



Case report

Two cases of atypical femoral fracture in cancer patients administered with bone-modifying agents

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Abstract

Objective: We report two cases of atypical femoral fracture (AFF) in patients with cancer.

Patients: Two patients, a 53-year-old woman with breast cancer and a 77-year-old man with prostate cancer, could not walk after being injured in a fall. They used bone-modifying agents (BMA) for the prevention of bone metastasis for three and four years, respectively.

Results: Intramedullary nails were placed to fix the femoral fractures in each patient. Neither of them had pathological metastatic femoral fractures based on fracture site specimens; however, severe suppression of bone turnover at the fracture site was suspected. Both patients could ambulate with a T-cane and were free of hip pain after surgery. Radiographs showed no callus formation at the fracture site.

Conclusion: Based on the two cases of AFF in patients with cancer related to BMA use, we should consider that the incidence of AFF may be associated with long-term BMA use.

Key words: atypical femoral fracture, bone-modifying agent, cancer patients, bone metastasis

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Introduction

Recently, an association between atypical femoral fracture (AFF) and bone-modifying agents (BMA), such as bisphosphonates and denosumab, has been established. These agents are used for the treatment of osteoporosis, and as the life expectancy of patients with cancer has increased, the incidence of AFF with long-term use of BMA is expected to increase¹⁾. We report two cases of AFF in patients with cancer who received long-term BMA therapy.

This case report was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from the patients for publication of this case report and any accompanying images.

Case presentation

Case 1

A 53-year-old woman, who weighed 68 kg and was 168 cm tall, was treated with total surgical resection of invasive ductal carcinoma of the breast in December 2001. Immediately after the cancer surgery, she was treated with tamoxifen for three years and eight months before discontinuing the therapy because of liver dysfunction. In September 2009, she had lung metastasis and bone metastatic disease (thoracic and lumbar vertebrae) detected on bone scan, and she was treated with monthly intravenous (IV) zoledronate for three years. She received 41 doses of 4 mg IV infusion until she stopped in September 2012. The total amount of zoledronate administered to the patient was 164 mg. Next, she started treatment with denosumab, receiving a total of 27 doses of 120 mg subcutaneous injections, on a monthly basis for three years (a total dose of 3,240 mg).

In July 2015, she was unable to walk after being injured in a fall accompanied with severe pain in her right thigh. Radiography revealed a right femoral subtrochanteric transverse fracture and an area of focal thickening of the left femoral lateral cortex (Figure 1). On the fourth day after the injury, she underwent open reduction and internal fixation (ORIF) with an intramedullary nail (Figure 2). The operative time was 2 h and 42 min, and the intraoperative blood

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loss was 530 g. After surgery, left hip pain worsened. On the seventh postoperative day, the patient underwent surgery on the left hip (Figure 2). The operative time was 53 min, and intraoperative blood loss was negligible. Surgery for the right hip pain revealed no pathological findings suggestive of bone metastasis. Laboratory data showed the following parameters: bone specific alkaline phosphatase (BAP) 4.1 $\mu\text{g/L}$ (2.9–14.5), tartrate-resistant acid phosphatase 5b (TRACP-5b) 62 mU/dL (120–420), and type 1 procollagen N-terminal propeptide (P1NP) 12.3 $\mu\text{g/L}$ (17.1–64.7). Dual energy X-ray absorptiometry (DEXA) showed 154% of the young adult mean (YAM) in the left femur and 141% of YAM in the lumbar spine.



Figure 1 Subtrochanteric transverse fracture on the right side and one area of focal thickening in the left femoral lateral cortex.

She received four units of packed red blood cell transfusions during hospitalization. Gradually, her bilateral hip pain decreased. Fourteen days after the surgery, the patient could stand while holding onto a handrail. She was transferred to another hospital for breast cancer treatment. Five months after surgery, she could walk assisted with a T-cane and was free of hip pain. Radiographs showed no displacement or callus formation at the fracture site (Figure 3). After bilateral surgery, the patient continued treatment with monthly denosumab.

Case 2

A 77-year-old man, weighing 78 kg and 161 cm tall, was diagnosed with prostate cancer in September 2010. Computed tomography (CT) revealed multiple bone metastases in the spine. The patient underwent treatment with docetaxel for seven years after hormone therapy for two years. In addition, he was treated with IV injections of 4 mg monthly zoledronate for bone metastasis in the spine due to prostate cancer between January 2015 and November 2019. The total dose of zoledronate administered was 192 mg.

In May 2020, he could not walk after being injured in a fall. He had been enduring thigh pain for several months. Radiographic examination revealed a subtrochanteric transverse fracture of the left femur (Figure 4). On the fourth day after the injury, he underwent ORIF with an intramedullary nail (Figure 5). The operative time was 1 h and 45 min, and intraoperative blood loss was 300 g. The patient did not receive any perioperative blood transfusion. Surgery for the left hip pain revealed no pathological findings suggestive of bone metastasis. Laboratory data showed the following parameters: BAP, 8.6 $\mu\text{g/L}$; TRACP-5b, 219 mU/dL; and P1NP, 55.7 $\mu\text{g/L}$. DEXA showed 105% of YAM in the right



Figure 2 We performed bilateral ORIF using intramedullary nails (Synthes PFNA nails®), the right side first and the left side seven days later.



Figure 3 Five months after surgery, radiographs showed no callus formation at the fracture site and no new fracture at the left side.



Figure 4 Subtrochanteric transverse fracture on the left side with bilateral thickening of the cortex.



Figure 5 We performed ORIF with an intramedullary nail (Smith & Nephew InterTAN®).

femur and 121% of YAM in the lumbar spine.

Rehabilitation was started on postoperative day 1. On postoperative day 22, the patient was transferred to a rehabilitation hospital. Five months after surgery, the patient could walk with a T-cane, and radiographs showed no callus formation at the fracture site (Figure 6).

After AFF surgery, he received 120 mg of denosumab monthly. He died of pneumonia seven months after surgery.

Discussion

The American Society for Bone and Mineral Research defines the major clinical features of AFF as follows: 1)



Figure 6 Five months after surgery, radiographs showed only a very mild callus formation at the fracture site.

atraumatic or minimal trauma, 2) transverse or oblique fracture from the lesser trochanter to the supracondylar area, 3) a medial spike in a complete fracture or crack of only the lateral cortex in an incomplete fracture, 4) no comminution, and 5) periosteal or endosteal thickening of the lateral cortex. Minor features include cortical thickening, prodromal pain, and bilateral complete or incomplete fractures. Our patients had all the major features and several minor features of AFF²⁾.

The optimal duration of the BMA exposure was not determined. However, the risk of AFF is higher with long-term BMA exposure than with short-term exposure, according to Dell *et al.*³. Shane *et al.* reported that the risk of AFFs is 2 per 10,000 persons after two years of BMA use and 78 per 10,000 persons after eight years⁴. Schilcher *et al.* showed that the risk decreases by 70% per year after drug discontinuation⁵. In contrast, Puhaindran *et al.* reported that the incidence of AFF is not related to the doses of intravenous bisphosphonates or the duration of treatment⁶. In case 1, AFF likely developed due to the long-term use of both denosumab and zoledronate. Schilcher *et al.* showed that suppression of bone turnover by denosumab may lead to a high risk of AFF and reported a similar case of AFF with denosumab after zoledronate use⁷. In another study, AFF caused by denosumab was reported after the discontinuation of alendronate⁸. Case 2 had received intravenous zoledronate for five years, and he complained of thigh pain. Therefore, in this case, we believe that the use of both drugs was the cause of AFF. Dell *et al.* analyzed the records of a large health maintenance organization and identified 102 patients with AFFs who had been on oral bisphosphonates for a mean of five and a half years³.

Lockwood *et al.* reported that surgical treatment should be considered for incomplete fractures with thigh pain⁹. As exemplified by case 1, who had a complete fracture on the right side and an incomplete fracture on the left side, the operative time and intraoperative blood loss were lower, and the surgery was minimally invasive for the left side compared to the right side. Therefore, even if there is an incomplete fracture accompanied by prodromal thigh pain,

surgical treatment may be considered. In cases 1 and 2, we believe that one of the main causes of the delayed union is an insufficient reduction of the fracture site, and it might have been better to use LIPUS¹⁰.

We think we should choose a middle or long nail with a large diameter to prevent nonunion of the fracture site. Isehuku *et al.* reported that sufficient reaming and insertion of an intramedullary nail with the largest possible diameter can help prevent nonunion¹¹.

As in our patients, the life expectancy of patients with cancer has improved in recent years due to advances in medical care. Long-term BMA therapy is expected to prevent the pain caused by bone metastasis. Cakmak recommended radiographic evaluation of both femurs during long-term BMA treatment lasting over five years¹². However, at present, AFF is not well recognized as a complication of long-term BMA use, except in the field of orthopedics. In the future, it will be necessary to disseminate knowledge regarding AFF and, at the same time, follow patients carefully, such that surgery can be performed before a complete fracture occurs.

This study had some limitations. First, there were only two patients, one with breast cancer and one with prostate cancer. Second, we could not confirm the bone union of the fracture site because the follow-up of these cases was only short-term.

Conclusion

We encountered two cases of AFF in patients with cancer related to BMA. We should consider that the incidence of AFF may be associated with long-term BMA use.

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