Open Journal of Rheumatology and Autoimmune Diseases, 2014, 4, 29-33
Published Online February 2014 (http://www.scirp.org/journal/ojra)
http://dx.doi.org/10.4236/ojra.2014.41004

Atypical Femoral Fractures in a Patient with Continuous Decreasing BMD after Only 1.5 Years of Bisphosphonate Treatment

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Received November 17th, 2013; revised December 17th, 2013; accepted December 24th, 2013

ABSTRACT

Objective: Bisphosphonates were accepted first line treatment for osteoporosis. Long-term bisphosphonate treatment has been reported to be complicated with osteonecrosis of jaw (ONJ) and atypical fracture of femur. It is proposed to be the result of impaired remodeling of minor injury of bone. An atypical fracture occurs on a patient received only 1.5 years of bisphosphonate treatment with continuous decreasing bone mineral density. Case Presentation: This is a 53-year-old female Taiwanese. She has rheumatoid arthritis and has received long-term glucocorticoid treatment. Continuous decrease of bone mineral density in the serial BMD examination after alendronate treatment can be found. Thigh pain occurs after only 1.5 years of bisphosphonate treatment and it progresses to atypical fracture. Conclusions: Atypical fracture can occur in patients receive only short-term bisphosphonate treatment even BMD is still decreased after bisphosphonate treatment. Autoimmune disease, glucocorticoid treatment, Asian and female may be the possible risk factors.

KEYWORDS

Atypical Fracture; Bisphosphonate; Rheumatoid Arthritis

1. Background

Bisphosphonates are widely accepted first line treatments for osteoporosis [1,2]. Though the efficacy in decreasing osteoporotic fracture risk is different between different bisphosphonate agents, they are proved to be able to decrease osteoporosis related fractures [2-4]. Atypical fractures of femoral subtrochanter or shaft are reported to be one of the adverse effects after long-term treatment of bisphosphonates [1,2,5-9]. We will present a case of atypical fracture after only 1.5 years alendronate treatment. Drug holiday has been suggested for patients after long-term bisphosphonates treatment.

2. Case Presentation

This case is a 53-year-old female Taiwanese. She has rheumatoid arthritis and has received long-term glucocorticoid treatment. She receives serial bone densitometry for her underlying disease. Bone mineral density (BMD) was 0.672 g/cm^2 (T-score = −1.8) over right hip in July 2003 and was 0.624 g/cm^2 (T-score = −2.3) in June 2006. BMD was 0.577 g/cm^2 (T-score = −2.7) in March 2009. She has received alendronate treatment since November 2009. She complained left thigh pain in mid 2011. Densitometer examination was performed and the result of bone density was 0.551 g/cm^2 (T-score = −3.0) while she complained thigh pain. There is 4.5% decrease in BMD compared with last densitometry study before alendronate treatment. X-ray examination is arranged and shows beaking of lateral cortex of subtrochanteric area of left femur (**Figure 1(a)**). The X-ray findings meet 5 major features of atypical femoral fracture defined by Second Report of a Task Force of the American Society

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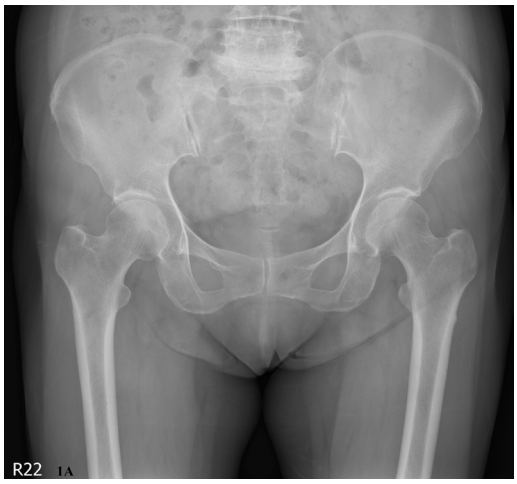
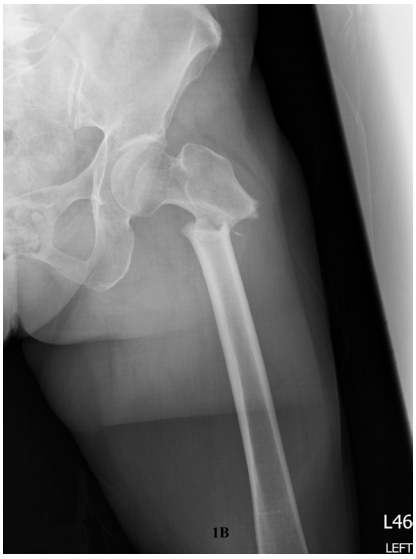


(a)



(b)

Figure 1. (a) showed beaking of lateral cortex of subtrochanteric area of left femur. (b) showed simple transverse fracture over the original lateral cortical beaking site of subtrochantric area of left femur.

for Bone and Mineral Research [11]. WHO Fracture Risk Assessment Tool (FRAX) is used to evaluate the fracture risk for postmenopausal women even with bisphosphonate treatment [12]. FRAX score result of the patient was 4.8% of 10 years risk of hip fracture and 13% of 10 years risk of major osteoporotic fracture. The patient is treated by non-weight bearing initially but continued to receive alendronate treatment. Minor trauma caused subtrochanteric fracture of left femur occurred in November of 2011. Plain X-ray film shows complete subtrochanteric short oblique fracture without comminution and thickening and beaking of lateral cortex over the fracture site (**Figure 1(b)**). She was transferred to Department of Orthopedics and received open reduction and internal fixation with 130-degree dynamic compression hip screw. Alendronate treatment was stopped after the surgery. Nonunion of the fracture site with implants failure were noted in July of 2012. Open reduction and autogenous bone graft were performed with 95-degree dynamic compression screw. Nonunion and implant failure was noted in November of 2012. Revision of the reduction, changing implant and autogeous bone graft was performed again and the patient was under follow up till now.

3. Conclusions

X-ray findings of this case meet all major features of atypical fracture that defined by Second Task Force Report of the American Society for Bone and Mineral Research [11]. Atypical fracture occurred after only 1.5 years alendronate treatment and the BMD is still decreasing after alendronate treatment. The patient has drug exposures to both glucocorticoid and bisphosphonate.

Long-term bisphosphonate treatment may over-suppress bone remodeling and cause deterioration of microstructure of bone [2,6-9,13-15]. Micro-damage of bone during daily activity cannot be repaired after long-term bisphosphonate treatment and which results in atypical fragility [3,13,15-18]. Bone shows mineral and matrix homogeneity after bisphosphonate treatment that may decrease bone toughing mechanism [19]. As above literatures reported, atypical facture occurs on the bone that had positive response [20] to bisphosphonate treatment. BMD is maintained or increased if the bone had positive response to bisphosphonate [21]. Drug holiday is suggested in the “low risk osteoporotic fracture group” patients with improvement of BMD to normal or osteopenia range, no further fracture history, and good adherence to bisphosphonate for at least 2 years [22,23].

Serial BMD examinations in this patient showed that BMD significantly decreases even with bisphosphonate treatment [24]. When considering the decrease of BMD in serial examinations and high osteoporotic fracture risk by FRAX, this patient can still be classified as high risk of osteoporotic fracture group. Long-term treatment of bisphosphonates or at least 10 years treatment before drug holiday is indicated and drug holiday is not suggested in this group of patients [10]. But atypical fracture occurs after as short as only 1.5 years after bisphosphonate treatment.

Literatures are reviewed and possible etiologies are proposed. Subsequent or combined use of glucocorticoid and bisphosphonate may increase the risk of atypical fracture is reported [25-29]. Inflammatory diseases are reported to have positive regulators for osteoclast and induce bone loss [30,31] and bone loss may be localized to joint or gross bone mass. Glucocorticoid and rheuma-

toid arthritis activity have been reported to increase bone remodeling and increase bone loss [32]. Rheumatoid arthritis and long-term glucocorticoid treatment may be the risk factors of this patient in atypical fracture after short-term bisphosphonate treatment.

Some literatures had reported that there is no association between bisphosphonate and atypical fracture [33, 34]. Atypical fracture has also been reported suggested to be one of the osteoporotic fractures [5,26,35]. Definite link between bisphosphonate and atypical fracture is controversial [2,11,34,36,37], so as the cause-effect association between bisphosphonate and atypical fracture [6,10, 26,38]. Reported risk factors associated with atypical femur fractures are history of fragility fracture, glucocorticoid therapy, active rheumatoid arthritis, Asian women over 60-year-old and hypo-vitamin D3 [11,39]. Severe curvature of femoral shaft is also reported as a factor of atypical fracture [40]. Generally speaking, data about the prevalence and risk factors of atypical fracture is still limited [25,26,41].

Postmenopausal osteoporotic Asian with concomitant glucocorticoid and bisphosphonate treatment may be a high-risk group of atypical fracture; even that BMD is still decreasing after bisphosphonate treatment. Detailed and immediate evaluation while these patients complained thigh pain is necessary.

Acknowledgements

We thank the doctors of Section of Allergic, Immune and Rheumatic Disease who transferred this patient to our department and had detailed discussion of the history and treatment plan of this patient.

Conflicting Interest

There is no non-financial or financial competing to declare in relation to this manuscript.

Research Ethics

IRB of Kaohsiung Veterans Hospital approves the study (VGHKS13-CT3-05), including that the consent form is not necessary.

Authors Contribution

Chia-Jung Hu M.D. is the resident who cared the patient and collected all necessary clinical data and wrote this article.

Jenn-Huei Renn Ph.D. moderated the writing of this manuscript and made the surgical and anti-osteoporotic treatment plan for the patient.

Shan-Wei Yang Ph.D. and Kai-Cheng Lin M.D. performed the surgical plan and procedures for the patient and care of the patient.

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Abbreviations

BP: bisphosphonate
BMD: bone mineral density
FRAX: WHO fracture risk assessment tool