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Case Report

Atypical fracture of the tibial diaphysis associated with bisphosphonate therapy: A case report

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ABSTRACT

Atypical subtrochanteric femoral shaft fractures (AFFs) have recently emerged as a potential long-term complication of bisphosphonate therapy. In 2010, the American Society for Bone and Mineral Research (ASBMR) Task Force published a definition for AFF consisting of 5 major and 7 minor features. Little attention has so far been paid to the possibility that bisphosphonate-associated atypical fractures may also involve the diaphysis of other long bones. We report here the case of a patient on long-term bisphosphonate therapy who presented a diaphyseal tibial insufficiency fracture fulfilling all the major criteria (except for the location), and a number of the minor criteria of an atypical fracture. Our case report suggests the need for greater awareness of the possibility of atypical fractures at other sites, particularly in weight-bearing long bones other than the femur, and suggests that long-term bisphosphonate therapy may also contribute to the occurrence of these atypical fractures.

Introduction

Amino-bisphosphonates are the most commonly prescribed medication for the treatment of osteoporosis, and their efficacy in reducing fracture risk has been amply demonstrated [1]. Growing concerns regarding the long-term oversuppression of bone turnover have arisen since the first report of spontaneous peripheral fractures after long-term therapy with alendronate [2], followed by several other reports of subtrochanteric or diaphyseal femoral insufficiency fractures during long-term bisphosphonate therapy [3–7]. Common defining features of atypical femoral fractures (AFFs) were reported in 2010 by the task force of the American Society for Bone and Mineral Research (ASBMR) [8], and were recently updated [9]. The AFF must be located along the femoral diaphysis, and the five main features include: minimal or no causative trauma, minimal or no comminution, a transverse or short oblique fracture originating at the lateral cortex, with an extension through both cortices, sometimes with a medial spike in complete fractures, and a localized periosteal reaction or endosteal thickening of the lateral cortex at the fracture site. Minor features may also be present, such as generalized cortical thickness, prodromal symptoms, or delayed fracture healing [8,9]. Although the subtrochanteric femur is the usual site of these atypical fractures, other weight-bearing sites have also been affected [2,10,11]. We report here the case of a woman who had received yearly intravenous zoledronate for 4 years, and who presented with a fracture fulfilling the criteria for atypical fracture, except for being located at the tibial diaphysis.

Case report

A 77-year-old Caucasian woman presented to the emergency department with a 6-week history of pain over the left tibia since a mild trauma to the leg when she almost tripped and hit a supporting post of a banister when going down stairs. The pain intensified with weight bearing, and she had used a cane since the incident. She did not report falling or any other trauma. Her symptoms suddenly worsened while she was going down a flight of stairs. No weight bearing was possible afterwards. Her relevant medical history included COPD, osteoarthritis, and osteoporosis with multiple previous vertebral fractures. In 1969, following a car accident, a bone graft was needed at the L4–L5 level, and the left tibia was used as the donor site. The patient had quit smoking a few years previously. Current drug intake included Calcium 500 mg bid, Vitamin D 400 U bid, Lyrica (pregabalin) 75 mg bid, Nexium (esomeprazole) 40 mg qd, and Ventolin (albuterol) and Flovent (fluticasone) as needed. There was no past history of oral glucocorticoid use. She had been intolerant to both alendronate and risedronate, which had prevented her from taking a prolonged course of oral bisphosphonates. She started yearly intravenous zoledronic acid in 2009, and had received a fourth infusion a few months prior to the fracture. On examination, she was in good general condition with a BMI of 24. There was edema and pain on palpation along the mid-shaft of the left tibia. A conventional X-ray demonstrated a non-displaced transverse fracture of the middle third of left tibial diaphysis (Figs. 1A and B). Cortical thickening

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and beaking were present at the site of the fracture. Radiographs of the right tibia (Figs. 1C and D) and of both femurs were unremarkable. A bone scan failed to reveal any other fracture sites. The T-scores for bone mineral density (BMD) on dual-energy x-ray absorptiometry in 2008 were −2.4 at the neck of femur and −2.6 at the spine. At time of the fracture, her serum biochemical parameters of bone metabolism were normal: 25-hydroxyvitamin D 110 nmol/L (normal range (N) 75–117), phosphate 0.84 nmol/L (N 0.80–1.45), total calcium 2.18 mmol/L (N 2.07–2.55), alkaline phosphatase 52 UI/L (N 35–105), C-telopeptide 0.271 µg/L (post-menopausal N 0.104–1.008), and creatinine 75 µmol/L (N 46–92). Treatment consisted of an intramedullary nail that immediately resolved the pain. Zoledronic acid was discontinued. A 4-month follow-up radiograph revealed progression of the bony callus and good progressive healing (Figs. 2A and B).

Discussion

Bisphosphonates are the most common first-line therapy for the prevention and treatment of osteoporosis. Their efficacy in reducing both vertebral and non-vertebral fractures is well supported, and the safety profile is usually good [1]. Over the last decade however, some concerns have arisen about the long-term safety of bisphosphonates, with cases of AFF and osteonecrosis of the jaw [1,12]. Several reports have suggested that long-term suppression of bone turnover might fragilize bone and contribute to the occurrence of these AFFs [3–7]. While secondary analysis of large randomized controlled trials did not find any significant relationship between AFF and the use of bisphosphonates for up to 10 years [13], this re-evaluation of RCTs may have suffered from information bias: only a minority of the patients had received bisphosphonates for more than 4 years, statistical power was low for these rare complications, and it was also impossible to review the radiographs. Furthermore, the definition of atypical fractures was not standardized before the ASBMR Task Force consensus in 2010 [8].

We describe here a case of diaphyseal tibial fracture occurring in a postmenopausal woman who had been treated with zoledronic acid for 4 years, and who was currently receiving a proton-pump inhibitor. A bony defect was observed distally to the fracture, corresponding to bone taken some 40 years ago for a spinal bone graft. This could have fragilized the tibial bone, although the lengthy interval makes this less likely to represent more than a fracture facilitator. Other risk factors for bone fragility in our case report include past smoking [14] and using steroid inhalers in the long-term treatment of COPD [15]. The ASBMR task force criteria for atypical fractures were not designed for fractures occurring in bones other than the femur, however, similar to AFFs, our patient exhibited a transverse, non-comminuted fracture following minimal trauma. At the fracture site in the mid-tibial diaphysis, a localized periosteal reaction and cortical thickening of the anterior cortex were clearly detected. The fact that the anterior cortex is involved in this tibial fracture, rather than the lateral cortex as defined in AFF, may be related to differences in the geometry and stress distribution along these bones. AFFs occur in the lateral cortex where the greatest tensing loading is exerted [12]. Likewise, stress fractures of the anterior cortex of the tibial mid-shaft result from tension stress rather than compression [16]. Thus, except for its location, this fracture

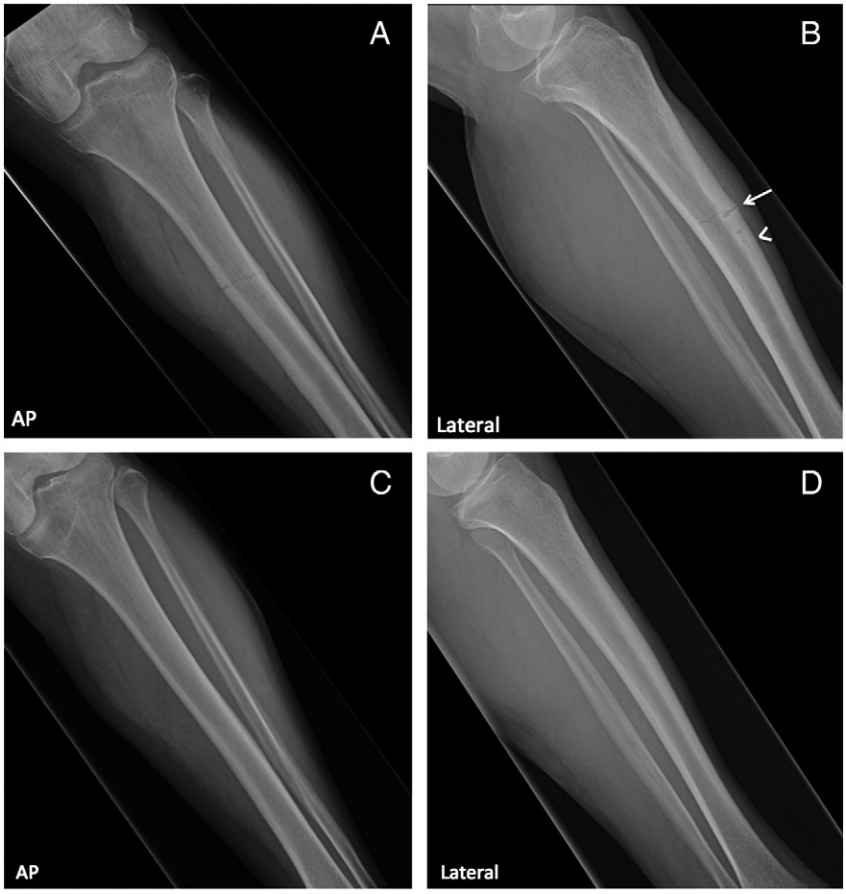

Fig. 1. Left mid-shaft fracture of the tibia in a patient on zoledronic acid for 4 years. A–B—The tibial fracture shares some of the radiographic characteristics of atypical fractures, being transverse, non-displaced, non-comminuted, and associated with a periosteal reaction of the anterior cortex, an anterior cortical beak (arrow), and a marked increase in cortical thickness of the diaphysis. Distally to the fracture, a putative bone graft taken from the left tibia is observed (arrow head). C–D—Anteroposterior and lateral x-rays of the right tibia.