Atypical Femoral Fracture in a Patient with Metastatic Breast Cancer During Denosumab Therapy

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Abstract

A case of a 62-year-old woman with breast cancer who developed an atypical femoral fracture during denosumab therapy for bone metastasis is reported. About 8.5 years before the fracture, she was diagnosed with breast cancer with liver and bone metastases and started receiving chemotherapy. Three and a half years later, zoledronic acid (40 mg every 4 weeks) was added, which was continued for 2 years and 4 months. At around 1.5 years after discontinuation of zoledronic acid, bone metastasis recurred and she began treatment with denosumab at 120 mg every 4 weeks. Fifteen months after starting denosumab, she sustained a left subtrochanteric fracture. Faint hot spots in the bilateral subtrochanteric regions were found on bone scintigraphy 2 months after the start of denosumab, and the tracer accumulation was slightly increased on bone scintigraphy 1 year later. Prior to the fracture, she had been experiencing a dull ache in her left thigh for a few months. Our case suggests that denosumab treatment for bone metastasis is a risk factor for atypical femoral fractures, and that thigh pain and subtrochanteric hot spots on bone scintigraphy could be signs of an impending fracture.

Keywords: Denosumab; Atypical femoral fracture; Bone metastasis

Introduction

Over the past decade, there have been an increasing number of reports in the literature on subtrochanteric or femoral shaft fractures, especially in patients who have been on prolonged courses of bisphosphonates (BPs). These fractures, which have invariably been non-committed transverse fractures through an area of thickened cortex and associated with minimal or no trauma, have been termed atypical femoral fractures (AFFs) [1]. More recently, a few cases of AFFs have been reported in patients treated with denosumab (60 mg every 6 months) for osteoporosis [2-7]. In this report, we present a case of an AFF which occurred during treatment for bone metastasis with denosumab (120 mg every 4 weeks).

Case Report

Our patient was a 62-year-old woman who fell at home and sustained a left subtrochanteric fracture. About 8.5 years before the fracture, she was diagnosed with stage IV breast cancer with liver and bone metastases, for which she received chemotherapy. Three and a half years later, zoledronic acid (ZOL) (40 mg every 4 weeks) was added to her regimen (Figure 1). Since these therapies were effective and the metastatic lesions had clinically disappeared, she underwent a right mastectomy 5 years after the diagnosis of breast cancer. After the mastectomy, she continued prophylactic single-agent chemotherapy and ZOL for prevention of cancer recurrence. Six months after the surgery, the chemotherapy was concluded. Although ZOL had been continued for an additional several months, it was terminated because of renal dysfunction. The total term of ZOL administration was 2 years and 4 months.

At around 1.5 years after discontinuation of ZOL, 18 fluoro-2-deoxyglucose positron emission tomography revealed recurrence of bone metastasis. The patient resumed chemotherapy and started receiving denosumab at 120 mg subcutaneously every 4 weeks. Oral calcium (390 mg per day) and alfacalcidol (1 μg per day) were administered with denosumab to prevent hypocalcemia. Fifteen months after starting denosumab, she fell at home and sustained a left subtrochanteric fracture. Prior to the fracture, she had been experiencing a dull ache and muscle pain in her left thigh for a few months.

Figure 1: Time course of therapeutic interventions. ZOL: Zoledronic Acid, DM: Denosumab.
Her past history included appendicitis, tonsillitis, uterine myoma, and breast cancer. She had never experienced rheumatoid arthritis or metabolic bone disease, such as vitamin D deficiency. Her regular medications at the time of the fracture included capecitabine, atorvastatin calcium, ecabet, esomeprazole magnesium hydrate, and etodolac, but no glucocorticoids.

**Figure 2:** X-ray of bilateral femurs shows a non-comminuted transverse fracture in the left subtrochanteric region (arrow) and localized periosteal thickening in the lateral cortex of the right femur (arrowhead).

X-ray of her left femur showed a non-comminuted transverse subtrochanteric fracture with a medial spike (Figure 2). Localized periosteal thickening of the lateral cortex was also detected in her right femur (Figure 2). Magnetic resonance imaging did not show any metastatic lesions in the bilateral femurs (Figure 3a and 3b). Bone scintigraphy was performed at 1 and 13 months before the fracture for the detection of bone metastasis. A faint hot spot in the lateral cortex of the left subtrochanteric region was shown on both studies, and there was increased tracer accumulation in the latter study (Figure 4).

In addition, a hot spot was also detected in the right femur on bone scintigraphy at 1 month before the fracture (Figure 4). Serum laboratory investigation revealed that serum levels were as follows: creatinine, 0.73 mg/dL (reference interval [RI]: 0.45-0.80); total calcium, 7.5 mg/dL (RI: 8.4-10.2); albumin, 3.4 g/dL (RI: 3.8-4.9); bone-specific alkaline phosphatase, 6.3 μg/L (RI: 3.8-22.6); tartrate-resistant acid phosphatase 5b (TRACP-5b), 73 mU/dL (RI: 120-420); and intact amino-terminal propeptide of type 1 procollagen (P1NP), 15.5 μg/L (RI: 21.9-79.1).

We concluded that this fracture was an AFF based on the mechanism of injury and X-ray findings. Although the patient had been on chemotherapy, her general medical condition was good and open reduction internal fixation of the femoral fracture was undertaken 6 days following the fracture with the insertion of a long intramedullary nail (Interiant; Smith & Nephew, Memphis, TN). However, as her femoral cortex was very hard, the reaming and nail insertion were performed particularly carefully. The operative time was 141 minutes and the intraoperative blood loss was 150 mL. No evidence of malignancy was observed on histological examination of bone samples taken at the time of surgery.

**Figure 4:** Bone scintigraphy performed at 1 month and 13 months before the fracture. A faint hot spot in the lateral cortex of the left subtrochanteric region is shown in both images (Figure 4a and 4b, arrows), and the tracer accumulation is increased in the latter (Figure 4b, arrow). On bone scintigraphy performed 1 month before the fracture, a hot spot is present in the right femur (Figure 4b, arrowhead).

After the operation, treatment with denosumab was discontinued because there was no evidence of active bone metastasis. We then initiated treatment with eldecalcitol and low-intensity pulsed ultrasound (LIPUS) to accelerate fracture healing. Weight bearing was not allowed for 3 months postoperatively; thereafter, it was gradually increased in accordance with the patient’s X-rays and pain level. X-ray performed 3 months postoperatively showed delayed bone union. Although the patient did not complain of any ache in her right thigh, we recommended that she undergo surgery of the right femur for fracture prevention. However, she refused the surgery for personal reasons, and has been subsequently followed up carefully for evidence of fracture and bone metastasis recurrence.

Six months after surgery, her serum level of TRACP-5b was 338 mU/dL and intact P1NP was 42.8 μg/L, which indicated that both markers of bone resorption and formation had increased to the normal range. A dual-energy X-ray absorptiometry scan was performed 1 year after the operation. The bone mineral density T-scores at the L2-4 spine and right femoral neck were -1.1 and -0.5, respectively.

**Discussion**

In the past decade, AFFs have emerged as a potential complication of BP therapy. More recently, a few cases have been reported with the
use of denosumab; however, all of these cases were associated with denosumab therapy for osteoporosis, for which a lower dose is used than with therapy for bone metastasis [2-7]. To our knowledge, this is the first report in the English literature describing an AFF that occurred during denosumab therapy for bone metastasis.

AFFs were defined by a task force of the American Society for Bone and Mineral Research in 2000, and has been recently updated [1]. The diagnostic criteria for AFFs comprise major and minor features [1]. The major features required to designate a fracture as atypical include: (1) non-comminuted or minimally comminuted fractures; (2) sustained with minimal or no trauma; (3) the fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur; (4) complete fractures extend through both cortices and may be associated with a medial spike, or incomplete fractures involve only the lateral cortex; and (5) localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site. Our patient met all the major and several of the minor features in the updated definition.

At present, we can use BPs and denosumab as bone-modifying agents targeting osteoclasts in the treatment of malignant bone diseases. Both drugs have been approved in Japan for the prevention of skeletal-related events in patients with multiple myeloma or bone metastases from solid tumors. ZOL is a BP that is one of the strongest inhibitors of farnesyl pyrophosphate synthase synthesis [8], with the potential to induce cancer cell apoptosis as well as osteoclast apoptosis [9]. Thus, ZOL has been reported to suppress not only bone metastasis, but also liver and lung metastases because of its synergistic effect with carcinostatic agents [10,11]. Denosumab is a human monoclonal antibody that works as an inhibitor of the receptor activator of glycoprotein nuclear factor-KB ligand (RANKL). The receptor activator of nuclear factor kappa B (RANK) is expressed on osteoclasts, and when RANKL is bound with RANK, osteoclast formation is promoted, hence increasing bone resorption [12]. Denosumab is an immunoglobulin G2 monoclonal antibody that binds with RANKL, preventing it from binding to RANK, thereby decreasing osteoclast activity and helping to modulate bone remodeling [12]. For the treatment of osteoporosis, 60 mg of denosumab is given subcutaneously every 6 months (low dose), and for bone metastasis, 120 mg every 4 weeks (high dose). Several studies have shown that denosumab is more effective than ZOL in the treatment of bone metastasis from breast cancer [13] and prostate cancer [14]. Furthermore, the limitations and adverse effects associated with ZOL, such as renal toxicity and acute-phase reactions, do not apply to denosumab.

The pathophysiology of AFFs is poorly understood and is thought to be related to oversuppression of bone turnover and failure to heal fatigue damage or microcracks, resulting in an insufficiency fracture [1]. Indeed, our patient showed suppression of bone turnover below the normal range for premenopausal women. On the other hand, cancer patients require larger and more frequent doses of denosumab than those used in osteoporosis treatment, so it might be anticipated that AFFs are more common in cancer patients. However, reports of AFFs caused by high-dose denosumab are rare, which suggests that oversuppression of bone turnover would not be a sufficient cause of AFFs. In any event, a causality between the fracture and denosumab use cannot be established in this case, and the patient’s history of ZOL use prior to denosumab could also have contributed to the occurrence of the fracture.

In the choice of treatment for AFFs, surgical fixation is generally recommended to avoid delayed union. Moreover, recent reports suggest that teriparatide may assist in AFF healing [15,16]. In this case, however, teriparatide therapy could not be adopted because it is contraindicated in Japan for patients with bone metastasis. Fortunately, our patient’s general medical condition was good enough for her to undergo general anesthesia and surgery. Furthermore, bone scintigraphy as well as histological examination of bone samples taken at surgery did not show bone metastasis. Consequently, we discontinued denosumab, although micro- to bone metastasis could not be excluded. We used eldecalcitol and LIPUS to accelerate fracture healing. In patients who have active bone metastasis or who cannot undergo surgical fixation, treatment of AFF would be more difficult.

Conclusions

Complications from fractures are often fatal in cancer patients, and AFFs are no exception. Our experience suggests that denosumab treatment for bone metastasis is a risk factor for AFFs as it is for treatment for osteoporosis. It is also important to be aware that thigh pain and subtrochanteric hot spots on bone scintigraphy could be signs of an impending fracture.

References


