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A subtrochanteric femoral stress fracture following bisphosphonate treatment in an adolescent girl

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Abstract

Atypical subtrochanteric and diaphyseal femoral fractures (AFFs) have emerged as a potential complication of bisphosphonate treatment in adults. Despite increasing off-label use of bisphosphonates in children and adolescents for a variety of skeletal disorders, there have been no reports of AFFs in children or adolescents outside of the osteogenesis imperfecta population. We present the case of a 16-year-old girl who developed a subtrochanteric femoral stress fracture following pamidronate treatment for idiopathic juvenile osteoporosis.

Introduction

Over the past decade, concerns have emerged regarding an association between long-term bisphosphonate use and an increased risk of atypical subtrochanteric and diaphyseal femoral fractures (AFFs) in adults [1]. In contrast to typical hip fractures, which are generally traumatic and occur in the femoral neck, trochanteric, and intertrochanteric regions, AFFs affect the subtrochanteric or femoral shaft regions, and arise spontaneously or with low-energy insult [2].

Bisphosphonates are increasingly used to treat disorders of low bone mineral density (BMD) in children and adolescents [3]; however the long-term effects of bone turnover suppression on the growing skeleton are incompletely understood. Case series of children with osteogenesis imperfecta (OI), a disorder of bone fragility due to abnormalities in type I collagen, report a potential association between bisphosphonate treatment and proximal femoral fractures [4–6]. To date, there have been no reports of AFFs in children or adolescents without primary collagen defects. We present the case of an adolescent girl with idiopathic juvenile osteoporosis who developed a subtrochanteric femoral stress fracture following bisphosphonate therapy.

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Case

An 11-year-old girl presented with a 1-year history of back pain and height loss due to multiple thoracic vertebral compression fractures (Figure 1A and B). A DXA scan showed low bone mineral density (BMD) with a lumbar spine Z-score of -3.9 and total body less head Z-score of -2.0 . An extensive workup, including a vertebral biopsy and testing for *COL1A1/1A2* mutations, did not reveal an etiology for her low BMD. She was diagnosed with idiopathic juvenile osteoporosis and treated with intravenous pamidronate starting at age 12. She was initially started on a regimen of 1 mg/kg given over 3 consecutive days at 4 month intervals, and after 2 doses was changed to a regimen of 1 mg/kg given as a single infusion at 3 month intervals. Over a 2-year treatment period she received a total dose of 11 mg/kg. During the treatment period she had partial reconstitution of her vertebral bodies and no additional fractures. Alkaline phosphatase levels were monitored prior to each infusion, and ranged from 185 U/L (Z-score -1.51) at the start of pamidronate to 131 U/L (Z-score -1.38) at completion of treatment. At pamidronate discontinuation at age 14 years, her lumbar spine Z-score had improved to -1.6 and total body less head to -0.6 (Figure 1C). Pubertal onset and progression were normal, including menarche at age 14 years, and completion of linear growth at age 15 years.

At age 16 years, the patient presented with a 3-week history of left thigh pain. Several weeks prior she had joined a cross-country team after many years of low sports activity, and was running 3–4 miles per day at the time of presentation. Radiographs showed diffuse cortical thickening of the bilateral femoral diaphyses, and a localized periosteal reaction at the medial cortex of the proximal left femur (Figure 2A). A technetium-99 bone scan showed focal tracer uptake in the medial aspect of the proximal left femur, consistent with a stress fracture. Stress-related changes were also noted in the right tibial and tarsal regions (Figure 2B). Screening for metabolic bone diseases continued to be unremarkable, including a normal 25-OH-Vitamin D level of 40 ng/mL. An alkaline phosphatase level was low at 83 U/L (Z-score -2.44).

The patient was treated with restricted weight-bearing and relative rest. She received physical therapy and was placed on a program of muscle strengthening and generalized conditioning. After a protracted 16-week course her pain improved and she was able to resume regular activities. Radiographs obtained eight months after her initial presentation with thigh pain showed resolution of the periosteal reaction.

Discussion

This adolescent's presentation with a femoral stress fracture 2 years after completing a course of high-dose pamidronate treatment shares several features in common with AFFs, including subtrochanteric location, localized periosteal reaction, and generalized cortical thickening of the femoral diaphysis. Her recent increase in physical activity following a period of deconditioning is a known risk factor for stress fractures [7], which is further supported by her concomitant tibial injury. Although stress fractures are common overuse injuries in adolescents, femoral diaphyseal stress fractures are relatively uncommon in this population [8, 9], raising concern for a possible association with pamidronate treatment. The

pathogenesis of AFFs is not well-understood; however evidence suggests that, similar to typical stress fractures, they may be related to skeletal damage from repetitive loading. This is supported by two case reports describing the evolution of AFFs on retrospective review of serial DXA scans [10, 11]. In both cases, periosteal callus formation occurred prior to the development of a transverse cortical fracture, a pattern characteristic of stress fractures. This supports the current hypothesis that AFFs arise when reduction in bone remodeling inhibits repair of microfractures that occur from repetitive loading, and that integration of these microfractures into a single cortical defect promotes formation of a transverse fracture. In keeping with this hypothesis, the American Society for Bone and Mineral Research (ASBMR) Task Force has recently classified AFFs as stress injuries [2]. It is possible that the higher doses of pamidronate used in treatment of this patient, particularly early in the treatment course, placed her at higher risk for bone turnover suppression. Alkaline phosphatase levels remained in the lower portion of the normal range during the treatment period; however a post-treatment at the time of her fracture presentation was frankly low, further supporting a potential pamidronate-related decrease in bone turnover. This patient's protracted clinical course with delayed healing is also typical of AFFs, potentially related to inhibition of bone modeling processes involved in fracture repair [2].

The unusual location of this patient's femoral fracture raises particular concern about a possible contributory effect of bisphosphonate treatment. This is supported by recent evidence in patients with OI. Nicolau et al reported a retrospective review of femoral fracture location in 176 bisphosphonate-treated OI patients compared to historical controls. In this series, 14/16 femoral fractures in the bisphosphonate-treated cohort occurred within the subtrochanteric location, in contrast to a widespread fracture pattern in the historical controls [5]. Hegazy et al reported a series of 6 bisphosphonate-treated children with OI who sustained minimally traumatic subtrochanteric and diaphyseal femoral fractures over preexisting intramedullary rods [4], and Vasanwala et al similarly reported an adolescent OI patient with recurrent, atraumatic femoral fractures following bisphosphonate treatment [6]. The contribution of the underlying collagen defect in the development of femoral fractures in these series is unknown, and to our knowledge there have been no reports of subtrochanteric femoral fractures in non-OI children treated with bisphosphonates.

Several features of this patient's fracture call into question the contribution of bisphosphonate treatment. Although causality between bisphosphonate use and AFFs in adults has not been definitively established, the number of high-quality epidemiologic studies demonstrating an association continues to mount. In particular several studies have demonstrated a positive correlation between treatment duration and AFF risk, as well as a decline in risk with bisphosphonate discontinuation [12–14]. This patient's fracture occurred 2 years after pamidronate discontinuation, at which time her risk of bisphosphonate-associated AFF should theoretically have been declining. Unlike bisphosphonate-associated AFFs in adults, which typically develop on the lateral tensile cortical surface [2], this patient's stress fracture occurred at the medial cortex. The lack of a transverse fracture line is also inconsistent with ASBMR 2013 Task Force Case Definition of AFFs, although this may have been related to early diagnosis and aggressive intervention preventing her fracture from progressing. Thus, while suggestive, the contribution of bisphosphonate treatment to the development of this patient's stress fracture is not known. Nevertheless, clinicians should

evaluate thigh pain in adolescents with a history of bisphosphonate treatment, particularly in those with low bone turnover and risk factors for stress injuries, and should include AFFs and other femoral stress fractures in the differential.

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Established Facts

- Atypical subtrochanteric and diaphyseal femoral fractures (AFFs) have been reported in association with bisphosphonate treatment in adults, and in children with osteogenesis imperfecta.
- Evidence suggests that AFFs are related to inhibition of bone remodeling, leading the American Society for Bone and Mineral Research Task Force to classify them as stress injuries.

Novel Insights

- Clinicians should evaluate thigh pain in adolescents with a history of bisphosphonate treatment, particularly in patients with risk factors for stress injuries, and should include AFFs and other femoral stress fractures in the differential.

Figure 1.

Pre- and post-treatment clinical images. A. The patient's growth curve showing growth deceleration between the ages of 10 and 12 years, consistent with vertebral height loss secondary to thoracic compression fractures. Height percentile improved after two years of pamidronate therapy. B. Lateral spine radiograph at age 10 years showing diffuse osteopenia and a T6 vertebral compression fracture (black arrow). C. Dual-energy X-ray absorptiometry of the lumbar spine showing a progressive increase in bone mineral density Z-score during pamidronate treatment between the ages of 12 and 14.

Figure 2.

A. Pelvic radiograph at age 16 years showing a periosteal reaction at the medial cortex of the left proximal femur (white arrow) and diffusely thickened diaphyseal cortices (black stars). Parallel sclerotic bands are visible along the curve of the iliac crest, marking the pamidronate infusions (white arrowheads). B. Technetium-99 bone scintigraphy showing focal tracer uptake in the medial aspect of the left proximal femur (white arrow), and mild uptake along the right tibial and tarsal area (white arrowheads).