Frequent fractures and sclerotic thick bands on physes related to oral alendronate treatments

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ABSTRACT

Bisphosphonate treatment has known effects of improving bone mineral density and preventing fractures in children with steroid-induced osteoporosis. However, there have been reports that high-dosage pamidronate therapy induces osteopetrosis in the borders of bones. A 10-year-old boy undergoing long-term treatment with oral alendronate developed frequent fractures throughout adolescence while playing basketball. Radiographs showed osteosclerotic bands on the metaphyses of his long bones and vertebrae, and fractures were evident in the regions surrounding the osteosclerotic lesions: a stress fracture in the fourth metatarsal, anterior limbus vertebra (T12), spondylolysis (L3 and L5), and osteochondritis dissecans of the left lateral femoral condyle. Alendronate had been taken for a period of 6 years when the treatment was discontinued. Approximately 18 months after discontinuation, sclerotic bands remained evident; however, 4 years after discontinuation, sclerotic banding still surrounded the wing of the ilium but appeared diminished in the knees. In children and adolescents who engage in sports activities and are being treated with steroids and bisphosphonates, the possibility of pathological stress fractures should be considered.

Introduction

Glucocorticoids are associated with an increased fracture risk, which is linked to both daily and cumulative doses. Reduced bone formation and increased cortical porosity are key pathogenic features of glucocorticoid-induced osteoporosis [1].

According to guidelines, treatment with prednisolone, a glucocorticoid, at a dosage of >5 mg/day in adults should be combined with oral alendronate (5 mg/day or 35 mg/week) [2]. It has been suggested that glucocorticoids should also be administered with bisphosphonates to improve bone density, prevent fractures, and remodel existing fractures in children with steroid-induced osteoporosis [3]. However, in one case report, high-dosage pamidronate therapy caused osteopetrosis in the bone regions surrounding the metaphyses in a child [4]. We herein report a similar finding: osteopetrosis-like sclerotic band formation on the borders of the metaphyses with frequent fractures despite the combination of an optimal dosage of oral bisphosphonate with corticosteroid therapy.

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Fig. 1. Oblique view of the right foot. Fracture (indicated by the triangle) of the right fourth metatarsal bone.

Fig. 2. Frontal radiograph (a) and CT images (b) show symmetric sclerotic bands (arrow) on proximal tibial and distal femoral metaphyses and framing (arrowhead) of the epiphyses. Follow-up radiographs show sclerotic bands on the wing off the ilium (c), but both knees appear almost normal (d).
Case report

A 10-year-old boy with membranoproliferative glomerulonephritis was administered intravenous methylprednisolone pulse therapy (1 mg/kg for 3 consecutive days once a week, three courses) upon onset of the disease, and oral alendronate therapy (35 mg/week) was initiated at the start of methylprednisolone pulse therapy. At age 11, proteinuria recurred. Mizoribine (200 mg/day) was initiated and gradually increased (to 300 mg/day), changed to mycophenolate mofetil (1000 mg/day) at age 12, and terminated at age 16. Corticosteroid treatment (20 mg/2 days oral prednisolone) was continued and increased (to 40 mg/2 days) because renal biopsy findings had not improved. As of May 2021, 10 years had passed since the onset of the disease; alendronate had been discontinued at age 16, prednisolone had been discontinued at age 17, and mycophenolate mofetil had been discontinued at age 20.

Three years after onset of the disease, at age 13, the patient sustained a stress fracture of the right fourth metatarsal bone while playing basketball; he had been taking alendronate weekly for 3 years. The fracture occurred in the base of the metatarsal, and cortical thickening was observed in the lateral cortical bone of the metatarsal on radiographs taken 2 weeks after his pain started (Fig. 1a). The patient refrained from playing basketball for several months, his fracture healed, and a normal callus was formed (Fig. 1b). Radio- graphs of both knees taken to determine the cause of pain showed symmetric sclerotic banding of the metaphysis of all bones of the knee (Fig. 2b). Computed tomography (CT) images showed more structured sclerotic banding on the metaphysis than was visible on the radiographs. Circumferential osteosclerosis was apparent on the epiphyses (Fig. 2a).

At age 14, 1 year after the first fracture, he visited the emergency department with left knee pain induced by landing on his left leg after issuing a pass while running. A CT image (Fig. 3b) showed marginal irregularity and defect of the sclerotic epiphyseal surface of the left lateral femoral condyle, and a thin bony fragment was observed near the irregular surface. Magnetic resonance imaging showed thick epiphyseal sclerotic banding and cartilage layers that were separated (Fig. 3a). Osteochondritis dissecans (OCD) was diagnosed. Because the cartilage piece was completely free and conservative treatment would not be effective, the bone fragment was fixed with multiple absorbable screws (Fig. 3c).

At age 16, approximately 3 years after the first fracture, he developed anterior limbus vertebra (T12) and moderate (L3) and complete (L5) spondylolysis (Fig. 4a). He was advised to wear an orthosis for 24 h a day and stop playing basketball until the fractures healed. After 6 months, CT images showed nearly full union of the L3 spondylolysis but no change of the T12 anterior limbus and L5 spondylolysis (Fig. 4b).
Upon occurrence of these vertebral injuries, alendronate was discontinued, approximately 6 years after treatment had been started. Follow-up radiographs taken 3 years 6 months after discontinuation showed sclerotic banding in the bone regions surrounding the wing of the ilium but no sclerotic banding in either knee (Fig. 2c, d).

Discussion

This young patient experienced several fractures. However, to determine the role of alendronate in these fractures, it was necessary to consider whether the fractures had been caused by osteoporotic change from long-term steroid treatments, high exercise intensity, or suppression of bone remodeling by bisphosphonate therapy.

Fig. 4. Lateral lumbar radiograph and CT image of anterior limbus vertebra (T12, black arrow) and spondylolysis (L3 and L5, black arrowhead) (a-1 and a-2). A CT image taken 6 months post-injury shows nearly full union of the L3 spondylolysis (black arrowhead), but no change in T12 anterior limbus and L5 spondylolysis (b-1 and b-2). An oblique CT projection (c) shows the excessive callus that formed between articular processes (arrow).
The incidence of fractures in children taking corticosteroids is high [3], making it, therefore it is difficult to assert that the frequent fractures experienced by this young patient were solely related to alendronate therapy. However, his fractures exhibited two known bisphosphonate-associated characteristics.

The first characteristic is “zebra lines.” Bisphosphonate in the blood accumulates in the metaphysis, where new bone formation actively occurs in children. One study showed that such accumulation formed “zebra lines” on the metaphysis when pamidronate was administered intravenously every few months in children [5]. The number and interval of “zebra lines” were found to be related to the administration interval and duration of pamidronate therapy. Thus, high-dose and long-term pamidronate may cause the formation of osteosclerotic bands, not multiple lines as a stripe pattern, on the same lesions. The bisphosphonate binding affinity to hydroxyapatite varies; pamidronate has the strongest binding affinity, and alendronate has the second strongest [6]. In our case, long-term continuous oral alendronate treatment resulted in osteosclerotic banding similar to that observed with high-dose intravenous pamidronate treatment.

The second characteristic is cortical thickening with beak formation or excessive callus formation, which suggests the breakdown of the fracture healing processes. The beak formation known to be associated with long-term bisphosphonate use, especially on the femur, is called an atypical femoral fracture (AFF) [7]. Oh et al. [8] reported that AFFs are stress fractures with or without minor trauma and are due to suppression of bone turnover by specific drugs.

Metatarsal fractures are known to be associated with years of sporting experience [9]. In this case, the stress fracture of the fourth metatarsal bone exhibited cortical thickening as seen in usual stress fractures. However, there was no beak formation (i.e., AFF) on the thick cortical bone. Therefore, bisphosphonate therapy might have been unrelated to this metatarsal fracture.

A CT image of our patient’s knee (Fig. 3) showed that the “thickened” lesion, resembling a zebra line, had been peeled off. OCD is caused by repetitive mechanical stress and circular and ossification disorders [9]. In this case, we speculate that the suppression of remodeling by bisphosphonate therapy caused the thickened cortical bone to become fragile, accumulate damage, and peel off.

Anterior limbus vertebra and spondylolysis are also stress fractures related to sports activity, but our patient showed atypical characteristics on radiographs. Anterior limbus vertebra in this case occurred solely where the thickest sclerotic band was observed, and excessive calluses similar to those in bisphosphonate-related AFFs were observed for L3 spondylolysis. In addition, bisphosphonate may have affected the fracture healing process, causing an excessive callus to develop on the spondylolysis. Thus, bisphosphonate therapy may have played a role in these two stress fractures (anterior limbus vertebra and spondylolysis).

Recent reports have indicated that bisphosphonates are associated with complications that can impair patients’ quality of life and that diet therapy (e.g., increased vitamin D intake) and exercise therapy are preferable to bisphosphonates [10]. Long-term oral bisphosphonate treatment should be avoided in children before epiphyseal closure. If prednisolone maintains renal function, typically no exercise restrictions are required in patients with membranoproliferative glomerulonephritis; however, when children on steroids and bisphosphonates engage in sports activities, the possibility of atypical fractures in the bone surrounding the metaphysis should be kept in mind.

Declaration of competing interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial or nonfinancial interest in the subject matter or materials discussed in this manuscript.

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