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Atypical femoral shaft fracture in a patient with non-metastatic prostate cancer on zoledronic acid therapy: effect of therapy or coincidence?

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ABSTRACT There have been recent concerns of atypical non-spinal fractures in patients with osteoporosis who are on long-term bisphosphonate therapy. These fractures are less commonly reported in cancer patients on zoledronic acid therapy, where it is used in higher doses as compared to patients with osteoporosis. We report the case of a 70-year-old man with non-metastatic prostate cancer who was on androgen deprivation therapy following bilateral orchiectomy. He was on bone protection with intravenous zoledronic acid 4 mg monthly for a period of two years. He presented with spontaneous acute right mid-thigh pain. Radiograph of the right femur showed an atypical femoral shaft fracture, which was treated with intramedullary nailing and teriparatide. This case report raises concerns of atypical fractures in cancer patients who receive high doses of zoledronic acid. Patients receiving bisphosphonates who present with thigh or groin pain must undergo radiographic examination of the femur to rule out atypical femoral fractures.

Keywords: atypical, diphosphonates, femoral shaft, fracture, prostate cancer
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INTRODUCTION

Zoledronic acid is a potent bisphosphonate that is used for the treatment of osteoporosis.[1,2] It is also used in prostate cancer patients with bone metastasis to reduce skeletal-related events.[3] In addition, zoledronic acid improves bone health in patients of non-metastatic prostate cancer on androgen deprivation therapy.[3] Side effects associated with bisphosphonates include oesophagitis, renal dysfunction, osteonecrosis of the jaw and infusion-related reactions with intravenous bisphosphonates.[1,2] There have been concerns regarding the occurrence of spontaneous unusual non-spinal fractures in patients on long-term bisphosphonate therapy for osteoporosis.[4-8] These unusual fractures are less commonly reported in cancer patients on zoledronic acid.[8,9] We report a case of spontaneous femoral mid-shaft fracture in a patient with non-metastatic prostate cancer who underwent bilateral orchiectomyand was on high-dose zoledronic acid therapy for bone protection.

CASE REPORT

A 70-year-old Indian man was diagnosed with locally advanced prostate cancer without skeletal metastasis in 2002. He underwent bilateral orchiectomy in the same year, and had since been on androgen deprivation therapy. He was prescribed oral bicalutamide 50 mg daily for four years after bilateral orchiectomy. He had been treated with 200 mg oral ketoconazole thrice daily with oral hydrocortisone replacement for the last four years. He was advised intravenous (IV) zoledronic acid therapy for prevention of bone loss following androgen deprivation therapy, and had received 4 mg IV zoledronic acid once a month for the last two years. He developed spontaneous, acute-onset, severe deep aching pain in the right mid-thigh. However, he did not recall any significant trauma or fall. Radiograph of the right femur (Fig. 1) showed a transverse fracture in the mid-shaft region with

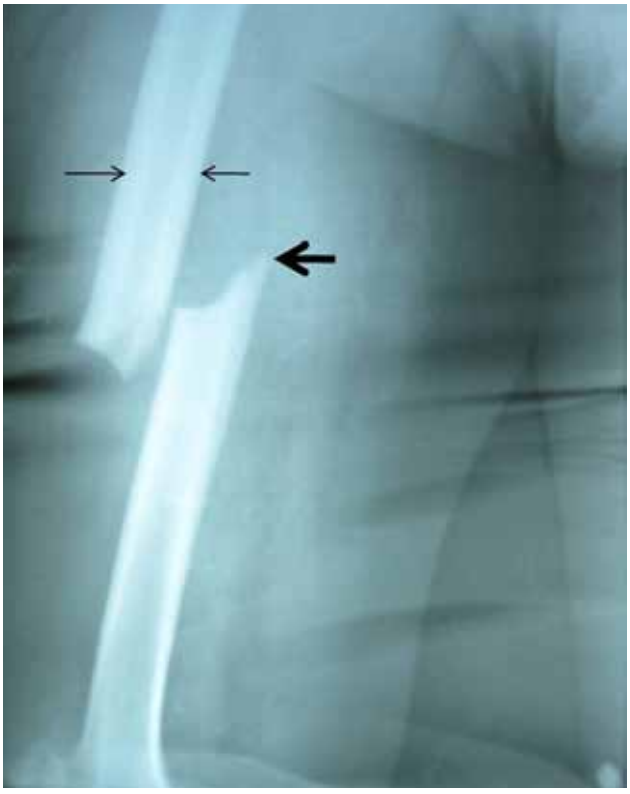

Fig. 1 Radiograph of the right femur shows transverse right femoral shaft fracture with cortical thickening (thin arrows) and sharp medial cortical spike (thick arrow).

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cortical thickening. The subtrochanteric region did not reveal any fractures. Radiograph of the left femur did not reveal any stress fractures. Bone mineral density (BMD) by dual energy X-ray absorptiometry showed osteoporosis with a T-score of –2.6 for lumbar spine (L1–L4), –2.4 for total hip and –2.0 for forearm. The patient's serum calcium was 2.4 (normal range [NR] 2.1–2.6) mmol/L, serum phosphorus 1.2 (NR 0.8–1.5) mmol/L, alkaline phosphatase 200 (NR < 150) U/L, intact parathormone (iPTH) 1.5 (NR 1.2–5.7) pmol/L and serum 25-hydroxyvitamin D 66.5 (Viamin D deficiency < 50) nmol/L. ^{99m}Technetium-labelled methylene diphosphonate (^{99m}Tc-MDP) bone scintiscan did not reveal any skeletal metastasis. The patient then underwent intramedullary nailing for fracture shaft of the right femur. During the operative procedure of nailing, he developed a new subtrochanteric fracture of the right femur (Fig. 2). He was treated with bed rest and teriparatide 20 μg daily subcutaneously for two months, with satisfactory healing. On follow-up three months later, his fractures were completely healed. Zoledronic acid was then stopped.

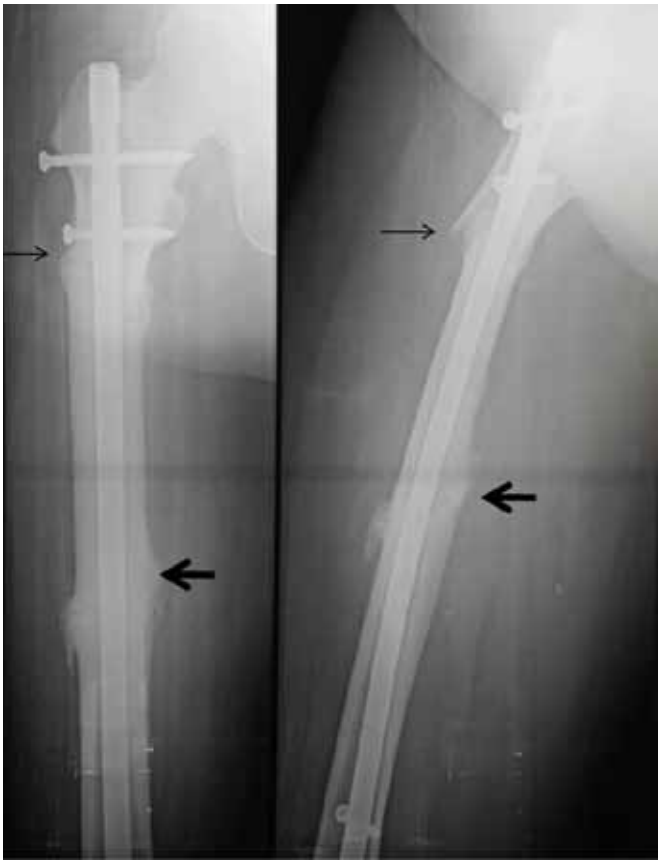

Fig. 2 Radiographs of the right femur post surgery show right subtrochanteric fracture (thin arrows) with intramedullary nail and partial healing of the femoral shaft fracture (thick arrows).

DISCUSSION

Bisphosphonates are widely used drugs for the prevention and treatment of osteoporosis. They have proven efficacy in BMD gains and future fracture risk reduction.[1,2] Zoledronic acid is a potent bisphosphonate used in osteoporosis in doses of 5 mg IV annually.[1,2] It is also used in metastatic prostate cancer to reduce skeletal-related events in doses of 4 mg IV every three weeks.[3] In addition, it is used in non-metastatic prostate cancer patients on androgen deprivation therapy to optimise their bone health, and are administered in doses of 4 mg IV once every three months.[3]

The adverse effects reported with bisphosphonates include oesophagitis, renal dysfunction, osteonecrosis of the jaw and hypocalcaemia.[1,2] IV bisphosphonates are also associated with infusion-related febrile reactions and myalgias.[1,2] Recently, there have been concerns about atypical or low-energy fractures associated with long-term use of bisphosphonates. Multiple case series and reports have documented atypical low-energy or spontaneous non-spinal fractures in patients on bisphosphonates for osteoporosis.[4-8] These studies have reported femoral subtrochanteric or diaphyseal mid-shaft fractures, which have been reported mainly in patients with osteoporosis. There are only a few case reports of atypical femoral fracture in the setting of malignancy described in patients with multiple myeloma and metastatic renal cell carcinoma who are on multiple infusions of pamidronate and zoledronic acid.[8,9] Our patient had non-metastatic prostate cancer with an atypical spontaneous right femoral mid-shaft fracture. He was administered IV zoledronic acid monthly for two years for bone protection following androgen deprivation therapy and did not have evidence of skeletal metastasis on bone scintiscan.

The clinical presentation of atypical femoral fractures includes severe thigh or groin pain, as in our case.[8,10] Up to 76% of cases document the presence of prodromal symptoms of thigh pain, vague discomfort or subjective weakness.[8,10] These fractures most likely represent the completion of a stress fracture.[8,10] Patients who present with atypical femoral fractures have been found to have stress fractures of the contralateral femur in up to 64% of cases.[8,10] As bilaterality is common, it is recommended that patients who present with unilateral atypical femoral fractures undergo radiographic screening of the contralateral femur to rule out stress fractures.[8,10] However, although radiograph of the contralateral femur was normal, our patient developed a subtrochanteric fracture of the ipsilateral femur during surgery.

The American Society of Bone Mineral Research task force[8] has defined major and minor features of complete and incomplete atypical femoral fractures. It recommends that all major features, including location in the subtrochanteric region and femoral shaft, transverse or short oblique orientation, minimal or no associated trauma, a medial spike when the fracture is complete and absence of comminution, should be present to designate a femoral fracture as atypical. Minor features include association with cortical thickening, periosteal reaction of the lateral cortex, prodromal pain, bilaterality, delayed healing, comorbid conditions and concomitant drug exposures including bisphosphonates, other antiresorptive agents, glucocorticoids and proton pump inhibitors.[8]

Multiple mechanisms have been proposed for these atypical fractures. It has been observed in bone histomorphometric studies

that bisphosphonate therapy is associated with adynamic bone disease due to severe suppression of bone turnover.[7,11] Long-term inhibition of bone turnover leads to accumulation of microdamage of the bones and development of hypermineralised bone with poor bone quality. Fracture healing is delayed or absent on bone biopsies. The clinical significance of this adynamic bone disease has not been well documented. Pathologic fracture due to skeletal metastases could be one mechanism, but this was excluded as our patient did not exhibit any evidence of skeletal metastases. Histopathological examination of the surrounding bone obtained during surgery was not performed in our case, as clinical probability of skeletal metastasis was low in the setting of a normal bone scintiscan.

In previous studies, few risk factors, including associated use of steroids, hormone replacement therapy, proton pump inhibitors and duration of bisphosphonate use, have been observed for these atypical femoral fractures.[5] These fractures have been implicated with all bisphosphonates – alendronate, zoledronic acid and pamidronate; no single agent has been implicated more often. Our patient was on high-dose zoledronic acid therapy (4 mg IV monthly) after hormonal therapy for prostate cancer. The dose of zoledronic acid used was up to three times the dose recommended for bone protection following androgen deprivation therapy for prostate cancer.[3] The dosage of zoledronic acid for such indications needs to be established in clinical studies.

The clinical implications of these fractures on long-term use of bisphosphonates remain unclear. A recent secondary analysis study using the results of three large randomised bisphosphonate trials showed that there was no significant increase in risk in patients on bisphosphonates, even for those receiving up to ten years of treatment.[12] These low-energy, non-spinal fractures were very rare, with an incidence rate of 2.3 per 10,000 patient-years of use.[12] A large population national registry based on an observational study from Denmark concluded that the risk of atypical femoral fractures in patients on bisphosphonate therapy is similar to that of those not on bisphosphonates and that these fractures are best classified as osteoporotic fractures.[13]

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.[14] The Society has also recommended that physicians prescribing bisphosphonates should be aware of this potential atypical subtrochanteric or femoral shaft 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.[14]

In conclusion, we report a rare case of low-energy atypical femoral mid-shaft fracture following high-dose zoledronic acid use for bone protection following androgen deprivation therapy in a patient with non-metastatic prostate cancer. This case report raises concerns for atypical femoral shaft fractures following high-dose zoledronic acid therapy. Physicians should be aware of this entity, and the exact dose of zoledronic acid for therapy of skeletal metastases and for bone protection following androgen deprivation therapy in patients with prostate cancer needs to be identified and optimised in clinical trials. Cancer patients receiving bisphosphonates, who present with spontaneous or traumatic thigh or groin pain, must be screened with radiography of the femur to rule out atypical femoral fractures. In addition, patients with a documented fracture should undergo radiographic examination of the contralateral femur.

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