CASE REPORT
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Drug-induced Hyperprolactinemia Results in Atypical Atypical Fracture

Ingyu Lee, MD, Dong-Wook Son, MD, PhD, Jun Hyoung Park, MD, Jai Hyung Park, MD, PhD

Department of Orthopaedic Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

We report a case of bilateral femur fracture which may have resulted in part from long-term administration of antipsychotic agents. A 43-year-old female patient with pain in both thighs visited our clinic. We conducted X-ray and magnetic resonance imaging (MRI) examinations which revealed bilateral femur fractures. The right proximal femur had a complete fracture, and the left proximal femur had an incomplete fracture, both of which were in the subtrochanteric area. The patient was treated by intramedullary nailing in the right femur. Laboratory analysis showed hyperprolactinemia and hypogonadism. Bone mineral density analysis showed osteoporosis. Antipsychotic drug-induced hyperprolactinemia is a well-known phenomenon. Despite concerns about hyperprolactinemia induced osteoporotic fracture in patients treated with only prolactin-elevating medications, the issue has not been extensively studied. If hyperprolactinemia patients suffer from uncontrolled pain, we recommend MRI examination as surgeons should be aware of the possibility of osteoporotic fracture induced by hyperprolactinemia.

Key Words: Hyperprolactinemia, Osteoporotic fracture, Antipsychotic agents, Prolactinoma

Hyperprolactinemia is a significant cause of female hypogonadism and premature bone loss[1]. Additionally, women with chronic hyperprolactinemia exhibit other features of prolonged estrogen deficiency such as vaginal dryness, dyspareunia, and decreased bone mineral density (BMD) with increased risk of osteoporotic fractures[2,3]. The most common cause of pathologic hyperprolactinemia in women is pituitary prolactinoma. The second most common cause is antipsychotics medications, which block D2 receptors in the pituitary tuberoinfundibular pathway[4,5].

Hyperprolactinemia interferes with the hypothalamic-pituitary-ovarian axis at both the central and ovarian levels. The main effect is inhibition of pulsatile secretion of hypothalamic gonadotropin-releasing hormone (GnRH), which is mediated by increased endogenous opioid activity[6]. Gonadal insufficiency is secondary to impaired secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Hyperprolactinemia is associated with decreased BMD due to significant bone loss, which is attributed to hypoestrogenemia. Hyperprolactinemia induced hypogonadism results in either failure to achieve adequate peak bone mass or loss of bone mass to an extent that is sufficient to cause osteoporosis[7,8]. Estrogens play a key role in skeletal homeostasis, regulating bone remodeling, and maintaining the structural integrity of bone. Alterations in

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Address reprint request to
Jai Hyung Park, MD, PhD
(https://orcid.org/0000-0001-9735-4291)
Department of Orthopaedic Surgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea
TEL: +82-2-2001-2168 FAX: +82-2-2001-2176
E-mail: wonnypia@hanmail.net

the ovarian endocrine system in premenopausal women has profound negative effects on BMD, leading to increased rates of bone loss, mainly at trabecular sites.

This article describes a case of bilateral subtrochanteric atypical atypical fracture that occurred without trauma due to hyperprolactinemia induced by antipsychotic drug use.

CASE REPORT

Informed consent was obtained from the patient included in the study.

A 43-year-old female patient with pain in both thighs visited our clinic. She suffered from radiating pain in both legs in the area from the hip joint to the knee joint. She had been undergoing neuropsychiatric treatment for schizophrenia with persecutory delusions and auditory hallucinations. She had been taking medication to treat schizophrenia for 7 years, including ziprasidone, clonazepam, propranolol, and lorazepam. Her drug compliance was good, and she had been in a stable mood. She had no surgical history. She had a history of inadequate exercise and social alcohol use but did not smoke. She had never taken anti-resorptive drugs, had no history of steroids, and had no family history of fractures. She was obese with a height of 159 cm, weight 65 kg, and body mass index (BMI) of 25.71 kg/m^2, but had no metabolic diseases and there was no evidence of cardiovascular disease. She suffered amenorrhea but not galactorrhea or breast tenderness.

The first X-ray taken after pain onset showed a slightly increased haziness compared to an X-ray taken three years prior, but there was no evidence of fracture and the patient was able to walk (Fig. 1A). Thus, we recommended conservative treatment. One month later, she complained of further aggravated pain, so X-ray (Fig. 1B) and computed tomography (CT) scans were performed at that time. Both X-ray and CT scans showed a fracture in the right proximal femur, including a suspicious focal benign bone lesion in the subtrochanteric area. BMD and magnetic resonance imaging (MRI) were required as the patient was young, and the fracture lines were atypical. A sequence of MRI T2-weighted images showed a right proximal femur fracture with perilesional soft tissue injury, suspicious focal bone lesions in the bilateral subtrochanteric areas, and an incomplete left proximal femur fracture in the same subtrochanteric area (Fig. 2A, B). BMD measurement showed osteoporosis, a femoral neck T-score of –2.6 with a Z-score of –1.6.

The patient had experienced no trauma that would explain the bilateral femur fractures at such a young age; therefore, bone scans were examined to identify other possible causes of fracture. A triple-phase bone scan using 25 mci of 99 mTc-DPD was done which indicated increased vascularity and bony uptake found only in the region of both femurs. A laboratory test was also conducted based on the patient's history having amenorrhea.

The test confirmed hyperprolactinemia. In women, the normal basal level of prolactin is 20 ng/mL whereas the patient's level was 246 ng/mL. We also checked the levels of other hormones, and results were as follows: basal LH, 6.30 mIU/mL; basal thyroid-stimulating hormone, 4.98 μlU/mL; basal FSH, 8.14 mIU/mL; basal cortisol, 6.75 μg/dL; basal adrenocorticotropic hormone, 22.10 pg/mL; estradiol, 43.109 pg/mL; testosterone, <0.137 ng/mL; and osteocalcin, 8.26 ng/mL. Other laboratory measurements and biomechanical tests were within the normal range.

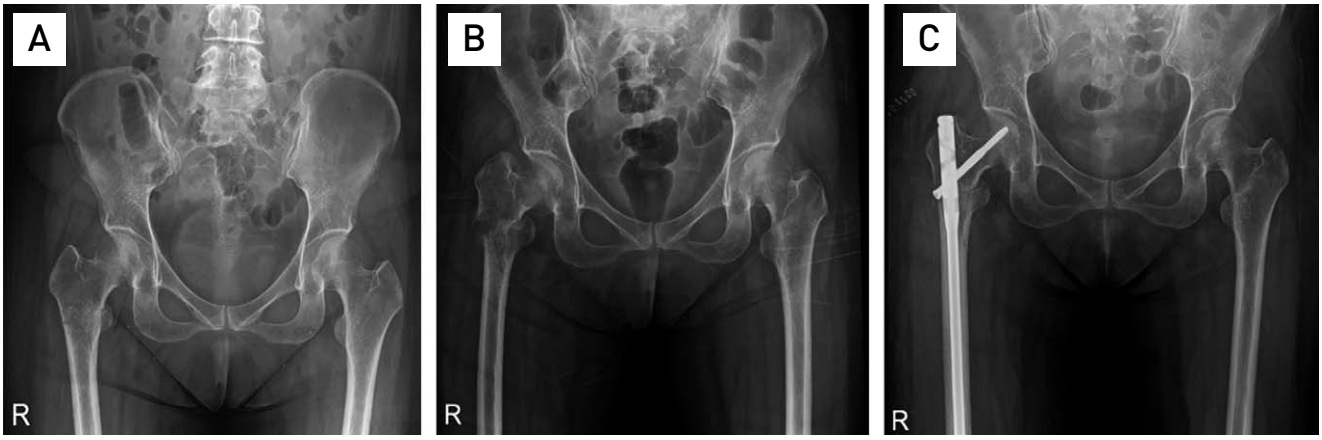

Fig. 1. (**A**) The first X-ray of the hips (anteroposterior [AP] view) was taken when the patient began suffering from pain. (**B**) One month later, a hip X-ray (AP view) demonstrated proximal femur fractures at the level of the subtrochanteric areas. (**C**) Postoperative X-ray of the hip (AP view).

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Prolactin secretion in the pituitary is normally suppressed by dopamine. Drugs that block the effects of dopamine in the pituitary or deplete dopamine stores in the brain may cause the pituitary to secrete prolactin. The patient had been taking medication to treat schizophrenia for an extended period, thus, we concluded that hyperprolactinemia was likely caused by antipsychotic medications. Thereafter, the patient was prescribed aripiprazole, paliperidone, clonazepam, and alprazolam. Ziprasidone, etizolam, and lorazepam were discontinued under the advice of a psychiatrist.

An MRI of the pituitary is indicated for patients with hyperprolactinemia where the etiology is not clearly due to medication. We believed that there was another cause of hyperprolactinemia such as a pituitary prolactinoma. Thus, we checked the sella on MRI, which showed no evidence of a definite focal lesion in the pituitary gland (Fig. 3).

The patient was treated by close reduction and intramedullary nailing in the right femur and conservative treatment with teriparatide for the insufficiency fracture of the left femur (Fig. 1C). The histopathological findings at the fracture site revealed some atypical hyaline cartilage, irregular woven bones, and fibrous tissue with granulation tissue formation (Fig. 4). After one month, the patient returned to her normal activities with a full range of motion in the hips. No perioperative complications occurred.

Seven months later, her basal prolactin level had decreased to 137 ng/mL and her estradiol levels increased to 95.00 pg/mL. Additionally, we confirmed bone union of the right femur fracture on X-ray, and an MRI was performed to evaluate the insufficiency fracture of the left femur. An MRI T2-weighted sequence of the pelvic area showed the incomplete fracture of the left proximal femur with healing of the perilesional soft tissue injury and disappearance of the signal change in the bone marrow and lesser trochanter of the proximal femur (Fig. 2C, D).

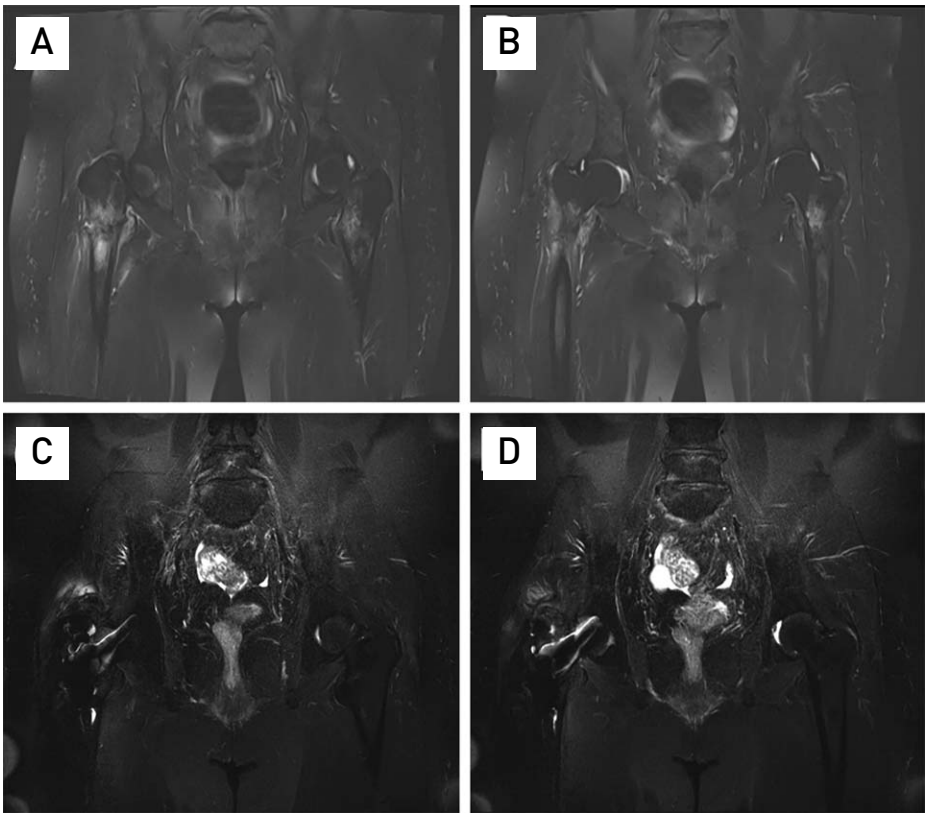

Fig. 2. (**A**, **B**) A magnetic resonance imaging (MRI) T2-weighted sequence of the pelvic area showed a right proximal femur fracture with a perilesional soft tissue injury, a suspicious focal bone lesion in the subtrochanteric area, and an incomplete fracture in the left proximal femur in the same subtrochanteric area. (**C**, **D**) Seven months later, X-ray and MRI were performed to evaluate the insufficiency fracture of the left femur. An MRI T2-weighted sequence of the pelvic area showed the incomplete fracture in the left proximal femur with healing of the perilesional soft tissue injury and disappearance of the signal change in the bone marrow and lesser trochanter of the proximal femur.

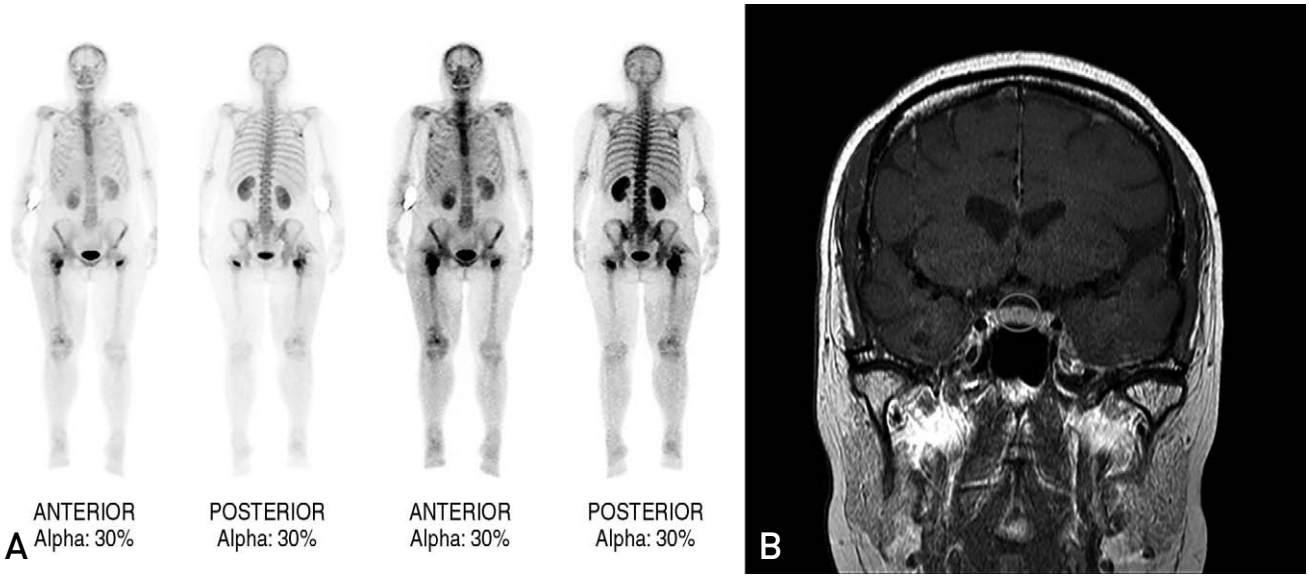

Fig. 3. (**A**) Triple-phase bone scan using 25 mci of 99 mTc-DPD showed increased vascularity and bony uptake only in the region of both the right and left femur. (**B**) The sella magnetic resonance imaging showed no evidence of definite focal lesion in the pituitary gland (circle).

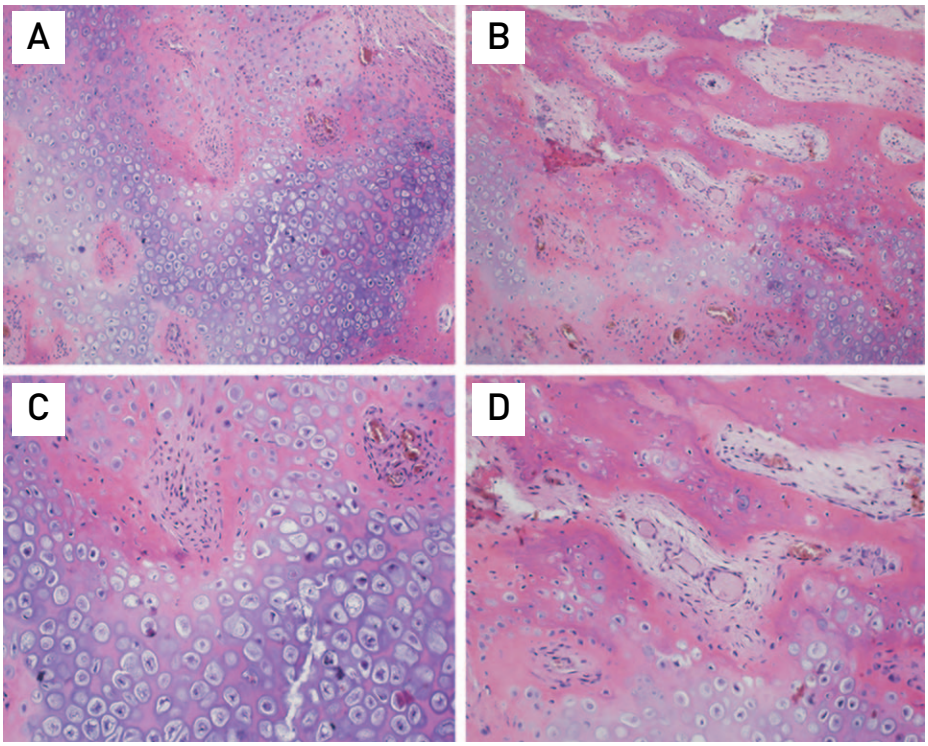

Fig. 4. Histopathology findings of the fracture site revealed some atypical hyaline cartilage, irregular woven bones, and fibrous tissue with granulation tissue formations (H&E stain, ×100: **A**, **B**, ×200: **C**, **D**).

DISCUSSION

Some pharmacological treatments indicated for schizophrenia have side effects that may further contribute to the risk of physical comorbidities. Among these side effects, the elevation of prolactin secondary to antipsychotic treatment is of growing concern due to its reproductive and sexual effects and its involvement in other medical complica-

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tions such as osteoporosis[9].

Several drugs that block the effects of dopamine in the pituitary or deplete dopamine stores in the brain may cause the pituitary to secrete prolactin. These drugs include the typical antipsychotics as well as the atypical antipsychotics[6]. The sleep drug ramelteon and a benzodiazepine analog can also increase the risk of hyperprolactinemia. In this case, the patient had been taking medication for schizophrenia including ziprasidone, clonazepam, propranolol, etizolam, and lorazepam.

According to Vartej et al.[10], the relative risk for developing osteoporosis in women with a prolactinoma is 4.5, indicating that hyperprolactinemia in women is a major risk factor for osteoporosis.

The underlying pathophysiology of atypical fractures in the subtrochanteric and diaphyseal regions of the femur is related to the inhibition of bone formation and resorption, resulting in a decrease in bone quality. However, the patient did not take anti-resorptive agents and had no evidence of congenital bone diseases with low bone turnover. The patient in this case had hyperprolactinemia associated with the use of antipsychotics. Hyperprolactinemia inhibits the secretion of GnRH from the hypothalamus, which in turn inhibits the release of FSH and LH from the pituitary gland and results in diminished gonadal sex hormone production (hypogonadism). Although hypogonadism is the main cause of bone loss in hyperprolactinemia, recent studies indicate other potential hormonal mechanisms that interfere with skeletal homeostasis, such as elevated parathyroid hormone-related peptide levels in the plasma of women with prolactinoma[11], or reduced calcitonin plasma levels in hyperprolactinemic women[12].

It is difficult to consider the mechanism of bilateral subtrochanteric fracture in this patient as the same mechanism as an atypical fracture. A subtrochanteric fracture occurs when a large load-bearing force is applied to the peritrochanteric region, where the femur medial cortex receives the compressive force, and the lateral cortex receives the tensile force. It is assumed that this patient had a large load-bearing force due to obesity; however, an atypical atypical subtrochanteric fracture may have occurred due to osteoporosis and deterioration of bone quality with long-term use of antipsychotic drugs. Additionally, since this patient had relatively strong gluteal and thigh muscle compared to bone quality, it is estimated that strong abduction force, external rotation force, and flexion force were applied to the proximal fragment and strong adduction force was applied to the distal fragment. Therefore, it can be hypothesized that bone loss and destruction of skeletal homeostasis associated with hyperprolactinemia may have caused atypical fractures in an obese patient with an active lifestyle. Therefore, we recommend that patients with drug-induced hyperprolactinemia, especially those with obesity and are physically active, should be checked bone quality with regular BMD. Furthermore, if the patients who meet these criteria complain of pain that occurs without trauma, it is recommended to consider the possibility of atypical atypical fracture and conduct further evaluation.

The molecular basis of the effect of prolactin on bone cells was not established until recently when the presence of prolactin receptors on human bone cells was discovered. These observations increase the likelihood that prolactin exerts biological effects on bone, pointing the way for future studies.

Teriparatide, a recombinant form of parathyroid hormone, enhances bone healing in patients with delayed healing or non-union. According to Saleh et al.[13], incomplete fractures without radiolucent lines are responsive to teriparatide alone. The results from a study by Im and Lee[14] shows that teriparatide is currently a viable treatment option to enhance fracture healing in atypical fracture. Likewise, in the current case, conservative treatment with teriparatide was performed for the left subtrochanteric insufficiency fracture, and good results were confirmed.

Although this case report is limited by the absence of a control group, it is clinically meaningful in that fractures were induced by hyperprolactinemia with a combined cause of microprolactinoma and use of antipsychotic drugs. Understanding the causes and correcting the patient's prolactin level was difficult in this case due to a variety of factors. However, recovery for the patient was possible due to communication between physicians, psychiatrists, and orthopedic surgeons who shared their opinions. Further prospective study of this issue is needed, including more cases and the inclusion of a control group.

The authors encountered a case of bilateral femur fracture possibly resulting in part from long-term administration of antipsychotic agents, which induced hyperprolactinemia in a 43-year-old female. The patient recovered a good postoperative range of motion after surgery and experienced no residual pain associated with the incomplete fracture in the left femur. The radiologic images confirmed good results. Therefore, if hyperprolactinemia patients report uncontrolled pain, they should be carefully assessed with MRI. Surgeons should recognize the possibility of atypical atypical fracture induced hyperprolactinemia.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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