

[ CASE REPORT ]

## Importance and Difficulty of Differentiating BMA-induced AFF Prodromal Symptoms from Hormonal Therapy-related Femoral Pain

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### Abstract:

We herein report a case of breast cancer in a 74-year-old woman treated with exemestane as fourth-line hormonal therapy and bone-modifying agents for long time. She suddenly developed a right femoral shaft fracture during treatment. Her femoral fracture had a beaking sign on radiogram. Given this finding, her fracture was ultimately diagnosed as atypical femoral fracture (AFF). In this case, it was difficult to recognize the difference between groin pain as a prodromal symptom of AFF and that due to an adverse reaction to hormonal therapy. Therefore, clinicians should recognize the difficulty of this differentiation and consider the situation with caution.

**Key words:** atypical femoral fracture, bone-modifying agents, breast cancer, hormone therapy

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### Introduction

Atypical femoral fracture (AFF) is a fracture of the distal lesser trochanter to the shaft of the femur caused by a slight external force. It has been reported that AFF occurs in osteoporotic patients on long-term treatment with bone-modifying agents (BMAs) (1, 2). BMAs are also widely used in cancer patients to prevent skeletal-related events due to bone metastasis, such as pathological fracture and spinal cord paralysis (3, 4). AFF begins with a dull or aching pain from the groin to the femur as a prodromal symptom in 70% of cases (5).

In the present case, the patient's bilateral groin pain was initially attributed to an adverse reaction to hormonal therapy for hormone receptor-positive advanced breast cancer with bone metastasis. However, it was later identified as a prodromal symptom of AFF after the onset of AFF.

### Case Report

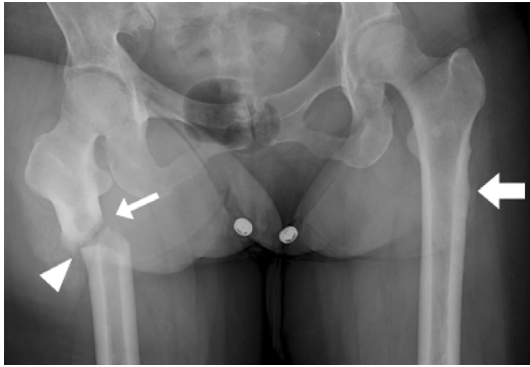
This case was a 74-year-old woman. Her medical history included surgery for right breast cancer. When she visited us with a chief complaint of cough, multiple pulmonary nodules were noted. A histopathological examination of the nodules led to a diagnosis of recurrent breast cancer. The breast cancer was strongly estrogen receptor- and progesterone receptor-positive and human epidermal receptor (HER)2-negative. A detailed examination revealed multiple bone metastases in the thoracic spine and bilateral ribs but not in either femur. Her performance status was 1.

As first-line treatment, hormonal therapy with letrozole was started in combination with the bone-modifying agent zoledronic acid for multiple bone metastases. Then, after first-, second-, and third-line hormonal therapies, exemestane was used as fourth-line treatment. During treatment with ex-

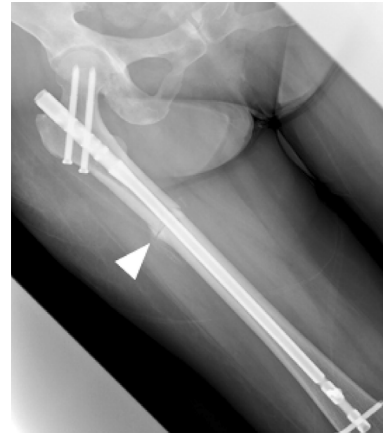
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**Figure 1.** This fracture shows the complete AFF running from one side to the other of the bone cortex of the right femoral shaft, transversely, and virtually non-comminuted (thin arrow). A beaking sign is noted at the site of complete AFF (arrowhead). The lateral bone cortex of the left femoral subtrochanter is thick with a spike shape, also presenting with a beaking sign (thick arrow).



**Figure 2.** A simple X-ray image after intramedullary nailing. A beaking sign is noted at the site of complete AFF (arrowhead).

emestane, grade 2 limb joint pain occurred as persistent toxicity, and concurrent bilateral groin pain was also considered to be due to pain in the hip as an adverse reaction to hormonal therapy.

Treatment with zoledronic acid was continued every three weeks for three years; however, given that denosumab significantly delayed skeletal-related events compared with zoledronic acid, the first BMA was replaced with denosumab at the start of second-line hormonal therapy, and this second BMA was administered every four weeks for another three years.

After BMA therapy with zoledronic acid and denosumab for a total of six consecutive years, the patient suddenly suffered a right femoral shaft fracture while walking. A radiogram of the right femur revealed transverse fracture (Fig. 1: thin arrow). Given that the fracture was caused by a slight external energy force, the fracture line was transverse, the fracture was not comminuted, and localized thickening-called a “beaking sign”-was noted in the outer periosteum of the affected lateral bone cortex (Figs. 1 and 2: arrowhead). Given these findings, we ultimately diagnosed the fracture as AFF.

Intramedullary nailing was performed immediately after the diagnosis (Fig. 2). A histopathological examination of the affected bone obtained during surgery was performed as a detailed examination to determine the cause of the fracture, resulting in no evidence of breast cancer metastasis. In parallel, bone mineral density testing did not indicate osteoporosis. In this case, pain was also noted in the contralateral left groin, and a radiogram revealed a beaking sign in the left femoral subtrochanter as well (Fig. 1: thick arrow). Conservative treatment was selected for the contralateral left femur. While treatment with exemestane was continued after intramedullary nailing, pain in the right hip did not occur. At present, the patient is not receiving denosumab.

## Discussion

In our case, it was difficult to differentiate between groin pain as a prodromal symptom of AFF and that as an adverse reaction to hormonal therapy for breast cancer. Since this differentiation can be difficult, caution should be practiced when encountering similar cases.

AFF is suggested to be associated with BMA-induced excessive suppression of bone turnover, called “severely suppressed bone turnover” (SSBT) (5), and the impaired repair and accumulation of microdamage may result in a fracture (6). The disease definition of AFF was established by the task force of the American Society for Bone and Mineral Research (ASBMR) (7). The most important feature to look for when diagnosing AFF is that the fracture affects only the area from the distal lesser trochanter to the supracondyloid of the femur. Other major features of AFF as defined by the ASBMR are fracture caused by a slight external energy force, transverse fracture line, non-comminuted fracture, complete fracture running from one side to the other side of the bone cortex, and localized thickening in the outer periosteum of the affected lateral bone cortex (beaking sign); the present case met all of these criteria. Among these criteria, beaking sign should be recognized as the only prodromal sign of AFF (7).

Ota et al. reported that AFF occurred in 8 of 64 limbs (12.5%) in breast cancer patients with bone metastasis receiving bisphosphonate or denosumab, showing that AFF is an adverse reaction to BMAs that should be evaluated with caution (8). Chang et al. reported that the median duration of BMA therapy was 5.9 years (range, 5.7-7.3 years) in breast cancer patients with bone metastasis and multiple myeloma patients who had AFF (9). Dell et al. investigated 128 patients who had AFF during bisphosphonate therapy and reported that the incidence rate of AFF was 1.78 cases/100,000 person-years after 0.1-0.9 years of treatment and 113.1 cases/100,000 person-years after 8.0-9.0 years of

treatment, showing that a longer duration of BMA therapy resulted in a higher incidence rate of AFF (10). Our patient received BMA therapy with zoledronic acid and denosumab for a total of six consecutive years and may therefore have had a high risk of AFF.

Shane et al. reported that AFF began with dull or aching pain in the groin as a prodromal symptom in 70% of patients with incomplete AFF, which precedes complete AFF (7). Kharazmi et al. reported that the prodromal symptom of AFF persisted for several months to several years (11). Furthermore, Banffy et al. reported that early internal fixation surgery for incomplete AFF prior to complete AFF reduced the duration of hospital stay and patient financial burden (12), and Shane et al. pointed out the importance of detecting the prodromal symptom as a characteristic finding to prevent AFF (7).

However, it was reported that limb joint pain occurred in 13-26% of patients receiving hormonal therapy for breast cancer (13-15). In our case, multiple joint pain involving the wrist and elbow occurred as an adverse reaction to hormonal therapy, and right groin pain was therefore also attributed to hormonal therapy-induced pain in the hip. After intramedullary nailing for AFF, however, the right groin pain resolved under the same hormonal therapy regimen as the preoperative hormonal therapy regimen, indicating that the right groin pain was a prodromal symptom of AFF.

In conclusion, clinicians should recognize the difficulty of differentiating groin pain as a prodromal symptom of AFF from that as an adverse reaction to hormonal therapy before the onset of AFF. Confirmation of the beaking sign by X-ray may aid in the differential diagnosis of such cases.

**The authors state that they have no Conflict of Interest (COI).**

## References

1. Feldstein AC, Black D, Perrin N, et al. Incidence and demography of femur fractures with and without atypical features. *J Bone Miner Res* **27**: 977-986, 2012.
2. Meier RP, Perneger TV, Stern R, Rizzoli R, Peter RE. Increasing occurrence of atypical femoral fractures associated with bisphosphonate use. *Arch Intern Med* **172**: 930-936, 2012.
3. Kohno N, Aogi K, Minami H, et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol* **23**: 3314-3321, 2005.
4. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* **28**: 5132-5139, 2010.
5. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover; a potential complication of alendronate therapy. *J Clin Endocrinol Metab* **90**: 1294-1301, 2005.
6. Kondo N, Yoda T. Morphological analysis of bone dynamics and metabolic bone disease. Does bisphosphonate treatment cause severely suppressed bone turnover (SSBT)? *Clin Calcium* **21**: 583-587, 2011.
7. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* **29**: 1-23, 2014.
8. Ota S, Inoue R, Shiozaki T, et al. Atypical femoral fracture after receiving antiresorptive drugs in breast cancer patients with bone metastasis. *Breast Cancer* **24**: 601-607, 2017.
9. Chang ST, Tenforde AS, Grimsrud CD, et al. Atypical femur fractures among breast cancer and multiple myeloma patients receiving intravenous bisphosphonate therapy. *Bone* **51**: 524-527, 2012.
10. Dell RM, Adams AL, Greene DF, et al. Incidence of atypical non-traumatic diaphyseal fracture of the femur. *J Bone Miner Res* **27**: 2544-2550, 2012.
11. Kharazmi M, Michaëlsson K, Hallberg P. Prodromal symptoms in patients with bisphosphonate-associated atypical fractures of the femur. *J Bone Miner Metab* **33**: 516-522, 2015.
12. Banffy MB, Vrahas MS, Ready JE, Abraham JA. Nonoperative versus prophylactic treatment of bisphosphonate-associated femoral stress fractures. *Clin Orthop Relat Res* **469**: 2028-2034, 2011.
13. Bonnetterre J, Buzdar A, Nabholz JM, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* **92**: 2247-2258, 2011.
14. Howell A, Robertson JF, Abram P, et al. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol* **22**: 1605-1613, 2004.
15. Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *Lancet* **388**: 2997-3005, 2016.

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