Bilateral atypical femoral fractures in macroprolactinoma with hypopituitarism: a case report

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Summary

Several case series have indicated that atypical femoral fractures (AFF) are associated with prolonged used of anti-resorptive agents. However, very few reports have demonstrated relationship between AFF and other osteoporosis-related conditions. We report a 63-year-old man with an unremarkable past medical history who suffered bilateral AFFs. He was never exposed to any anti-resorptive therapy. Prolactin-producing pituitary adenoma was diagnosed from very high serum prolactin level and a pituitary macroadenoma from MRI findings. Other pituitary functions revealed hypopituitarism (growth hormone deficiency, hypogonadotropic hypogonadism, central hypothyroidism and secondary adrenal insufficiency). His bone mineral density showed osteoporosis by a dual-energy X-ray absorptiometry. The osteoporosis was considered to be secondary from growth hormone deficiency and hyperprolactinemia-induced hypogonadism. Interestingly, the measurement of bone markers revealed suppressed bone resorption. To our knowledge, this is the first report of bilateral AFFs in a male patient who was diagnosed with osteoporosis from macroprolactinoma and hypopituitarism. This highlights that other factors, besides the use of anti-resorptive agents, can be related to AFF. Suppression of bone resorption markers in such conditions might be one of the main contributing factors.

KEY WORDS: atypical femoral fractures; osteoporosis; prolactinoma; pituitary adenoma; hypopituitarism.

Introduction

Pituitary hormones exert remarkable direct effects on the skeleton (1). Thus, pituitary disorders with hyper- or hyposecretion of hormones can influence many effects on bone mass and bone metabolism. Prolactin (PRL)-secreting adenomas are the most common hyper-secreting pituitary tumors accounting for about 40-60% of all pituitary adenomas (2). An increase in bone resorption and a decrease in bone mineral density (BMD) were reported as frequent clinical features in both men and women with PRL-secreting adenomas (3). The hard end-point of bone loss in hyperprolactinemia is fragility fractures, which mostly occur at vertebrae (4). PRL-induced hypogonadism is believed to be the main underlying factor of bone loss in these patients (5, 6). Frequently, patients with macroprolactinoma (>10 mm in diameter) may experience hypopituitarism, including growth hormone deficiency (GHD) caused by a pressure effect of the expanding mass on the normal pituitary gland (7, 8). GHD may also contribute to bone loss and fractures in patients with macroprolactinoma (9). However, the exact pathogenic mechanism remains elusive.

Recently, atypical fractures of the femoral shaft have been reported in the literature at an increasing rate. Several case series have indicated an association between atypical femoral fractures (AFF) and prolonged used of anti-resorptive agents (10-12). There are, however, scanty reports of AFF in other osteoporosis-related conditions. We herein present a first report of bilateral AFFs in a male patient who was subsequently diagnosed with macroprolactinoma and hypopituitarism.

Case presentation

The patient was a 63-year-old Thai male with an unremarkable previous medical history. He was never exposed to any anti-resorptive therapy. He has no history of glucocorticoid use and no family history of fracture. At first presentation, he had bilateral hip pain with inability to fully flex his left hip. These symptoms persisted for about a year prior to his first hospital visit. The initial physical examination revealed a limitation in range of motion of his bilateral hips due to pain. His pelvic radiography showed transverse fracture line involving only the lateral cortex of both femoral shafts (Figure 1). The bilateral prodromal hip pain and the radiologic findings were compatible with incomplete bilateral AFFs, according to the 2013 American Society for Bone and Mineral Research (ASBMR) Task Force Case Definition of AFF (13). Detailed investigations were scheduled, but the patient failed to show up on the follow-up visit. One month later, he accidentally slipped on the wet floor and fell from standing height. He developed a severe left hip pain and went to the nearby district hospital. He had radiographic examination which revealed a displaced fracture of his left femoral shaft. He underwent an open reduction internal fixation (ORIF) operation on his left femur with no complication. The patient was scheduled for a prophylactic rodding of the right incomplete femoral stress

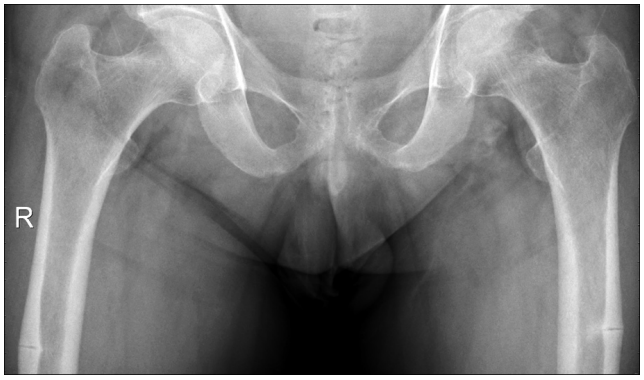

Figure 1 - Bilateral transverse fracture lines at both femoral shafts, consistent with bilateral incomplete atypical femoral fractures (AFF).

fracture, but he did not follow-up again. Three months after the operation, the patient slipped off from his walker frame and suffered another displaced femoral fracture at his right femoral shaft. Anteroposterior radiograph of the right femur shows a displaced AFF characterized by non-comminuted complete fracture extend through both cortices with a medial spike, consistent with the 2013 ASBMR case definition of complete AFF (13) (Figure 2). Spinal X-rays excluded occult vertebral fractures. Measurement of BMD by a dual-energy X-ray absorptiometry showed osteoporosis based on the T-score of -4.1 at L1-L4 vertebrae. Measurement of bone markers revealed beta-CTx 0.274 ng/ml (0.359-0.464), P1NP 106.9 ng/ml (48-68.6), osteocalcin 38.43 ng/ml (17.17-22.19). He had additional blood tests during the admission as followed; calcium 9.0 mg/dl, phosphorus 3.2 mg/dl, ALP 88 U/L, PTH 32.20 pg/ml (15-65), 25(OH)D 23.09 ng/ml (>30), prolactin > 470 µg/L (0-20), IGF-1 68 µg/L (20-176), TSH 2.560 mIU/ml (0.2-3.2), free T4 0.71 ng/ml (0.78-2.11), testosterone < 0.025 ng/ml (1.93-8.36), LH 0.36 mIU/ml (0-8), FSH 0.76 mIU/ml (0-6), cortisol 8 AM 0.42 µg/dl (6.02-18.4).

MRI pituitary was performed regarding biochemical evidence of hyperprolactinemia and hypopituitarism. The study revealed pituitary macroadenoma, about 1.8 x 2 x 1.4 cm in width, AP and height. The tumor exhibits isosignal on T1w, heterogeneous hypersignal on T2FS with solid enhancement. A round-shaped, non-enhanced part is seen at left paramedian aspect, about 6 mm in diameter, representing the cystic part of the tumor. Optic chiasm and optic tracts were normal. Additional information revealed no clinical history of prolonged immobilization, alcohol intake, smoking, complaints of visual field defects, or headache. Macroprolactinoma with hypopituitarism and secondary osteoporosis were diagnosed. After the uneventful second ORIF operation on his right femoral shaft, the patient was treated with bromocriptine and hormonal supplementation of levothyroxine, prednisolone and testosterone enanthate. Teriparatide was prescribed daily for osteoporosis treatment, combined with vitamin D and calcium supplementation.

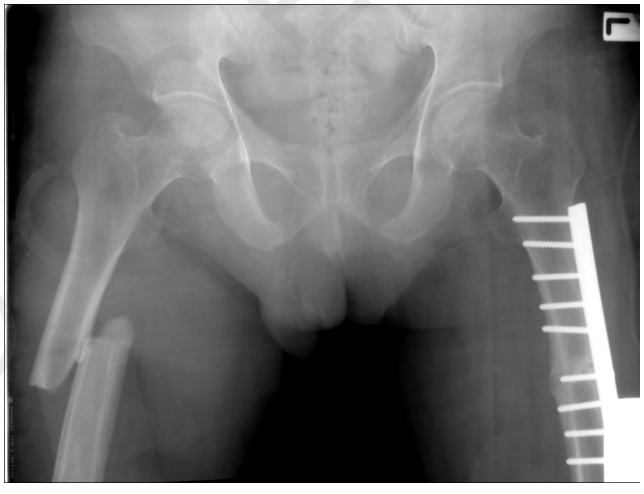

Figure 2 - Atypical femoral fracture (AFF) at right femoral shaft. Previous atypical fracture which has been fixed with plate and screws was seen at left femoral shaft.

Discussion

Recent literature shows increasing information about AFF amongst patients receiving prolonged anti-resorptive therapy, bisphosphonate (10, 11) and denosumab (12). This unusual type of femur fractures was described by Lenart et al. as 'atypical' in that it involved the strongest part of the femur, namely the subtrochanteric and diaphyseal region, and was characterized by features distinctly different from 'typical' osteoporotic femur fractures (14). The 2013 ASBMR case definition of AFF divided these characteristics into major and minor features. Radiographic findings of our patient represent all five major features of the definition, including transverse fracture line located along femoral diaphysis which originated at the lateral cortex which become oblique as it progresses medially across the femur, involving both cortices with a medial spike, localized periosteal thickening of the lateral cortex, association with minimal trauma, and lack of comminution (13). The underlying pathophysiology of AFF seems to be related to the suppression of bone formation and bone resorption markers contributing to reduce bone material quality (15, 16). The suppression of bone resorption marker, beta-CTx, is also evident in our patient. This finding supports the predominant role of suppressed bone resorption in the pathogenic mechanism of AFF.

As mentioned earlier, evidences have demonstrated strong association between anti-resorptive agents including bisphosphonate and RANK ligand inhibitor as the cause of AFF. However, case reports of AFF that are not related to anti-resorptive use are very limited. Some congenital bone diseases characterized by low bone turnover, such as hypophosphatasia (17, 18) or pycnodysosthosis (19), have been linked with AFF. To our knowledge, this is the first report of hyperprolactinemia and hypopituitarism causing AFF. PRL-induced hypogonadism is considered the main mechanism causing osteoporosis in patients with hyperprolactinemia (5, 6). Sustained hyperprolactinemia results in the negative effects on gonadotrophin-releasing hormone pulsatility which lead to the inhibition of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and subsequently the decrease of estradiol and testosterone secretion (20). This effect has been confirmed in animal studies in which animals' testosterone levels were lowered by castration or by being administered PRL. In such animals, PRL blocked the expected rise in LH and FSH levels. Studies in male rabbits show that PRL also acts at the gonadal level inhibiting testosterone secretion in response to both endogenous LH and ex-

ogenous human chorionic gonadotropin (21). However, an increase rate of morphometric vertebral fractures was reported in postmenopausal women with prolactinoma (4) and in men with prolactinoma who have normal testosterone values (22), supporting that PRL excess *per sé* may be an independent factor in contribution of fragility fractures. Several recent studies have demonstrated variable degrees of bone loss in patients with hyperprolactinemia. However, there are limited reports that focus on the resultant bone loss and osteoporosis in men (5, 23, 24). Patients with hyperprolactinemia usually have high bone turnover, with elevated bone resorption and suppressed bone formation markers (25). Bone resorption increases as a result of testosterone and estrogen deficiency in such patients (26). In contrast, low bone turnover is reported in patients with hypopituitarism which is likely to be the result of GHD (1). To date, there are no available data on bone turnover markers in patients who experienced both hyperprolactinemia and GHD. Interestingly, our patient revealed suppressed beta-CTx with elevated P1NP and osteocalcin. This finding suggests that low bone turnover in GHD play the dominant role among mechanism regulating bone metabolism in our patient.

Conclusion

We report a case of bilateral AFFs in a male patient who was diagnosed with osteoporosis from macroprolactinoma and hypopituitarism, which is most likely due to the suppression of bone resorption. This finding highlights the fact that other conditions associated with low bone turn over state, besides the use of anti-resorptive agents, can be related to atypical fractures.

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