

## Effective Treatment of Paget's Disease of the Bone in a Chinese Woman

### Dear Editor,

Paget's disease is caused by increased bone resorption and ineffective bone formation. Unrecognised and untreated disease can cause significant morbidity and reduced quality of life. Paget's disease is seen in 2.3% to 9% of the elderly population in Europe. Incidence is low in Scandinavian countries, Africa and Asia.<sup>1</sup> Only a few cases of Paget's disease in Asians have been reported in medical literature with the largest one describing 5 cases of Paget's disease diagnosed over an 8-year period in Singapore.<sup>2</sup> The incidence of Paget's disease is decreasing most possibly due to environmental changes such as improved nutrition, more sedentary lifestyle and reduced exposure to infections.<sup>1</sup> However, due to asymptomatic disease, the incidence of Paget's disease may be grossly underestimated.

### Case Report

We describe a case of Paget's disease in a 63-year-old Singaporean Chinese woman with renal impairment, type 2 diabetes, hypertension and hyperlipidaemia. She was referred by her general practitioner for persistently elevated alkaline phosphatase levels which was initially found on routine testing. On questioning, the patient admitted to having vague bilateral lower limb aching. She denied having hearing loss. On examination (apart from very mild bowing of the left tibia), she did not have any other signs.

Her blood tests were normal except for an elevated alkaline phosphatase 312 U/L (normal 30-150). Heat fractionated alkaline phosphatase measurements showed increased levels of heat labile alkaline phosphatase indicating bone origin. Calcium, 25-hydroxy-vitamin D and phosphate levels were normal. She had chronic renal impairment with a creatinine clearance of 23 ml/min. Skeletal survey showed increased sclerosis and mild bone expansion associated with coarsening of the trabecular pattern affecting the left iliac and pubic bones (Fig. 1). There was also bowing of the left distal tibia shaft (Fig. 2).

As the patient was symptomatic, treatment was indicated. However, due to the renal impairment, bisphosphonates were contraindicated. After discussing the treatment options, she agreed to be started on denosumab. She was given denosumab 60 mg subcutaneously. The alkaline phosphatase levels normalised (118 U/L), within 3 months of starting

treatment and the bilateral lower limb aching resolved. The patient refused bone scan due to financial constraints.

Her alkaline phosphatase levels and symptoms are being monitored in clinic. She is on 6-monthly denosumab injections.

### Discussion

Interaction between genetic and environmental factors is thought to trigger the disease. Twelve percent to 40% of patients with Paget's disease have a positive family history.<sup>3</sup> The inheritance appears to be autosomal dominant with variable penetrance. Some recent observations have led to the hypothesis that viral infections such as measles virus, respiratory syncytial virus and canine distemper affecting osteoclasts may cause Paget's disease.<sup>4</sup> Further studies are needed to prove this hypothesis.



Fig. 1. Plain radiograph of pelvis.



Fig. 2. Plain radiograph of bilateral tibia.

Most patients with Paget's disease are asymptomatic. The commonest symptom is pain but a survey of 863 patients indicated that pain is not a good index of the extent of disease.<sup>5</sup>

Biochemical markers of bone turnover can be tested in serum or urine to support the diagnosis and monitor response to treatment. Bone-specific alkaline phosphatase, procollagen type I N-terminal propeptide, C-telopeptide, urinary N-telopeptide, urinary pyridinoline and urinary deoxypyridinoline are usually elevated in active disease.<sup>5</sup> Total and bone alkaline phosphatase have the highest sensitivity (78% and 84%, respectively) and specificity (almost 100%) for diagnosis.<sup>6</sup> Nonetheless, a normal total alkaline phosphatase level does not rule out the diagnosis.<sup>5</sup> When the total alkaline phosphatase levels are normal, bone-specific alkaline phosphatase levels are elevated in 60% and urinary pyridinoline is increased in 40% of the patients with symptoms of Paget's disease.<sup>7</sup> Calcium and phosphate levels are normal in Paget's disease except when there is immobilisation.

Features of Paget's disease can be seen on plain radiograph. Bone scintigraphy is more sensitive compared to plain radiographs especially in early disease<sup>7</sup> and in patients with normal alkaline phosphatase levels, bone scintigraphy can be used to monitor the response to treatment.<sup>7</sup> Patients with osteolytic lesions should have repeat plain radiographs in about 1 year after diagnosis to determine whether there has been improvement.<sup>7</sup>

The aim of treatment is to prevent or minimise the complications of the disease. Nitrogen containing bisphosphonates (aminobisphosphonates) is the current mainstay of treatment. The recommended treatment by the guidelines published by the Endocrine Society is a single dose of intravenous zoledronic acid 5 mg.<sup>8</sup> A randomised controlled study showed that a single infusion of zoledronic acid produces more rapid, complete and sustained response compared to daily treatment with risendronate.<sup>9</sup> There was also significant improvement in quality of life, including pain relief in patients treated with zoledronic acid and remission of up to 6 years may be achieved.<sup>9</sup> Improvement is evidenced by normalisation of serum biochemical markers of bone turnover, reduced activity on bone scintigraphy and improvement of symptoms. Alkaline phosphatase levels start to drop 10 days after initiation of treatment and reach a nadir between 3 and 6 months.<sup>10</sup> Medications may need to be reinstated if there is a rise in bone turnover marker levels or if the symptoms return.

The PRISM (Paget's Disease Randomized Trial of Intensive versus Symptomatic Management) study compared symptomatic treatment against bisphosphonate treatment in 1324 patients with Paget's disease. As expected the bone turnover markers were lower in the bisphosphonate group; however, it did not translate to improvement in

quality of life and symptoms.<sup>11</sup> Due to the lack of benefit of treatment in symptomatic patients, it was concluded that asymptomatic patients will not benefit from treatment. But the PRISM study has been criticised for its limitations such as high usage of bisphosphonates prior to enrolment in the study and short follow-up period.

Most authors and experts agree that symptomatic patients should be treated. Also young patients should have lower threshold for treatment in order to prevent future complications.<sup>11</sup> A clinical update from Mayo Clinic recommended asymptomatic patients with active disease of sites where complications are likely to develop such as the skull, spine and long bones to be initiated on treatment.

Bisphosphonates are contraindicated in patients with renal impairment with previous data showing incidences of nephrotic syndrome and acute tubular necrosis.<sup>11</sup> There are newer studies on the use of risendronate<sup>12</sup> and alendronate<sup>13</sup> in patients with estimated glomerular filtration rate (eGFR) as low as 15 ml/min which showed no significant change in serum creatinine concentration over a 2-year period. Due to the lack of consensus on the safety of bisphosphonates in renal impairment, they should be avoided, if possible.

Calcitonin can be used for the treatment of Paget's disease in the setting of renal impairment. It has been shown to reduce the biochemical markers of bone turnover by 40% to 50% and induce partial healing of lytic lesions on plain radiographs.<sup>14</sup> However, normalisation of bone turnover markers is not achieved in most patients. The use of calcitonin may result in neutralising antibodies, down regulation of calcitonin receptors and secondary hyperparathyroidism.<sup>14</sup> Given the limited efficacy and the inconvenience of injections, it is not an ideal choice for treatment.

There is some emerging evidence for using denosumab to treat Paget's disease, but it is not licensed for this indication yet. While there are case reports on denosumab being used to treat Paget's disease in the Caucasian population, there is none reported in the Asian population.

Denosumab is a monoclonal antibody which mimics osteoprotegerin (OPG). OPG is a basic glycoprotein, produced by the osteoblasts and marrow stromal cells which, as a decoy receptor, inhibits the binding of receptor activator of nuclear factor kappa-B ligand (RANKL) to receptor activator of nuclear factor  $\kappa$  B (RANK).<sup>15</sup> RANK is a surface receptor on osteoclasts and osteoclast precursors which, when activated, increases the proliferation and differentiation of cells to form the osteoclast phenotype and inhibits osteoclast apoptosis.<sup>16</sup> The activation of bone remodelling therefore depends on the dynamic balance between RANKL and (OPG + denosumab). Denosumab is thus an antiresorptive agent.

There are case reports on denosumab being used successfully to treat juvenile Paget's disease.<sup>17</sup> Small

studies have shown denosumab result in more rapid normalisation of alkaline phosphatase in Paget's disease compared to bisphosphonates.<sup>18</sup>

However, several points should be considered before denosumab is used. A case report by Reid IR et al indicated that while denosumab lead to improvement in biochemical markers and symptoms, bone scintigraphy did not completely normalise. This led to the conclusion that denosumab only partially corrects Pagetic bone activity.<sup>19</sup> Larger studies are needed to further examine and validate this finding.

Also, unlike the prolonged action of bisphosphonates, the effectiveness of denosumab is short. Studies on the use of denosumab in osteoporosis showed that within 12 months of stopping denosumab, the bone mineral density returned to baseline.<sup>20</sup> The duration of remission of Paget's disease induced by denosumab is unknown. As such, patients treated with denosumab will need to be monitored closely for relapse. Patients with Paget's disease and osteoporosis will certainly require alternative therapy for osteoporosis if the Paget's disease is in remission and the denosumab is stopped.

## Conclusion

As there are no long-term studies on the use of denosumab in Paget's disease, the relatively shorter duration of action and the absence of randomised controlled trial comparing denosumab against bisphosphonates, bisphosphonates should remain the first treatment choice. Denosumab can be considered when bisphosphonates are contraindicated and in those with treatment failure.

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