 in a randomised controlled trial of genetic testing and targeted zoledronate therapy to prevent SQSTM1-mediated Paget’s disease. 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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References