Bone Reports 15 (2021) 101112

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Case Report

Bilateral atypical fractures of the femur: Ten years AFTER ten years of bisphosphonate therapy

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ARTICLE INFO

Keywords:
Osteoporosis
Atypical femur fracture
Bisphosphonates
Drug holiday

ABSTRACT

Background: Atypical femur fracture (AFF) is a clinically important complication of bisphosphonate (BP) use in the treatment of osteoporosis. The benefits of long-term BP therapy in preventing osteoporotic fractures have been shown to outweigh the risks of treatment. Discontinuation of BPs or "drug holidays" have been implemented as a strategy to reduce the risk of rare complications such as AFF.

Case report: We present the case of a 70-year-old postmenopausal woman who suffered bilateral AFF ten years after discontinuation of BP treatment. Management of this patient included fixation of the complete AFF with an intramedullary rod. A single dose of denosumab was administered prior to referral to endocrinology and seemed to contribute to callus formation. Denosumab was discontinued to prevent progression of the contralateral incomplete AFF. Teriparatide was indicated for the treatment of this patient's osteoporosis and also led to the resolution of the incomplete AFF.

Conclusion: Patients receiving long-term BP therapy should be periodically reevaluated in order to maximize the benefit and minimize the risk of treatment. Current research supports the implementation of drug holidays to decrease the risk of AFF; however, this case report confirms the need for continued monitoring after discontinuation of BP therapy. Additionally, our review of current literature highlights the need for more specific research regarding duration of BP treatment and drug holidays.

1. Introduction

Atypical femur fracture (AFF) is an uncommon complication in patients on long-term bisphosphonate (BP) therapy. It was first described in 2005 and has since been widely discussed in the literature because it is associated with high morbidity in patients receiving treatment for osteoporosis. AFF is not only reported in patients on BP but has also been associated with other antiresorptive drugs such as denosumab. Yet, antiresorptives are the mainstay of treatment for osteoporosis because of their efficacy in increasing bone density and reducing osteoporotic fractures. Practitioners must be aware of the risks associated with antiresorptives and must weigh the risks and benefits of long-term therapy. While no specific guidelines currently exist, a drug holiday is a possible strategy for balancing the benefits and risks of long-term BP treatment. A recent cohort study found a decreased incidence of AFF after a minimum twelve-month drug holiday in women with at least three years of prior BP therapy (Adams et al., 2018). Additionally, a task force of the American Society for Bone and Mineral Research (ASBMR) found the absolute risk of AFF to be higher in patients on prolonged BP therapy but decreased with discontinuation (Shane et al., 2014). While preventative measures for osteoporotic fractures are a top priority, it is important for clinicians to prevent and effectively manage patients who suffer from this rare complication. In this case report, we present the management of a patient with bilateral AFF after a ten-year holiday from long-term BP therapy.

2. Case presentation

A 70-year-old postmenopausal woman with a history of osteoporosis suffered a complete AFF of the right femur after falling from a standing height. Imaging studies revealed a complete right midshaft femoral fracture with a localized periosteal reaction involving the lateral cortex of the left femoral shaft (beaking) without radiolucency consistent with the diagnosis of AFF by ASBMR criteria. She underwent open reduction

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https://doi.org/10.1016/j.bonr.2021.101112
Received 4 June 2021; Received in revised form 23 July 2021; Accepted 28 July 2021
Available online 31 July 2021

and internal fixation with an intramedullary rod of the right femur followed by a 60 mg dose of denosumab prior to referral to endocrinology. The patient was first seen in the osteoporosis clinic five months after the denosumab dose. Prior history included osteoporosis that was diagnosed at age 50 by bone mineral density (BMD) for which she was treated with alendronate for ten years. Alendronate was discontinued around the age of 60, ten years prior to the current AFF. Additional past medical history was significant for chronic obstructive pulmonary disease, coronary artery disease, and hypertension. Medications included metoprolol, benazepril, aspirin, atorvastatin and 600 mg of elemental calcium two times daily. Risk factors for osteoporosis included a remote history of heavy smoking, poor dietary calcium intake, and a positive family history of osteoporosis. Pertinent physical exam findings included poor balance and significant thoracic kyphosis. Laboratory studies were within normal limits, including normal serum levels of calcium, phosphate, creatinine, alkaline phosphatase, TSH, vitamin D-25 (36 ng/dl), PTH (20 pg/dl), sedimentation rate, and serum protein electrophoresis. BMD revealed a significant change from a previous scan four years prior with 8.7% loss at L3-L4 vertebrae, 6.2% loss at the femoral neck, and 6.9% loss in total hip. Initial management of this patient included limited weight bearing plus adequate calcium and vitamin D supplementation. Denosumab was discontinued because of its antiresorptive properties and association with AFF. However, callus formation around the site of the right AFF was seen on X-ray 6 after the injection with no change in the left femoral shaft beaking (Fig. 1a). Teriparatide was initiated at 20 μg subcutaneously daily for osteoporosis therapy with the additional benefit of treating AFF based on previous reports. Resolution of the left femoral shaft beaking was noted after three months on teriparatide (Fig. 1b). The treatment plan was to continue teriparatide for 24 months; however, this patient was lost to follow-up due to other medical complications.

3. Discussion

Atypical femoral fractures have been associated with long term bisphosphonate therapy, but a cause-and-effect relationship has not been established according to the task force report by the American Society for Bone and Mineral Research (Shane et al., 2014). The incidence of AFF in patients exposed to bisphosphonate therapy varies, with epidemiological studies citing 3.2-55 fractures per 100,000 cases (Meier et al., 2012; Schilcher et al., 2011). Although the relative risk described in these studies is increased in patients on BP therapy, the absolute risk of AFFs is considered to be low, especially when compared to the protective effects of BP use in preventing osteoporotic related fractures. Specifically, one study reported that approximately 100 hip fractures were prevented for every AFF in elderly patients on BP therapy (Wang and Bhattacharyya, 2011).

The risk of AFFs associated with long-term BP treatment is not the same in all patients due to a number of factors. Importantly, longer duration of BP exposure is correlated with an increased risk for AFF. Dell et al. (2012) showed that the incidence of AFF significantly increases for every 2 years of BP therapy, with the highest incidence of 113.1 fractures per 100,000 patients was noted after 8-10 years of treatment. Similarly, Meier et al. (2012) found an increased risk with the duration of bisphosphonate therapy with the highest rate of AFF in patients with 5 or more years of bisphosphonate. Based on these findings, current

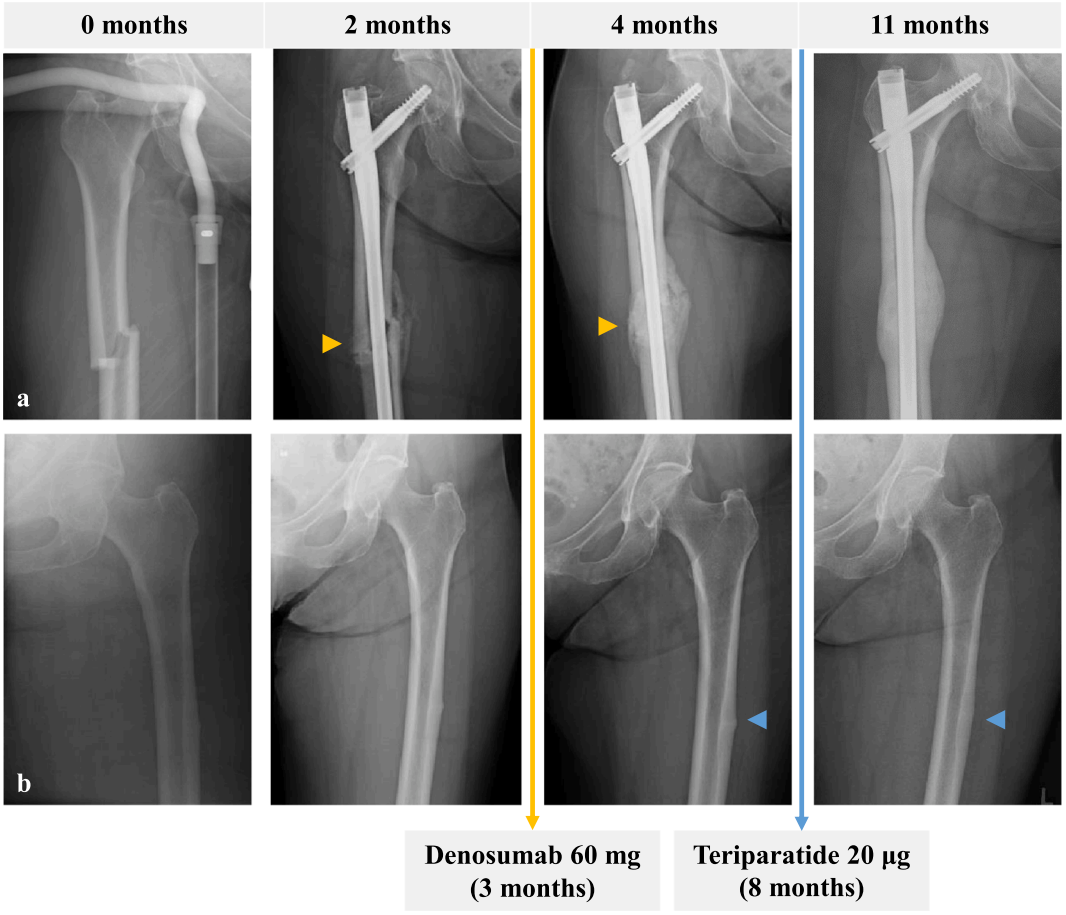

Fig. 1. a Anteroposterior radiograph series with complete AFF of the right femur. Subsequent imaging studies demonstrate healing response with callus formation 6 weeks after administration of denosumab. b Anteroposterior radiograph series showing incomplete AFF of the left femur with localized periosteal reaction of the lateral cortex without radiolucency. Follow-up images reveal radiographic resolution of the left femur "beaking" after 3 months of teriparatide therapy.

recommendations suggest evaluation of continued BP use on a yearly basis after 5 years of therapy (Alder et al., 2016). Patients at high risk for osteoporotic fractures should be continued on therapy despite the increased risk for AFF and should be reassessed after 10 years according to guidelines from the American Association of Clinical Endocrinologists (Watts et al., 2010). This is consistent with our patient's history, who was at increased risk for AFF in the setting of continued exposure with 10 years of BP therapy.

In recent years, drug holidays have been recommended as a strategy to prevent complications from prolonged BP therapy (Alder et al., 2016). While there is no consensus on when to discontinue BP use or for how long, there does seem to be a clinically important benefit of a drug holiday with regard to AFF risk (Black et al., 2020). Schilcher et al. (2011) describe a significant reduction in AFF after just one year of discontinuation of BP therapy. However, this study only included four AFFs after greater than one year of discontinuation and did not report the exact number of years of drug holiday in these patients. Another consideration for a BP drug holiday is the risk of osteoporosis-related fractures. A recent cohort study on this topic did not find an increased risk of fragility fractures in patients on a >12-month BP holiday compared to persistent BP users (Adams et al., 2018). This study also reported a decreased rate of AFF in the BP holiday group but did not describe the timing of these fractures in relation to the last dose of BP. Interestingly, our patient's last dose of BP was more than 10 years prior to her presentation with AFF. Cases of atypical femur fracture have been reported during BP drug holiday, but no long-term studies on drug holidays currently exist. Lovy et al. (2015) report two patients with 10-year and 14-year histories of BP therapy that experienced AFF after 5 and 4-year drug holidays, respectively. To our knowledge, there are no reports of AFF after a prolonged drug holiday of greater than 10 years.

Management of AFF depends on the severity of the fracture, but the general principle of discontinuing antiresorptive medications is a common practice (Dell and Greene, 2018). This serves to prevent the progression of an incomplete AFF to a complete fracture, or to prevent an AFF in the contralateral leg. Patients on a BP drug holiday require different management because they are not actively taking antiresorptive medications at the time of the fracture. Another unique feature of this case is the fact that the patient was administered a single dose of denosumab roughly 3 months after the complete fracture of her right femur. The use of an antiresorptive drug in this patient should have been more carefully considered by the referring service due to the presence of an incomplete AFF in the patient's left femur. There was callus formation at the site of complete fracture with some disappearance of the lucency of the fracture after the administration of denosumab, although it is unclear to what extent denosumab may have contributed to fracture healing. There was additionally no progression on the incomplete AFF as seen on X-ray. This finding has not previously been reported with denosumab use in AFF.

The average union time after operative treatment of AFF is around 5 months with roughly 20% of patients experiencing contralateral fractures within two years (Bogdan et al., 2016). Although there is evidence of callus formation 2 months after the fracture, additional callus formation around the site of the right AFF was noted on X-ray after the denosumab injection at 4 months post-operatively. There was no change in the left femoral shaft beaking (Fig. 1b). We are unable to definitively state that denosumab improved fracture healing given the average post-operative union time of AFF; however, our patient demonstrated a good healing response while on denosumab without any adverse effects. According to the FREEDOM trial, a sub analysis of patients with fractures comparing denosumab versus placebo did not show an increased risk of complications associated with fracture healing (Adami et al., 2012). However, AFF has been reported in patients on denosumab although the association has been difficult to establish due to a smaller number of patients and remote exposure to bisphosphonate therapy. In a long-term FREEDOM extension study, AFF was exceedingly rare with only two patients experiencing this complication in the 10-years of denosumab exposure (Bone et al., 2017). Since the patient presented with an atypical fracture of the right femoral shaft and a contralateral incomplete fracture of the left, we considered it appropriate to discontinue denosumab upon referral. An increase in BMD might be due to modeling-based bone formation as studies on ovariectomized monkeys shows that denosumab does not seem to affect modeling bone formation (Ominsky et al., 2015). We found this particularly relevant as cortical bone strength from bone modeling might improve and possibly decrease the predisposition to AFF after long standing denosumab therapy, contrary to BP treatment.

Finally, this patient also had an incomplete fracture of the contralateral femur at the time of the complete AFF that was treated with teriparatide. The incomplete fracture resolved on radiographs after 3 months of therapy, which is consistent with other reports documenting radiographic resolution. The use of teriparatide has been increasingly published from case reports to case series with interesting findings that need further prospective studies to corroborate their validity. In a large retrospective case series, Miyakoshi et al. (2015) showed that teriparatide was associated with quicker healing time and lower rates of complications, such as delayed union and nonunion, in patients undergoing surgery for complete and incomplete bilateral AFF. Similar to our case, Saleh et al. (2012) reported a series of five incomplete AFF without radiographic radiolucency treated with teriparatide and conservative measures responded after three months of therapy with resolution of edema on magnetic resonance imaging. However, only two of nine patients with radiographic radiolucency progressed to fracture healing after three months of teriparatide therapy, and the remainder underwent prophylactic nail fixation. The author concluded that perhaps more time for conservative measures will be required to heal incomplete AFF with radiolucency. Prospective studies comparing conservative management of AFF with and without pharmacological therapy are still needed to assess the healing impact of teriparatide.

4. Conclusion

Our patient presented with bilateral AFF after a 10-year drug holiday from prolonged exposure to BP for the treatment of osteoporosis. Use of antiresorptive medications, such as BPs and denosumab, is not recommended after AFF, but our case report demonstrates no adverse effect of denosumab administered 3 months after AFF. This case report supports the use of teriparatide as previously reported in the healing of incomplete AFFs without radiolucency. Whether the remote long-term use of bisphosphonates prior to a long drug holiday is mechanistically related to the development of AFFs seen during prolonged use remains uncertain. As the cohort of patients on long-term BP therapy continues to age, we must be aware of potential long-term complications, along with the potential benefits and risk of BP drug holidays.

Informed consent

Written informed consent was obtained from the next of kin of the patient who participated in this case.

Financial disclosure

The authors declare that this case has received no financial support.

CRediT authorship contribution statement

MDS: Writing – original draft, Data curation, Visualization; OJH: Writing – review & editing, Data curation; JAV: Writing – review & editing, Supervision; JMB: Conceptualization, Resources, Supervision, Writing – review & editing. All authors have approved the final version of the manuscript.

Declaration of competing interest

None.

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