Zoledronic Acid induced Atypical femoral fracture in Post-menopausal Osteoporosis: A Case Report

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ABSTRACT
Zoledronic Acid is a highly potent intravenous bisphosphonate, that reduces the overall risk of fractures among patients with osteoporosis, and this beneficial effect is long-lasting. However, since bisphosphonates inhibit bone remodeling, they may enhance the formation and propagation of micro-cracks over time and patients may therefore be prone to atypical fatigue fractures, mainly in the subtrochanter region and femoral shaft. **Case Preparation:** A 45-year-old Postmenopausal osteoporotic woman presented to us with generalized bone pain. She was given an infusion of Zoledronic Acid and was kept on regular monthly follow-up. She reported, after three months of infusion, with spontaneous, mild-to-moderate, dull aching pain in her right upper thigh and right upper leg, with no history of associated trauma. Her X-rays confirmed an incomplete right subtrochanteric femoral fracture.**CONCLUSIONS:** Previous case series have reported that long-term bisphosphonate use is associated with atypical femoral fractures, and certain criteria have been established to help identify such rare fractures. We present this case report of a potentially rare and serious side effect of bisphosphonate use, estimated to affect 2.3 in every 10,000 patients. In addition, most of the documented cases have been associated with long-term bisphosphonate use, whereas our patient has presented only after 3 months after the infusion of first dose of zoledronic acid.

**Keywords:** Zoledronic Acid, Bisphosphonates, Atypical femoral fracture, Osteoporosis

INTRODUCTION
Zoledronic Acid is a highly potent intravenous bisphosphonate widely used for the treatment of osteoporosis in postmenopausal women¹². After using bisphosphonates in many patients, some unexpected possible adverse effects have been reported, including oesophagitis, renal dysfunction, osteonecrosis of the jaw, atrial fibrillation, and infusion-related reactions with intravenous bisphosphonates³. Recently, there have been concerns regarding the occurrence of atypical femoral fractures in patients on long-term bisphosphonate therapy for osteoporosis⁴. We report a rare case of a possible complication of bisphosphonate use and take the opportunity to discuss the characteristics of bisphosphonate-induced fractures.

**CASE REPORT**
A forty-five year old postmenopausal women presented to us with generalized bone pain since last two to three years. She had a T-score of -0.9, which was performed on 7th July 2013. She had no previous history of any fracture or any prolonged illness. She was on regular calcium therapy for the last two years. The patient was explained regarding the treatment of osteoporosis with once-a-year therapy with zoleodronic acid infusion. After investigating for her normal renal profile, the patient was infused 5mg/ 100 ml of zoledronic acid infusion on 13th July 2013, with all the necessary precautions. The patient was advised to continue with her calcium therapy, and regular follow-up on monthly intervals. She reported in October 2013 with spontaneous, mild-to-moderate, dull aching pain in her right upper thigh and right upper leg. She had no history of associated trauma or any other obvious predisposing factors. On examination, she had tenderness in her right trochanteric region and right upper leg. X-rays of the concerned region revealed an incomplete right subtrochanteric femoral fracture and right proximal tibial fracture. Since the patient had an incomplete fracture with mild pain, she was treated conservatively by the advice of continuing calcium therapy, partial weight-bearing mobilization with use of a walker and avoidance of strenuous activity.

**Figure 1:** X-ray Antero-posterior and Lateral view of the right hip showing an incomplete subtrochanteric fracture of right femur on the lateral cortex.
Taskforce defined major and minor diagnostic features for complete and incomplete atypical fractures of the femur (Table 1). All major features must be present in order to diagnose an atypical fracture and distinguish it from more common hip fractures. Minor features may or may not be present in individual patients. Of note, association with bisphosphonate therapy was included as a minor feature.

Table 1: Major and minor features of atypical fractures

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<th>Major features</th>
<th>Minor features</th>
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<td>• Located anywhere along the femur from just distal to the lesser trochanter to proximal to the supracondylar flare</td>
<td>• Localized periosteal reaction of the lateral cortex</td>
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<td>• Not associated with trauma or minimal trauma, as in a fall from a standing height or less</td>
<td>• Generalized increase in cortical thickness of the diaphysis</td>
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<td>• Transverse or short oblique configuration</td>
<td>• Prodromal symptoms such as a dull or aching pain in the groin or thigh</td>
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<td>• Non-committed</td>
<td>• Bilateral fractures and symptoms</td>
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<td>• Complete fractures extend through both cortices and may be associated with a medial spike;</td>
<td>• Delayed healing</td>
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<td>incomplete fractures involve only the lateral cortex</td>
<td>• Comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatemia)</td>
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<tr>
<td></td>
<td>• Use of pharmaceutical agents (e.g., bisphosphonates, glucocorticosteroids, proton pump inhibitors)</td>
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The clinical implications of these fractures on long-term bisphosphonates use remain unclear. Black and fellow researchers performed post-hoc analysis of the FIT, FLEX, and HORIZON trials but could not find a significant increase in bisphosphonate-related fractures as compared with placebo. These low-energy, non-spinal fractures were very rare, with an incidence of 2.3 per 10,000 patient years of use. A large population national registry based on an observational study from Denmark performed by Abrahamsen et al. in 2009 concluded that there was no evidence of an increased risk of atypical femoral fractures with either short- or long-term use of bisphosphonate. The Endocrine Society has recommended that although low energy fractures have been reported with bisphosphonate use, the incidence of these atypical fractures is similar to the risk in the general population. The Society also recommends that physicians prescribing bisphosphonates should be aware of this potential atypical femoral fractures with typical radiologic pattern. At present, evidence suggests that these fractures are very rare in patients on long-term bisphosphonate therapy. The benefits of bisphosphonate therapy with clearly proven efficacy in fracture risk reduction among osteoporotic patients still clearly outweigh the risks of rare atypical fractures of the femur. With the increasing evidence of the characteristic atypical femoral fracture and the potential implications of long-term use of bisphosphonates, there has been a search for...
the best alternative drug to bisphosphonates. According to guidelines of the National Institute for Health and Clinical Excellence, strontium ranelate and raloxifene should be used as a second-line agent. However, in atypical femur fracture attributed to bisphosphonates, Schneider\textsuperscript{13} supported the use of teriparatide because of its osteoblast stimulating activity. Denosumab, which is a monoclonal antibody that reduces osteoclast activity, can be used for patients who are intolerant or not suitable for bisphosphonates. However, denosumab is still a new drug and the knowledge regarding its long-term safety is still relatively limited. Although, the use of denosumab is associated with a small risk of osteonecrosis of the jaw, a similar complication of bisphosphonates, which Schneider and others associate with atypical femoral fracture\textsuperscript{13}.

**CONCLUSION**

We report a rare case of atypical femoral fracture within three months following zoledronic acid infusion for osteoporosis in a postmenopausal woman. This case report raises concerns for atypical femoral shaft fractures following zoledronic acid therapy. Bisphosphonates have been and are still being used widely in the treatment of osteoporosis. The causal relationship between prolonged bisphosphonate use and occurrence of a atypical femoral fractures has not yet been established. Large-scale randomized studies are needed in order to improve our understanding of the long-term safety of bisphosphonates and to reach a universal agreement for an alternative medication to manage patients with bisphosphonate-associated fractures, as these are very rare and may require more prolonged and complex treatment. Clinicians should remember that bisphosphonates significantly reduce the risk of fragility fractures in patients with osteoporosis and that overall the antifragility effects of bisphosphonates far outweigh their potential risks.

**REFERENCES**