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Case Report

Atypical femur fracture in a woman with osteogenesis imperfecta and multiple myeloma

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Abstract

Use of intravenous bisphosphonates has been demonstrated to improve clinical outcomes in children with osteogenesis imperfecta (OI). However, efficacy and safety of bisphosphonates in adults with OI remains unclear. Atypical femur fractures (AFF) are rare insufficiency fractures associated with long-term bisphosphonate use. We report on a 56 year old woman with OI type 1 and long-term bisphosphonate use who was diagnosed with multiple myeloma (MM) following a severe vertebral fracture. During workup, an asymptomatic incomplete AFF of the left femur diaphysis was noted. Multiple factors may have contributed to the occurrence of AFF, including bisphosphonate exposure, bowing of the proximal femur, as well as the intrinsic collagen defect of OI. To reduce the risk of skeletal complications from MM, intravenous pamidronate was administered in addition to chemotherapy, though in reduced dose and frequency. Orthopedic consultant recommended against prophylactic surgery for the AFF. Follow-up radiograph showed no progression of the AFF, though delayed healing was present. This case highlights the importance of close monitoring of patients on long-term bisphosphonate therapy who have additional risk factors for developing AFF, such as underlying genetic bone disorders or lower limb deformities. A multidisciplinary approach is recommended for optimal management of such complex patients.

Keywords: Osteogenesis Imperfecta, Multiple Myeloma, Atypical Femur Fracture, Bisphosphonate, Femur Geometry

Introduction

Osteogenesis imperfecta (OI) is a rare genetic disorder characterized by increased bone fragility and recurrent fractures throughout life. Intravenous bisphosphonates are the mainstay of medical therapy in children and adolescents with moderate to severe OI[1,2]. The treatment is generally well tolerated, and has been shown to increase spinal bone mineral density (BMD), improve mobility, reduce pain, and reduce fracture risk. However, in adults with OI, the benefit of bisphosphonates remains uncertain, and data on the safety of bisphosphonate use are lacking in this population.

Atypical femur fractures (AFF) are insufficiency fractures located along the femoral diaphysis. The American Society of Bone and Mineral Research (ASBMR) defines AFF as minimal or low-traumatic fractures originating from the lateral cortex of the femur[3]. They are non-comminuted or minimally comminuted, and transverse in configuration. Complete fractures extend through both cortices and may be associated with a medial spike, while incomplete fractures involve only the lateral cortex. In addition, localized periosteal or endosteal thickening of the lateral cortex is often present. Patients may report prodromal pain in the groin or thigh and delayed fracture healing has been noted. Typically, AFF have been observed in patients receiving extended bisphosphonate therapy for osteoporosis or malignant bone disease[4], although they have also been reported in people without bisphosphonate exposure[5].

Previous cases of AFF occurring in patients with genetic bone disorders, including OI and hypophosphatasia have been reported, and some have been successfully managed through discontinuation of bisphosphonate and use of teriparatide[6-9].

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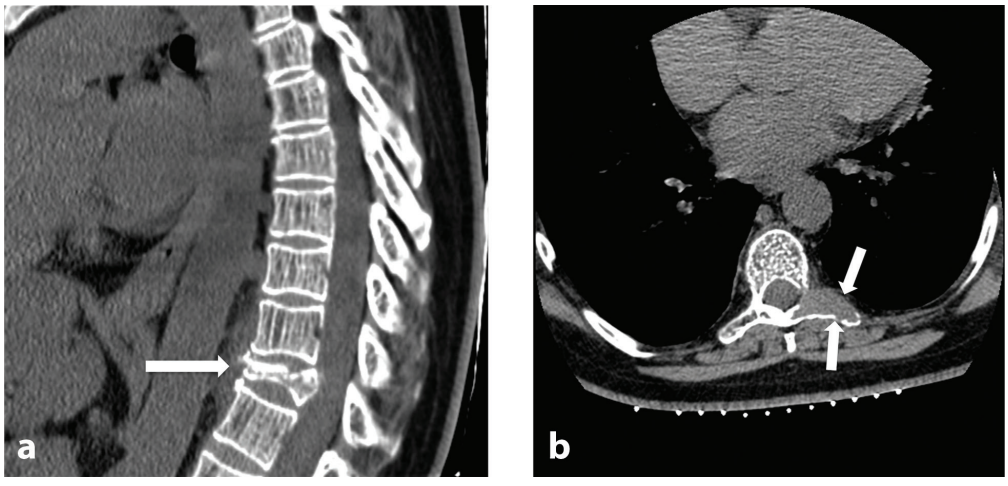

Figure 1. Computed tomography scan of thoracic spine showing (a) compression fracture of 11th thoracic vertebra, and (b) soft tissue lesion involving the left transverse process of the 7th thoracic vertebra.

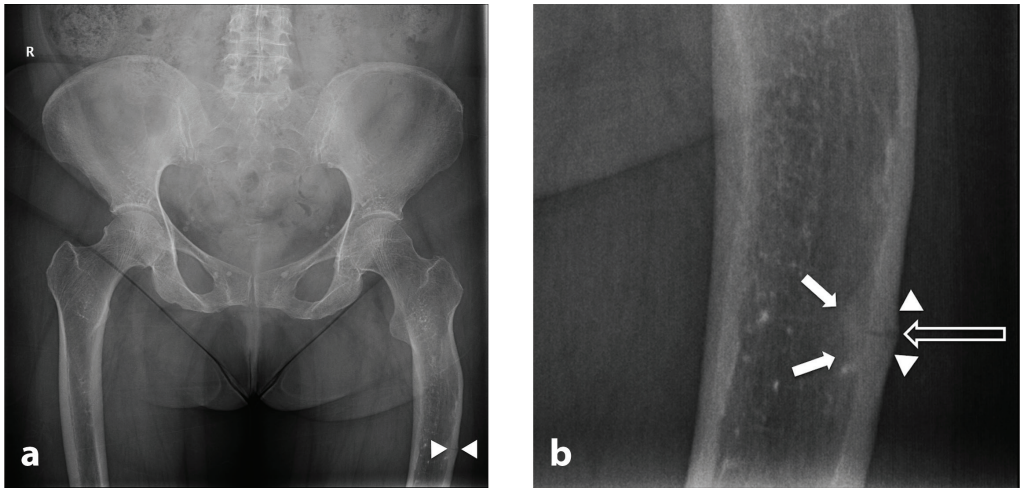

Figure 2. (a) X-ray of the pelvis and hip showing left incomplete diaphyseal atypical femur fracture and bowing of bilateral proximal femurs; (b) magnified image showing transverse fracture line (open arrow) originating from lateral cortex with localized endosteal thickening (solid arrows) and periosteal reaction (arrowheads).

We describe a post-menopausal woman with OI type 1 on long term bisphosphonate therapy for recurrent fractures, whose management for newly diagnosed multiple myeloma (MM) was complicated by the concomitant discovery of an incomplete diaphyseal AFF.

Case report

A 54 year old woman with OI type 1 presented in October 2014 with acute back pain without any history of trauma or fall. Computed tomography (CT) scan of the thoracic spine demonstrated a burst compression fracture of the 11th thoracic vertebra (T11), as well as a 2.6x1.3x1.5 cm soft tissue density involving the left transverse process of the 7th thoracic vertebra (T7) (Figure 1). A CT-guided biopsy of the T7 lesion revealed a heavy infiltration by kappa restricted CD138 expressing plasma cells. Further investigations confirmed the diagnosis of kappa light chain myeloma with lytic lesions involving the right parietal bone and right iliac bone, normal renal function and 30% light chain restricted plasma cells in the bone marrow. A radiographic skeletal survey demonstrated a radiolucent line at the left femur

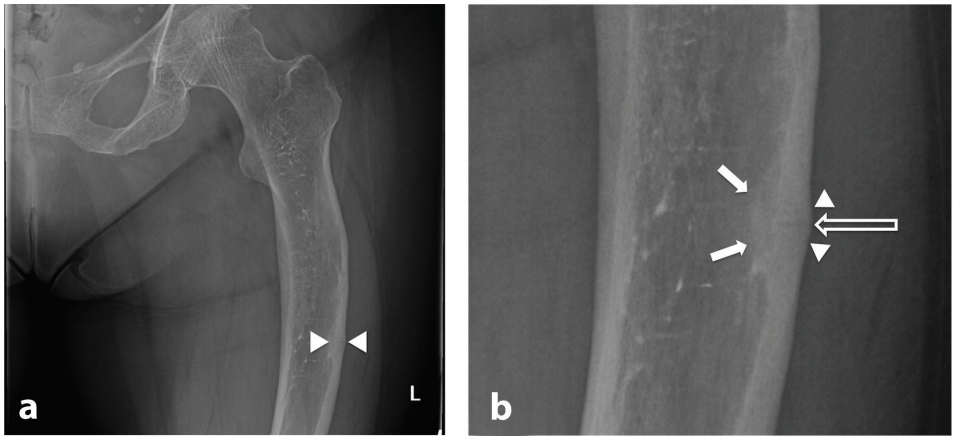

Figure 3. (a) X-ray of left femur at follow-up (2017) showing no progression of the left incomplete atypical femur fracture; (b) magnified image showing left incomplete atypical femur fracture (open arrow) with persistent periosteal reaction (solid arrows), suggesting delayed healing.

Table 1. Laboratory results before initiation of pamidronate and 20 months after last dose of pamidronate.

	Before Initiation	20-Month Post	Reference value
C-telopeptide	0.119 ug/L	0.066 ng/mL	0-1.010 ug/L
Osteocalcin	13 ug/L	8 ng/mL	15-46 ug/L
Alkaline phosphatase	66 U/L	75 U/L	42-98 U/L
25-hydroxy vitamin D	105 nmol/L	Not available	75-250 nmol/L

diaphysis with localized periosteal reaction compatible with an incomplete insufficiency fracture, consistent with the diagnosis of AFF (Figure 2). There was no involvement of the contralateral femur, but both femurs were noted to be significantly bowed. The cortices were not thought to be thickened. Correlation with radionuclide bone scan demonstrated focal increased radiotracer uptake at the left femur fracture site. The patient denied thigh or groin pain. Orthopedic consultation was sought and the consultant recommended against prophylactic femoral nailing in view of the absence of symptoms and of the concurrent diagnosis of MM that might negatively affect the post-operative course.

The patient had been diagnosed with OI type 1 in early childhood and never received bisphosphonates until the age of 40 years, when alendronate was initiated for ongoing bone loss at the time of menopause and a patellar fracture. Calcium and Vitamin D supplementation was begun, and low dose transdermal estrogen (estradiol 0.025 mg/day twice a week) was prescribed to alleviate menopausal symptoms. Alendronate was stopped after 10 years of continuous therapy since her bone density had stabilized and the patient had remained fracture free. Four years later, in March 2014, the patient sustained a right scapular fracture following a fall. Risedronate was initiated but was discontinued in October 2014, upon diagnosis of MM and the discovery of the left diaphyseal AFF.

The patient subsequently underwent chemotherapy with cyclophosphamide-bortezomib-dexamethasone (CyBorD), resulting in clinical, biochemical and hematological remission. Intravenous pamidronate was administered simultaneously to reduce myeloma-related skeletal complications. In view of the presence of AFF, dosage and frequency of pamidronate was reduced from 90 mg per month to 60 mg every 2 months, and planned for a shorter duration of 1 year instead of 2 years. Dexamethasone was also reduced from 40mg to 10mg per week given her overall increased fracture risk. Pamidronate was stopped after 8 months of treatment at the patient's request. Bortezomib administered every two weeks was continued as maintenance therapy for an additional 24 months. In addition, the patient received radiation therapy to the T7 lesion for pain control.

At follow-up in July 2017, the patient remains on maintenance bortezomib, and free of fractures and detectable myeloma. On questioning, she does report occasional low-grade pain in the left groin upon walking or standing. Radiograph of the left femur (Figure 3) shows no progression

of the small fracture line and persistence of the endosteal-periosteal reaction. Laboratory results reveal suppressed bone turnover markers 20 months following discontinuation of pamidronate (Table 1).

Discussion

Atypical femur fractures in patients with OI receiving bisphosphonate have been reported. Meier et al and Manopoulos et al described two post-menopausal women with OI who sustained AFF after prolonged bisphosphonate therapy initiated in adulthood. Both patients had prodromal thigh pain. One patient was treated with surgical stabilization for the complete fracture, which was well-healed at 1-year follow-up[6]. The other patient had bilateral incomplete fractures and both femora appeared bowed on plain radiographs. This patient was treated with cessation of bisphosphonate and initiation of teriparatide, although results of follow-up were not reported[7].

To our knowledge, this report is the first to describe an AFF in a post-menopausal woman with OI after prolonged bisphosphonate therapy, complicated by a new diagnosis of MM. Unlike previous reports, our patient did not report prodromal groin or thigh pain, making the diagnosis of AFF challenging. Due to the diagnosis of MM with lytic bone disease, the potential benefits of intravenous bisphosphonate therapy had to be weighed against the risks of worsening her pre-existing AFF, or causing one on the contralateral femur. Although the incomplete AFF remained stable 2 years later, radiographs continue to show evidence of delayed fracture healing, and bone turnover markers remain suppressed, suggesting the persistent effect of pamidronate.

Etiology of AFF

The pathogenesis of AFF is still poorly understood, however multiple factors may have contributed to the formation of AFF in this patient.

Prolonged bisphosphonate use, over a ten-year period, is important to consider. Bisphosphonates are pyrophosphate analogues with an affinity for hydroxyapatite in bone[10]. These compounds attach to the bone mineral surface, and are then internalized by osteoclasts during bone resorption. Intracellularly, bisphosphonates act on key enzymes within the mevalonate pathway, altering signaling proteins crucial to normal osteoclast function and survival. This results in inhibition of osteoclast function, reduced osteoclast bone resorption, as well as increased osteoclast apoptosis. Bisphosphonates improve bone mineral density and reduce fracture rates in patients with postmenopausal osteoporosis, as demonstrated in large clinical trials[11]. However, prolonged exposure can also lead to suppression of bone remodeling, reduced bone heterogeneity and alteration in the bone material properties[12]. Lloyd et al compared the compositional and mechanical properties of bone biopsies from bisphosphonate-treated patients with AFFs to those from patients with typical osteoporotic fractures. They noted that long-term bisphosphonate use reduced the intrinsic toughness of bone, and also reduced crack splitting and deflection[13]. These results suggest that, over time, bisphosphonates can impair toughening mechanisms in cortical bone and allow the initiation and propagation of insufficiency fractures.

In addition, the intrinsic collagen defect of OI may contribute to formation of insufficiency fractures. Results from animal studies suggest that bone in OI models may have reduced ability to withstand accumulation of naturally occurring microdamage[14,15]. Normally, bone remodeling allows the bone to respond to mechanical loading and repair microdamage. Bone properties of patients with OI, due to the underlying collagen defect, differ from those of post-menopausal women, and it is also unknown if their response to long-term bisphosphonates would be similar. This requires further investigation.

Finally, the role of femur geometry parameters cannot be overlooked. Case control studies have demonstrated femoral curvature to be associated with a higher risk of developing AFF in patients with or without receiving bisphosphonate therapy for osteoporosis[16,17]. In a study by Koh et al, the authors measured fracture distance from the greater trochanter in patients with AFF, and demonstrated that AFF clustered in regions of maximal tensile loading, on the lateral cortex of the femur[18]. By evaluating radiographs of 14 patients with AFF, Saita et al found that the femorotibial angle (FTA) of patients with diaphyseal AFF was significantly larger compared to the FTA of patients with typical proximal femur fractures[19]. Morin et al examined 3-Dimension femur geometric parameters of 16 women with bisphosphonate-associated AFF and matched controls, and demonstrated that lateral femur bowing was significantly associated with an increased risk of AFF[20].

Bone-active agents used in multiple myeloma

In patients with myeloma-associated bone disease, bisphosphonate therapy decreases myeloma-related skeletal events such as pathologic fractures and spinal cord compression, improves performance status[21,22], and possibly provides a survival benefit in a subset of patients[23]. Current guidelines recommend that all patients with MM and bone disease, including lytic lesions on imaging, osteoporosis or osteopenia, be treated with bisphosphonates[24], typically intravenous pamidronate or zoledronic acid for a period of at least 2 years. Observational data suggest that development of AFF in people with underlying malignancy, notably breast cancer and MM, may be associated with the cumulative dose and/or duration of exposure[25]. Thus, for our patient, decision was made to proceed with pamidronate with reduction in dose, frequency, and duration.

Another bone-specific agent, denosumab, has recently been shown to reduce the risk of skeletal-related events in MM following the results of a large international phase 3

trial[26]. Denosumab, a monoclonal antibody against receptor activator of nuclear factor kappa B ligand (RANKL), is currently used for the treatment of osteoporosis and bone metastases from solid tumors. However, its use has also been associated with AFF[27,28]. Myeloma bone disease is thought to be mediated by factors that promote osteoclast activity, including RANKL. Malignant myeloma cells interact with the bone microenvironment to increase production of RANKL and decrease osteoprotegerin (OPG) production, which upregulates osteoclast bone resorption, leading to bone destruction[29]. Despite the preliminary positive findings for denosumab in MM, RANKL inhibition should still be considered with caution in patients at increased risk of developing AFF.

Management of AFF in adults with OI

The optimal management of AFF is currently still unclear, especially so in people with genetic bone disorders such as OI. The ASBMR Task Force recommends discontinuation of potent antiresorptive agents, optimization of calcium and vitamin D intake status, and consideration of prophylactic nail fixation for incomplete fractures accompanied by pain[3]. Individuals with incomplete AFFs, especially in the setting of femoral bowing, are at risk of progressing to complete fractures, and may benefit from prophylactic surgical fixation to reduce pain, progression to fracture completion, as well as total hospital admission time[30,31]. More recently, Kang et al reported a case of successful treatment of an incomplete diaphyseal AFF using a new femoral nailing technique[32] in an adult female with Paget's disease and anterolateral femoral bowing[33]. The clinical status of our patient at follow-up in July 2017 has changed since her initial diagnosis of MM and AFF, as she is now free of detectable myeloma. In view of the persistence of the incomplete AFF, as well as new symptoms of intermittent pain in the left groin, prophylactic nailing of the AFF should be reconsidered.

Teriparatide, a parathyroid hormone analogue, has also been proposed as a potential therapy for AFF[34]. A recent report by Tan and Seow[8] described successful treatment of an incomplete AFF with teriparatide followed by 6-monthly denosumab in an adult male with OI type IV after prolonged bisphosphonate therapy. After one year of teriparatide, the patient showed substantial improvement in lumbar spine and hip BMD, as well as healing of the incomplete fracture. Despite this anecdotal evidence, reports have emerged of multiple myeloma occurring in patients receiving teriparatide, although a causal relationship has not been established[35]. In addition, teriparatide may increase the risk for developing osteosarcoma, based on data from animal studies[36]. According to the United States Food and Drug Administration (FDA), teriparatide is relatively contraindicated in patients at baseline increased risk for osteosarcoma, including those who have undergone skeletal radiation[37]. Consequently, in adults with OI who also have multiple myeloma or have undergone prior radiation to bone, it would be prudent to avoid using teriparatide to treat AFFs until more evidence for safety is available.

Role of bortezomib

Our patient received bortezomib as part of her chemotherapy regimen, then as maintenance therapy. Bortezomib, a proteasome inhibitor, has been postulated to have effects on bone metabolism outside of its effect on tumor cells. Proteasome inhibition has been shown to increase osteoblast function, as well as to decrease RANKL-dependent bone resorption[38]. Small studies have demonstrated increased lumbar BMD, increased bone healing, and reduced bisphosphonate use in MM patients treated with bortezomib[39,40]. More recently, Sezer et al reported on a phase 2 trial evaluating bortezomib in patients with MM-related bone disease who had achieved partial response or better after autologous stem cell transplant[41]. The authors found no significant difference in BMD with bortezomib consolidation versus observation, but the evaluation period was only for 4 months, likely too short to show a significant change in BMD. Whether bortezomib had any meaningful effect on the evolution of myeloma bone disease or AFF in our patient is unknown at this time.

Conclusion

In summary, we described the case of an adult woman with OI type 1 and a 10-year history of bisphosphonate exposure, in whom the management of newly diagnosed MM was complicated by discovery of an incomplete AFF. Our case demonstrates the treatment dilemmas that may arise in adults with OI who develop other bone diseases or bone complications of treatment. With the increasing use and duration of use of bisphosphonates in children and adults with OI, this case also highlights the importance for a better understanding of how long-term bisphosphonate therapy affects bone material properties and function in OI throughout the lifespan. Furthermore, we hope to increase awareness about patients at increased risk for developing AFF, such as those with an underlying genetic bone disorder or lower limb deformities, who require bisphosphonate therapy for other reasons. A high index of suspicion for AFF, and close monitoring of patients for early symptoms of AFF are recommended.

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