Bisphosphonate Associated Atypical Femur Fracture and Contralateral Impending Atypical Femur Fracture in a Pediatric Patient with Osteogenesis Imperfecta: A Case Report

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ABSTRACT

Atypical femur fractures are rare, low-energy fractures that involve a specific constellation of radiographic findings. These fractures have been well described in adult osteoporotic patients on long-term bisphosphonates; however, little to no literature exists on atypical femur fractures in pediatric patients on long-term bisphosphonates. The use of bisphosphonates as treatment of osteogenesis imperfecta is common to reduce fracture rate and improve bone mineral density. We describe a 15-year-old adolescent boy with type I osteogenesis imperfecta on long-term bisphosphonate therapy. He presented with an atypical right femur fracture and an impending left femur fracture. To the authors' knowledge, these findings represent the first case of an atypical femur fracture with a contralateral impending atypical femur fracture in a pediatric patient on long-term bisphosphonate treatment. This case highlights the importance of evaluating pediatric patients for bisphosphonate-associated complications, as is typical in adult patients. Physicians should carefully weigh the risks and benefits of bisphosphonate therapy in pediatric patients to better understand the potential adverse effects.

Keywords: Osteogenesis Imperfecta, Bisphosphonates, Subtrochanteric Fractures, Pediatrics

INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disorder affecting type I collagen production, resulting in bone fragility. OI has been associated with several genes, most commonly COL1A1 and COL1A2. There are four common types of OI. Type I includes minimal long-bone deformities or issues with mobility, type II is lethal, type III is the most severe and survivable form of the disease with skeletal deformities and limited ambulation, and type IV is of moderate severity.[1]

Bone fragility caused by OI typically results in fractures throughout the patient's life. The most common medical treatment for children with recurrent fractures is bisphosphonate therapy, which is typically continued throughout skeletal maturity. Bisphosphonate therapy has been used to treat children with OI for 30 years, with increasing acceptance.[2] The goal of bisphosphonate therapy is to improve bone mineral density and bone pain, decrease the incidence of fractures and skeletal deformity, and increase functional independence in patients.

Long-term bisphosphonate therapy in adults has been linked to atypical femur fractures, and risks of these fractures appear to increase drastically with prolonged usage.[2] It is currently recommended that osteoporotic adults limit bisphosphonate use to 5 years to avoid the increased risk of atypical femur fractures.[2] Atypical femur fractures are defined by meeting at least four out of the five criteria: minimal trauma, transverse fracture line through the lateral cortex, complete fracture often associated with medial spike, non-comminuted or minimally comminuted fracture, and periosteal or endosteal thickening of the lateral cortex.[3]

There are a small number of case reports of suspected bisphosphonate-associated atypical femur fractures in children with OI.[2-5] We describe an adolescent boy with OI on long-term bisphosphonate therapy. He sustained an atypical subtrochanteric femur fracture with a contralateral impending atypical femur fracture. To our knowledge, this is the first case report describing atypical femur fractures in a patient with type I OI.

CASE REPORT

A 15-year-old adolescent boy with a history of type I OI presented to our institution after tripping over a step while hiking. He fell on the right side of his body,

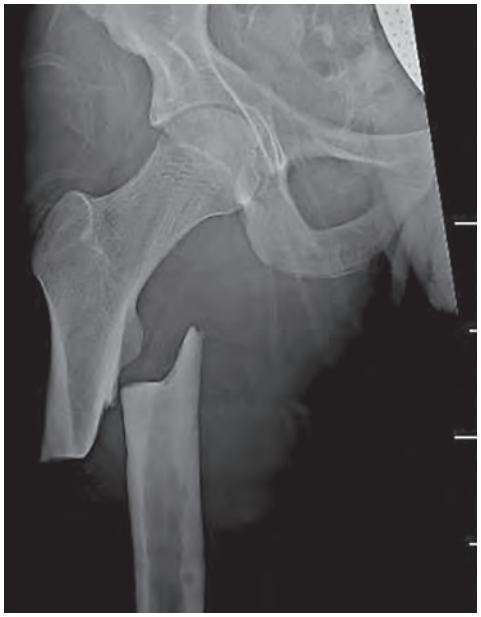

Figure 1. *A transverse atypical subtrochanteric fracture of the right femur with lateral cortical thickening, small medial spike, lack of comminution, and intramedullary canal narrowing, which is consistent with a cortical stress response to increased stress from long-term bisphosphonate use. Sequelae of prior right femoral shaft open reduction internal fixation with residual screw holes are visible distal to the fracture.*

sustaining a right subtrochanteric femur fracture and a right proximal humerus fracture. The patient had a history of multiple fractures, including right and left femur fractures in 2014 and 2007, respectively. The prior right femur fracture was treated with open reduction and plating, with subsequent removal of hardware. The left femur fracture was treated with a closed reduction and hip spica casting. Before his most recent fall, he denied any prior pain in his right and left hip and legs. He had been on bisphosphonate therapy for 12 years, and at the time of injury, was being treated with IV Palmidronate infusions every 4 months.

Upon presentation to our institution, radiographs of the right femur were obtained. The patient was found to have an atypical transverse femur fracture of the right subchondral femur with lateral cortical thickening (Figure 1). The patient's right proximal humerus fracture was assessed radiographically and treated nonoperatively with a cuff and collar sling. Radiographs of the left femur were obtained, owing to the atypical appearance of the right subtrochanteric femur fracture and the history of long-term bisphosphonate use. Radiographs showed considerable lateral cortical beaking with transverse lucency through the lateral cortex in the subtrochanteric region (Figures 2A and 2B). Considerable deformity to the left femur was evident, which was secondary to prior fracture.

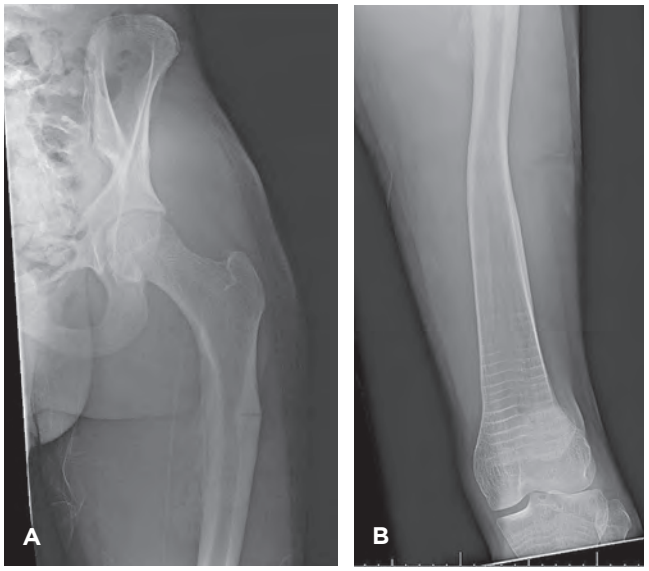

Figure 2. *A) Left femur with transverse subtrochanteric lucency within the lateral cortex and surrounding lateral cortical thickening, and a medial cortical stress reaction. B) Zebra lines visible within the distal femur and sequelae of prior left femoral shaft fracture with resultant deformity preventing passage of intramedullary nail.*

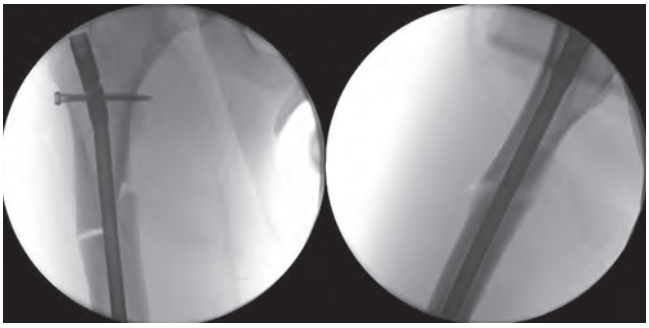

Figure 3. *Intraoperative radiographs of right femur following closed reduction and intramedullary nailing.*

The patient was placed into Buck's traction for comfort. He was brought to the operating room for trochanteric entry intramedullary nail fixation of the right subtrochanteric femur fracture using an 8.5-mm trochanteric entry intramedullary nail for adolescents (Smith and Nephew; Watford, UK) (Figure 3).

Postoperatively, the patient was made weight bearing as tolerated. A discussion about prophylactic fixation of the left femur was had with the patient and his father. It was emphasized that due to the deformity of the left femur from the prior fracture, the left leg would require an osteotomy to facilitate the intramedullary nail passage. Given that the patient was from out of town, he and his father elected to return home for definitive treatment of the impending left femur fracture. The patient was able to ambulate postoperatively and demonstrated good pain control. He was discharged 2 days postoperatively to return home for further recovery and rehabilitation. We were in contact with his home orthopaedic surgeon before and after the

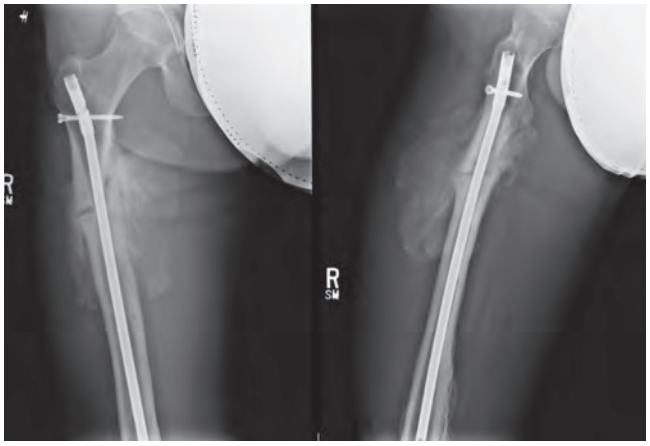

Figure 4. *Final follow-up radiographs of right femur fracture at 6 months postoperatively showing bridging callus formation and heterotopic ossification.*

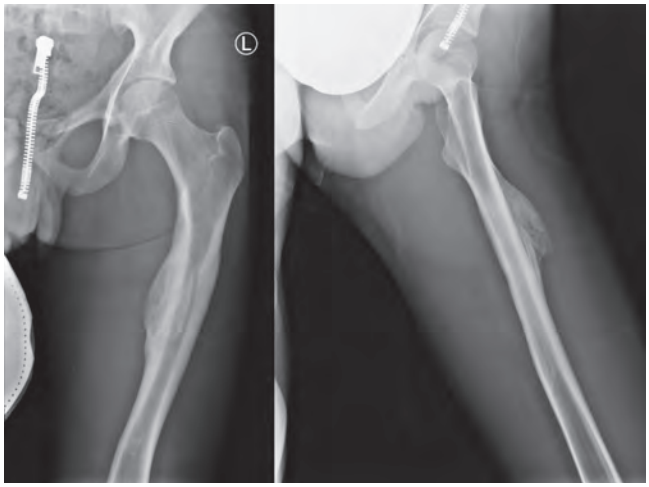

Figure 5. *Final follow-up radiographs of left femur impending fracture treated nonoperatively showing remodeling of cortex and callus formation at prior subtrochanteric lucency site.*

surgery to ensure the appropriate transition of care was coordinated. The patient's right femur fracture went on to form bridging callus and healing without pain with asymptomatic heterotopic ossification (Figure 4). His left impending femur fracture was treated nonoperatively with continued weight bearing and observation by his home orthopaedic surgeon, and it went on to heal without complication (Figure 5).

DISCUSSION

In the past few years, multiple case reports have been published on atypical femur fractures in children with OI treated with long-term bisphosphonate therapy (Table 1). There has been increasing recognition of atypical femur fractures in osteoporotic adults receiving long-term bisphosphonate therapy. It is important to consider this same possibility occurring in children with OI.

Bisphosphonates work by inhibiting osteoclast activity and inducing apoptosis. There are two classes of bisphosphonates. The first is nitrogenous, which inhibits farnesyl diphosphonate synthase, causing cytoskeleton disruption, loss of ruffled border, and eventual apoptosis. The second is non-nitrogenous, which induces osteoclast apoptosis.[6] Atypical femur fractures associated with bisphosphonate use is thought to occur because of 1) its relationship to impaired bone turnover secondary to osteoclast inhibition, and 2) resultant poor remodeling potential of the bone in high-stress areas like the lateral cortex of the proximal femur, with resultant microfractures weakening the bone leading to eventual fatigue with complete fracture.[5,7]

A retrospective study compared femoral shaft fractures within patients with OI and no bisphosphonates to patients with OI treated with bisphosphonates.[8] It showed a trend of increasing fractures in the subtrochanteric region among patients treated with bisphosphonates. This study suggests that the change in femur fracture pattern sustained by these patients may be related to bisphosphonate usage.[8]

Another study retrospectively examined children with OI who sustained femur fractures. The authors evaluated x-rays for signs of atypical femur fracture and stratified patients by those who did and did not receive bisphosphonate therapy. They found that 22.0% of those who did not receive bisphosphonate therapy had radiographic evidence of atypical femur fractures, and 27.0% of those who did receive bisphosphonate therapy had radiographic evidence of atypical femur fractures. They concluded that no difference existed between the bisphosphonates group and the non-bisphosphonates group in terms of atypical femur fracture risk. They found the increasing severity of disease type to correlate with the increased risk of atypical femur fractures.[1]

Patients with OI do not have the same bone quality as osteoporotic adults, and atypical femur fracture diagnosis was not designed for this patient population.[9] Prior studies have shown that children with OI can sustain low-energy fractures that mimic atypical femur fractures without bisphosphonate therapy.[9] However, the changing pattern of femur fractures seen in children treated with bisphosphonates and the increasing prevalence of case reports detailing atypical femur fractures in children on bisphosphonate therapy are cause for concern. Recent literature suggests that bisphosphonate therapy improves bone mineral density and may lower fracture rates in children with OI.[4] Bisphosphonate therapy does not appear to change functional outcomes and bone growth or affect bone pain as previously thought.[4] Risks and benefits of bisphosphonate therapy in pediatric patients should be weighed carefully to understand the potential adverse effects better.

This case report details an atypical femur fracture and contralateral impending atypical femur fracture as a sequela of long-term bisphosphonate therapy in a pediatric patient with OI. To our knowledge, this is the

first described account of a simultaneous contralateral impending atypical femur fracture in this population. Further research is needed to determine the efficacy and safety of bisphosphonate therapy in children with OI. There is a large variation in the dose, the interval between infusions, and the duration of intravenous bisphosphonates between institutions. Consistent treatment protocols and cumulative dose and length of appropriate treatment guidelines need to be established in this population. Practitioners must maintain vigilance when detecting these impending fractures in patients on bisphosphonate therapy and order appropriate imaging for patients with prodromal pain.

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