CASE REPORT

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SUBTROCHANTERIC FRACTURE IN A PATIENT RECEIVING ZOLEDRONIC ACID THERAPY FOR METASTATIC BREAST CANCER

YASUZUMI KISHIMOTO[1], TOSHIKI IWASE[1], ATSUSHI KOYAMA[1], TETSUO MASUI[1], GO YOSHIDA[1], HIDEO MATSUO[1] and NAOKI ISHIGURO[2]

[1]*Department of Orthopedic Surgery, Hamamatsu Medical Center, 328 Tomitsuka-cho, Hamamatsu, Shizuoka 432-8580, Japan*
[2]*Department of Orthopedic Surgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showaku, Nagoya 466-8550, Japan*

ABSTRACT

A 61-year-old woman presented with acute pain of the right thigh after falling on a public street. She had been diagnosed with metastatic breast cancer and bisphosphonate therapy along with zoledronic acid. Radiographs demonstrated transverse subtrochanteric femoral fracture with thickening of the lateral cortex and spike of the medial cortex at the site of fracture. The contralateral femur showed thickening of the lateral cortex at the same site. This type of stress fracture is related to severe suppression of bone turnover (SSBT) under bisphosphonate therapy. Our patient had been receiving zoledronic acid therapy for 3.6 years, and the radiographic findings were typical of stress fracture associated with bisphosphonate. Therefore, the facture in our patient was considered related to SSBT under zoledronic acid therapy. Zoledronic acid is administered to patients with osteoporosis or complications due to cancer such as hypercalcemia of malignancy. Recently stress fractures associated with zoledronic acid therapy for osteoporosis have attracted attention. However, there are few reports of fracture associated with zoledronic acid therapy for cancer. Doses of zoledronic acid recommended for cancer patients are much greater than those for patients with osteoporosis. Clinicians treating such cancer patients need to cautiously manage stress fractures as a complication of zoledronic acid therapy.

Key Words: Bisphosphonate, Zoledronic acid, Breast cancer, SSBT, Femoral fracture

INTRODUCTION

Zoledronic acid, a third-generation bisphosphonate, is widely administered to patients with osteoporosis or complications due to cancer such as hypercalcemia of malignancy. Recently stress fractures associated with zoledronic acid therapy for osteoporosis have attracted attention. However, there are few reports of fracture associated with zoledronic acid therapy for cancer. Herein we report a patient with subtrochanteric fracture while receiving zoledronic acid therapy for metastatic breast cancer.

Corresponding Author: Yasuzumi Kishimoto
Department of Orthopedic Surgery, Hamamatsu Medical Center, 328 Tomitsuka-cho, Hamamatsu, Shizuoka 432-8580, Japan
Telephone: +81-53-453-7111, Fax: +81-53-451-2768, Email address: halfgodhasgone@msn.com

CASE REPORT

A 61-year-old woman presented with acute pain of the right thigh after falling on a public street. She had been diagnosed with metastatic breast cancer five years earlier and then started on chemotherapy with capecitabine and hormonotherapy with medroxyprogesterone for cancer. She was also started on bisphosphonate therapy with incadronate (250mg/2 weeks) for hypercalcemia due to malignancy. After three months of incadronate administration, the regimen was changed to pamidronate (90mg/month), and then 3.6 years before the fracture, the regimen was changed from pamidronate to zoledronic acid (4mg/month).

Radiographs demonstrated transverse subtrochanteric femoral fracture with thickening of the lateral cortex and spike of the medial cortex at the site of fracture (Figure 1A). The contralateral femur showed thickening of the lateral cortex at the same site (Figure 1B). Findings on magnetic resonance imaging before surgery demonstrated a tumorous lesion of the right trochanter, but did not involve the fracture site. The tumorous lesion showed a low intensity on T1WI and iso intensity on T2WI (Figure 2).

The patient underwent osteosynthesis for subtrochanteric femoral fracture with a long gamma nail (Stryker Osteosynthesis, Kiel, Germany) and radiotherapy for tumorous lesion of the right femur. One month postoperatively, zoledronic acid therapy was discontinued. Five months later, we found slight callus formation as a sign of fracture healing at the medial femoral cortex.

DISCUSSION

Zoledronic acid is a third-generation bisphosphonate and has 10,000- to 100,000-fold greater antiresorption potency than the previous generations of agents, such as etidronate[1]. In 2002, the US FOOD and Drug Administration approved an expanded indication for zoledronic acid that included its use in patients with metastatic breast cancer and myeloma. American Society of Clinical Oncology (ASCO) has also recommended zoledronic acid for breast cancer patients[2]. In many other countries, zoledronic acid is administered to cancer patients with complications such as hypercalcemia of malignancy.

Bisphosphonates are frequently administered for osteoporosis as well as for complications of cancers. However, stress fractures related to severe suppression of bone turnover (SSBT) under bisphosphonate therapy have attracted attention recently[3]. There were previous cases of atypical femoral fractures associated with alendronate therapy[4] or risedronate therapy[5]. Concerning zoledronic acid therapy for osteoporosis, there was a report in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Pivotal Fracture Trial (HORIZON-PFT)[6,7]. However, there have been few reports of fracture associated with zoledronic acid therapy for complications of cancer. Only a few reports have described subtrochanteric fractures in myeloma patients under pamidronate and zoledronic acid therapy[8].

Concerning stress fractures under bisphosphonate therapy, Kwek et al. found typical fracture findings in all of the patients they observed[9]: (a) cortical thickening in the lateral subtrochanteric region; (b) transverse fracture; and (c) medial cortical spike. They also found lateral cortical stress reactions on the subtrochanteric region of the contralateral femur in some patients. Lenart et al. defined a positive X-ray pattern in patients on long-term bisphosphonate administration with cortical thickening and a beak in the cortex of the subtrochanteric/shaft fracture[10]. Radiographs of our patient showed both the typical fracture findings described by Kwek et al. and the positive X-ray patterns defined by Lenart et al.

We demonstrated magnetic resonance imaging before surgery in order to determine whether

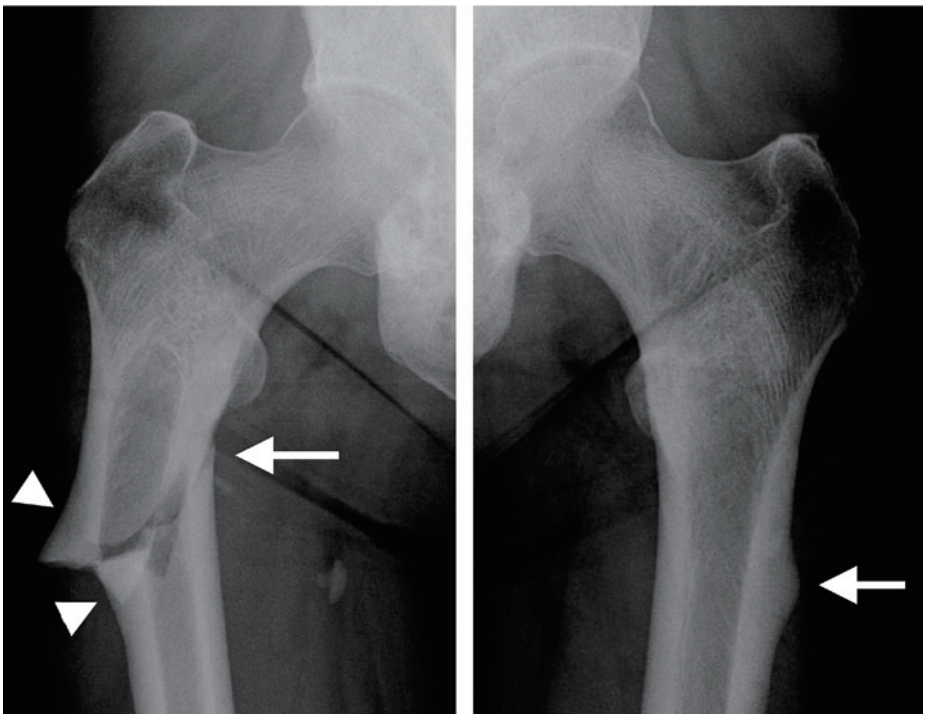

Figure 1 A: Subtrochanteric transverse fracture. Lateral cortical thickening (arrow) and medial spike at the edge of the cortex (arrow head) were seen.
B: Lateral cortical stress reactions in the subtrochanteric region of the contralateral femur.

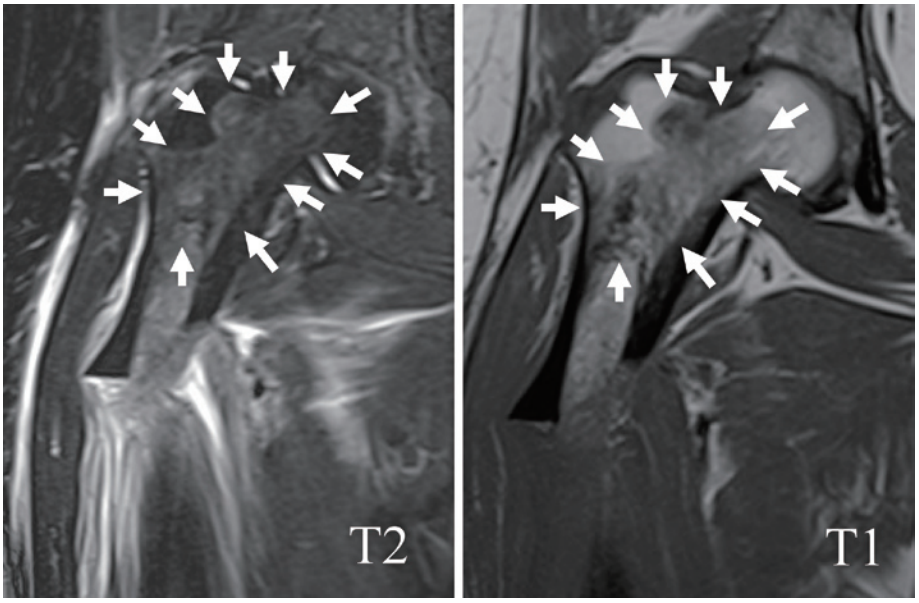

Figure 2 Magnetic resonance imaging before surgery demonstrated a tumor lesion at the trochanter (arrows). The lesion was demonstrated a low intensity on T1WI and iso intensity on T2WI.

this was a pathological fracture due to cancer, but there was no sign of metastatic breast cancer at the fracture site.

Odvina et al. reported histological findings of stress fracture related to SSBT under bisphosphonate therapy for osteoporosis[11]. These findings were suppression of bone formation with a low osteoblastic surface or diminished matrix synthesis with absence of double-tetracycline labeling. In our case, there was no histomorphometric analysis because we did not perform a bone biopsy at the fracture site.

Our patient was under zoledronic acid therapy for 3.6 years, and the radiographic findings were typical of stress fracture associated with bisphosphonate. Therefore, the facture in our patient was related to SSBT under zoledronic acid therapy. Because our patient experienced thigh pain only after the fall, we thought the fracture occurred at the pathological lesion, which had become weakened by SSBT.

Sayed-Noor and Sjödén described a patient with a subtrochanteric fatigue fracture after surgery for contralateral subtrochanteric fatigue fracture related to the bisphosphonate therapy[12]. Radiographic findings in our patient showed thickening of the cortex at the contralateral femur. Therefore, the risk of contralateral femoral fracture was increasing and further follow-up should be performed.

Hillner et al. recommended that bisphosphonate should be continued until evidence of substantial decline in a patient's general performance[2]. Odvina et al. reported that fracture healing was absent or incomplete in patients who continued alendronate therapy after onset of fractures[11]. It is true that this therapy is needed for patients with complications of cancers, but bisphosphonate therapy should be stopped after the onset of fractures associated with this treatment.

Park et al. reported prescribing bisphosphonate for more than five years to older women who showed increased risk of subtrochanteric or femur shaft fracture[13]. However, Black et al. reported the risk associated with bisphosphonate including zoledronic acid was not increased significantly in HORIZON-PFT[6]. In this trial, patients received 5mg zoledronic acid once a year. However, cancer patients are recommended to receive 4mg zoledronic acid once every three or four weeks. Therefore they receive significantly higher doses of zoledronic acid than patients with osteoporosis. We emphasize that clinicians treating such cancer patients need to cautiously manage stress fractures as a complication of zoledronic acid therapy.

CONCLUSION

We present a patient with subtrochanteric fracture after 3.6 years of zoledronic acid therapy for metastatic breast cancer. The fracture was thought to be associated with severe suppression of bone turnover due to zoledronic acid therapy.

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