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CASE REPORT

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Gross vertebral collapse associated with long-term disodium etidronate treatment for pelvic Paget's disease

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Abstract Inhibition of skeletal mineralisation is a well-recognized complication of disodium etidronate therapy that was identified in the earliest studies of its use in osteoporosis and Paget's disease. The effect is seen at lower doses in Paget's disease than in osteoporosis. Several cases of spontaneous fractures occurring in unaffected bones of Paget's patients have been reported. However, we believe the case described here is the most severe example of etidronate-induced osteomalacia published in the literature, featuring widespread vertebral collapse occurring as a consequence of nearly 10 years of uninterrupted etidronate treatment for isolated hemipelvic Paget's disease.

Key words Etidronate · Osteomalacia · Paget's disease · Vertebral collapse · X-rays

Introduction

Etidronate was the first bisphosphonate proposed for clinical use in 1971, when its action in decreasing both bone resorption and formation was demonstrated in a patient with Paget's disease [1]. As a pyrophosphate analogue it has been demonstrated both in vitro and in vivo to bind avidly to hydroxyapatite crystals, with preferential accumulation under osteoclasts. There follows inhibition of osteoclasts as they endocytose etidronate-containing bone. The effect on resorption precedes formation.

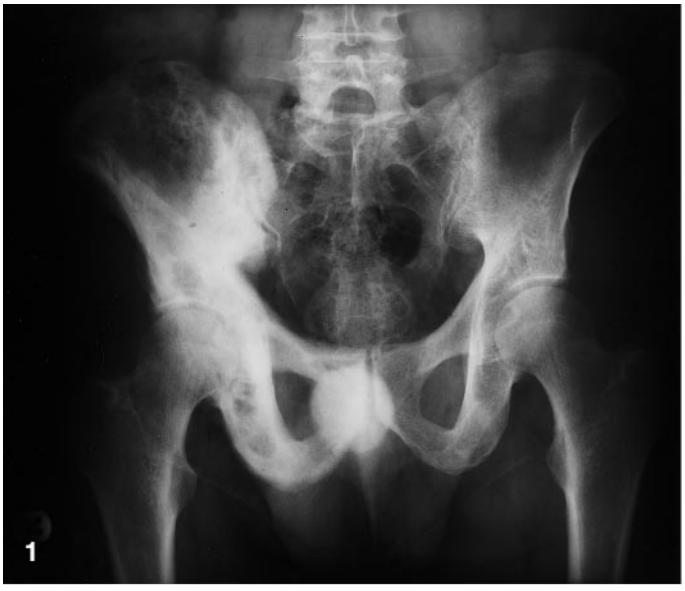
The major complication of etidronate treatment is the inhibition of normal skeletal mineralisation, leading to a clinical and histological picture of "focal" osteomalacia. We describe a case of severe vertebral collapse due to generalised osteomalacia consequent upon an inappropriately protracted "course" of etidronate for Paget's disease, which lasted nearly 10 years.

Case report

A 72-year-old Caucasian man was referred by his general practitioner in June 1997 with a 6-month history of progressive difficulty in walking, pains in the thoracic spine, generalized bone pain, and height loss of 5 in. (12.7 cm). He denied, however, that his disability was due to pain. Paget's disease of the right hemipelvis had been diagnosed in 1979, when he presented with pain in the right sacroiliac region (Fig. 1). In 1987 his pain had worsened and he was referred to an orthopaedic surgeon. He was commenced on disodium etidronate at a starting dose of 300 mg. This was rapidly escalated to 800–1200 mg (up to 17 mg/kg), in an attempt to titrate the dose required to normalise the serum alkaline phosphatase (ALP), which varied between 199 and 883 u/l (normal range 35–115 u/l). This was notably unsuccessful, and over a period of 10 years he had just two drug free periods, lasting 14 and 7 months.

The patient gave a past medical history of benign prostatic hypertrophy and stable angina. His other medications were aspirin and simvastatin. There were no features in the history to suggest undue exposure to aluminium.

On examination, his gait was slow and unsteady owing to weakness. He had a marked thoracic ky-



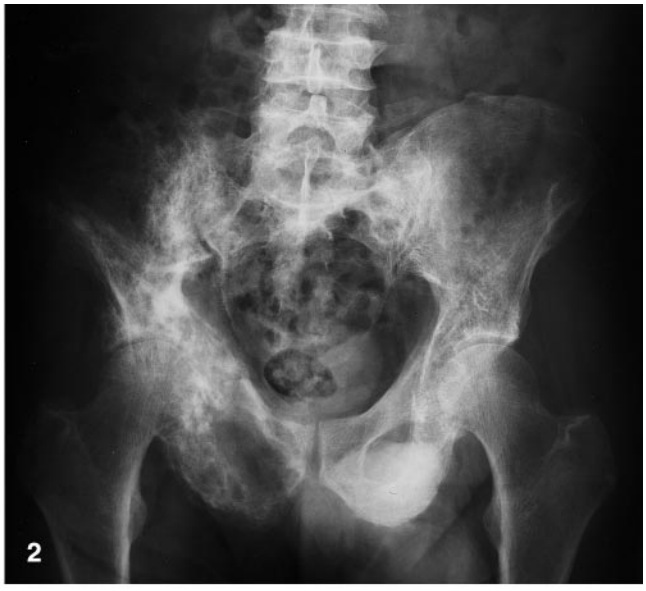
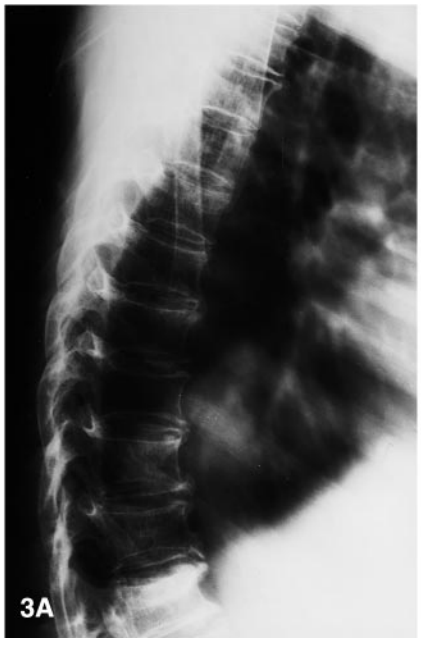


Fig. 1 Radiograph of the pelvis (1987), showing predominantly sclerotic Paget's of the right hemipelvis

Fig. 2 Radiograph of the pelvis (1997), showing the apparent lytic change within the previously sclerotic right inferior pubic ramus



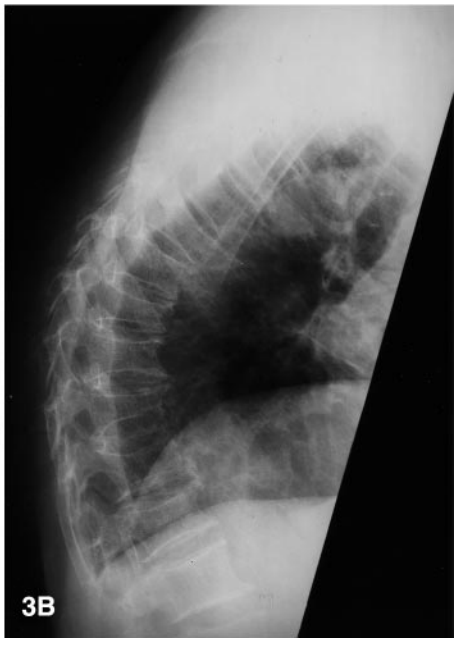


Fig. 3 **A** Radiograph of dorsal spine (1994), showing osteopaenia, but minmal loss of vertebral height. **B** Radiograph of dorsal spine (1997), showing widespread vertebral crush fractures and prominent kyphosis

phosis. Examination of the appendicular skeleton was unremarkable. Proximal myopathy was manifested by difficulty rising unaided from a chair. Otherwise there was no neurological deficit.

Radiographs demonstrated the development of marked, apparently lytic change within the previously sclerotic Pagetic right hemipelvis (Fig. 2), together with numerous compression fractures of the thoracic and lumbar vertebrae (Fig. 3). A full pathology screen, including haematological profile, erythrocyte sedimentation rate, urea and electrolytes, bone biochemistry, 25-OH-vitamin-D3, serum and urine electrophoresis, serum testosterone, cortisol and thyroid stimulating hormone, was normal. ALP was 248 u/l (normal range 35–115 u/l) and prostatic specific antigen was 0.6 ng/ml (normal range 0–0.4 ng/ml). An iliac crest biopsy was performed from the unaffected side, and undecalcified sections revealed severe osteomalacia with extensive but *focal* coverage of trabeculae with wide osteoid seams (Fig. 4). The maximum number of birefringent lamellae of osteoid, visualised under polarising light, was 24, i.e. well above the four that are required for mineralisation to be judged defective [6]. Neither a plain radiological skeletal survey nor isotope bone scan was performed, as it was not felt that these investigations were likely to influence the patient's management.

Etidronate was discontinued, and, in view of the alarming extent of apparently porotic vertebral collapse,

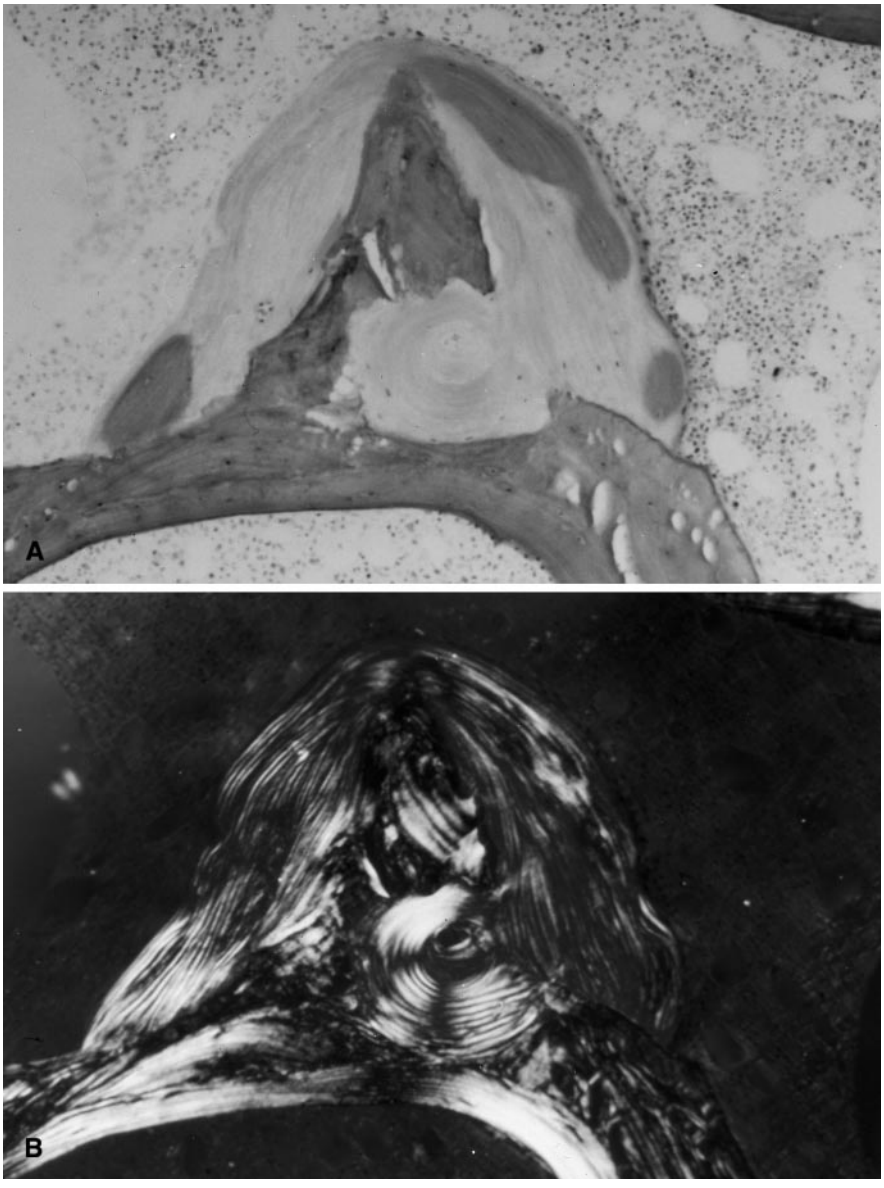


Fig. 4 **A** Undecalcified resin-embedded section of iliac crest bone biopsy stained with haematoxylin and eosin. Focal areas of gross excess osteoid and some bone lining cells are apparent. There is no evidence of active resorption. **B** The same section viewed with matching polarised light to highlight large areas of osteoid

treatment was instituted with intravenous pamidronate (45 mg). In addition, it was uncertain whether the persistently elevated ALP might represent ongoing Pagetic activity, despite the prolonged therapy with etidronate. This was repeated at 2-monthly intervals for 10 months until January 1998, when the ALP finally normalised. The patient reported significant improvement in his generalised bony pain and arthralgias within 2 months of the first infusion. This continued such that, upon review in December 1998, residual symptoms were of only minor low back pain on prolonged sitting or standing. Clinically there was improvement in his muscle weakness and walking had become easier.

In January 1999 he died unexpectedly from an acute myocardial infarction.

Discussion

Etidronate-induced osteomalacia was described originally in preliminary trials of its use in osteoporosis, which were conducted in the early 1970s, where high doses were used (20 mg/kg/day) [2], and in Paget's disease (10–20 mg/kg/day) [3]. Boyce et al. showed that prolonged, continuous treatment at 5 mg/kg/day for months or longer could adversely affect mineralisation and induce "focal" osteomalacia in non-pagetic bone, whilst failing to adequately suppress disease activity in pagetic bone [4]. The term "focal" in this respect refers to the *histological* appearance of coverage of trabeculae, with osteoid of increased thickness, but normal extent. This seems to be related clinically to bony pain similar to that observed in nutritional

osteomalacia [5]. The iliac crest biopsy from the non-pagetic side in our patient shows clearly the focal nature of the mineralisation defect. Another form of osteomalacia, also usually focal, that is associated with increased risk of fracture, is that due to toxic inhibition of mineralisation by aluminium [6].

The ability of etidronate to inhibit mineralisation at lower doses in Paget's disease than in other conditions is thought to relate to the focal nature of this disease, there being an increased uptake of bisphosphonate at areas of high turnover [7]. Discontinuation of etidronate appears to result in fairly rapid correction of the mineralisation defect.

Etidronate-treated patients with Paget's disease who are felt to be most at risk of fracture are those with severe, albeit microscopically focal, osteomalacia within lytic lesions in weight-bearing bones. This risk is further increased if the resorptive effect of active osteoclasts is inadequately suppressed by therapy. Since persistent osteoclastic activity has been demonstrated in studies with high- as well as low-dose therapy [11], and in view of the advanced nature of our patient's condition, it was felt justified to institute treatment with intravenous pamidronate.

It remains difficult to make a dosage recommendation for etidronate in Paget's disease, since the active dose required in some patients is near that inducing osteomalacia. In general, a course of 400 mg daily for no more than 6 months is suggested. Courses should be interrupted for a minimum drug-free period of 3 months. However, up to 70% of patients will not normalise bone turnover on this regimen and may develop resistance if more prolonged or too frequently repeated courses are given [8]. With the advent of potent second- and third-generation bisphosphonates such as pamidronate and risedronate, which have no significant effect on mineralisation at therapeutic doses, etidronate might justifiably now be regarded as redundant in so far as the management of Paget's disease is concerned.

Spontaneous fractures of uninvolved bones of patients with Paget's disease during treatment with disodium etidronate have been described in the past [9–11]. Of one series of 737 patients treated with disodium etidronate, 4 were found to have non-traumatic, non-pagetic fractures, of which 3 involved single vertebrae [12]. However, the case described here represents a considerably more devastating example of extensive vertebral collapse and can only serve to highlight the perils of long-term high-dose etidronate treatment.

Khairi et al. showed that 18 of 116 patients treated with etidronate (5, 10 or 20 mg/kg/day) or placebo sustained one fracture or more. Two non-traumatic fractures through pagetic bone occurred in patients receiving placebo. Of those patients treated with etidronate, non-traumatic fractures of pagetic bone were observed in eight instances, and of non-pagetic bone in five [11]. No non-traumatic fractures were observed before 3 months of therapy, four were observed between 3 and 6 months of therapy and nine occurred after 9–24 months of etidronate therapy. Whether indeed the overall incidence of fracture in Paget's disease is increased by etidronate cannot be accurately assessed, since there is no information in the literature on the fracture incidence in untreated patients with symptomatic Paget's disease. However, the data available would suggest that prolonging treatment beyond 6 months might increase the risk of fracture. Patients with predominantly lytic lesions may be at especially increased risk [11].

The development of radiolucent areas in pagetic bone of patients treated with inappropriately high doses of disodium etidronate is recognised [13]. However, to our knowledge, the radiological transition of sclerotic to *apparently* lytic bone in such patients has not previously been described.

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