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Multiple Fractures Associated With Alendronate Use

Alendronat Kullanımına Eşlik Eden Multipl Kırıklar

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Summary

Bisphosphonates are the most widely used medicines in osteoporosis and effect by reducing the bone resorption. However, the long term effects of this medicine are not known exactly. In the literature, subtrochanteric diaphysis stress and failure fractures have been defined associated with long term bisphosphonate use. A case is presented here who has been receiving alendronate treatment for 10 years and who has developed multipl fractures (femoral diaphysis, pubic ramus, sacrum) with spontaneously or low energy trauma. *Turk J Phys Med Rehab 2012;58:66-8.*

Key Words: Bisphosphonate, fracture

Özet

Bifosfonatlar, osteoporoz tedavisinde en sık kullanılan ilaçlar olup, kemik rezorbsiyonunu azaltarak etki gösterirler. Ancak bu ilaçların uzun dönem etkileri tam olarak bilinmemektedir. Literatürde uzun dönem bifosfonat kullanımı ile ilişkili subtrokanterik, diyafiz stres veya yetersizlik kırıkları tanımlanmıştır. Burada yaklaşık 10 yıldır bifosfonat tedavisi alan ve spontan femoral diafiz fraktürü, sol pubik ramus kırığı ve sakrum kırığı ile düşük enerjili travmaya bağlı sağ pubik ramus kırığı gelişen olgu sunulmuştur. *Türk Fiz Tıp Rehab Derg 2012;58:66-8.*

Anahtar Kelimeler: Bifosfonat, kırık

Introduction

Bisphosphonates are the most widely used medicines in the management of osteoporosis and they are effective in the improvement of certain clinical measures of osteoporosis such as increase in bone mineral density and decrease in biochemical turnover markers and fragility fractures (1,2). Bisphosphonates bind to the inorganic component of the bone; target osteoclasts and decrease bone resorption and turnover by triggering apoptosis of osteoclasts (3). Effects of long-term use of bisphosphonates on bone metabolism have not been known. Bone turnover is a natural component of the treatment; the microdamage continuously occurring in the bone cannot be repaired and thus, bone stability decreases gradually (4). Thus, femur fractures can occur spontaneously or with minimal trauma. This condition is not often observed in osteoporosis. These fractures are characteristically simple transverse or oblique fractures and come along with hypertrophy in diaphyseal cortex (5). In this study, the case of a patient, who has been receiving bisphosphonate treatment for 10 years and developed multiple fractures (left femoral diaphysis, bilateral pubic ramus and sacrum), was presented and the literature was reviewed.

Case Report

A 77-year-old female patient with a complaint of left hip pain was admitted to our outpatient clinic in January 2009. Her pain increased by walking or standing up for a long time and did not respond to analgesics. The patient had diabetes mellitus for the last 22 years and she has been using insulin besides alendronate and combined tablets of calcium and vitamin D for 10 years with the diagnosis of osteoporosis. Any trauma, steroids or other drugs use, smoking or alcohol consumption were not found in her history.

In the physical examination of the patient, there was palpation sensitivity in the 1/3th middle part of the left thigh. Hip and knee range of motions were normal but painful. Neurologic examination was normal. X-ray examination of the pelvis and femur and

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ultrasonography examination of the soft tissue revealed no pathologies. Magnetic Resonance Imaging (MRI) of the femur which was performed due to the persistent pain, showed a fracture line in the left femur (Figure 1). Whole-body bone scintigraphy demonstrated an increase in focal activity in the left femur diaphysis. Results of laboratory analyses were normal: Urea: 44 mg/dl, Creatinine: 0.9 mg/dl, Na: 130 mmol/l, K: 4,6 mmol/l, Cl: 96 mmol/l, Ca: 8,9 mg/dl, I Ca: 4.53 mg/dl, Phosphor: 3.8 mg/dl, Mg: 1,7 mg/dl, PTH: 4 pmol/l (normal values: 1.3-9.3) Vit D: 8,4 ng/ml (normal values: 6.3-46.4). Liver function tests were also within normal limits. ALP: 73 U/L (normal values 32-91). ESR: 25 mm/h, CRP: (-). BMD T-scores were -3,2 for L1-L4 and -2,7 for femur neck. Tumor markers, protein electrophoresis, serum and urine immune electrophoresis were normal. Fracture of the left superior pubic arm developed in the patient following a low-energy fall in February 2009. Positron emission tomography (PET) scans revealed a minimal increase in metabolic activity which is thought to belong to an old stress fracture in the cortex of the left femur diaphysis 1/3 middle section, and an increase of metabolic activity involvement in left side of sacrum and left superior pubic ramus fracture line.

The patient has undergone an intramedullary nail fixation of left femur by orthopedists in February 2009. The patient, who had a pain on her right hip in April 2009, was reevaluated and new fracture lines were observed in the right superior and inferior pubic ramus, and in the left inferior pubic ramus (Figure 2). There were no multiple fractures or findings of osteomalacia in vertebral radiographies.

Any organic pathology to explain these multiple fractures were not determined. These fractures were thought to be arising because of long-term alendronate treatment. Daily subcutaneous teriparatide 20 mg was started in May 2009 and no new fractures have been determined up to now.

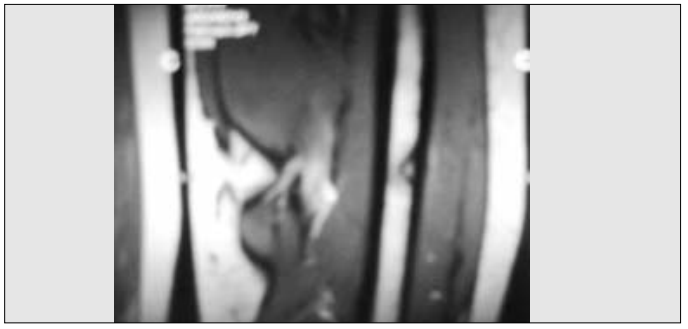

Figure 1. Microfracture line in left femur MRI.

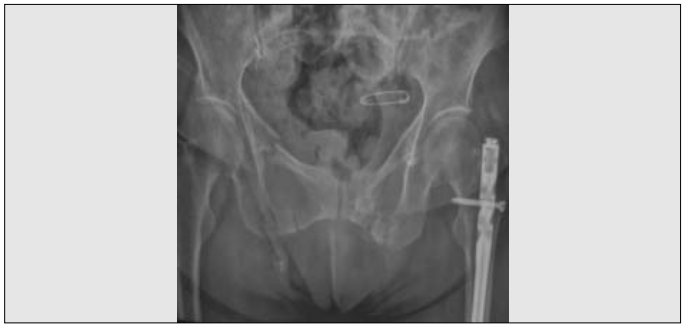

Figure 2. New fracture lines in right superior and inferior pubic ramus and left inferior pubic ramus, old fracture line in left superior pubic ramus with callus formation and intramedullary fixation material in left femur.

Discussion

Osteoporotic fractures affect the vertebra, hip, distal radius and proximal humerus, however, they are rarely observed in proximal femur (6). Subtrochanteric area of the femur is the strongest part of the bone and it is difficult for a fracture to occur in low-energy traumas (7). Subtrochanteric fractures are rather associated with hypophosphatemic osteomalacia, picnodisostosis and florid treatment (8).

To assist case finding and reporting, the task force of the American Society for Bone and Mineral Research defined major and minor features for complete and incomplete atypical fractures of the femur (Table 1). All major features should be presented in order to designate a fracture as "atypical" and it should be distinguished from more common hip fractures (ie, femoral neck, intertrochanteric, etc.). Minor features have commonly been described in association with atypical fractures but they may or may not be presented in individual patients (9). All major features together with four minor features (prodromal dull pain in the thigh, bilateral fractures, delayed healing, use of bisphosphonates) were present in our case.

Our patient was 77 years old. Epidemiologic studies show that, fractures of the subtrochanteric region of the femur and the femoral shaft follow an age and sex distribution similar to osteoporotic fractures (9). After a retrospective analysis of 13 patients, who had low-energy subtrochanteric fracture, it has been reported that 9 patients of those 13, who were using alendronate, were younger with a mean age of 66.9 years (55 to 82) vs. 80.3 years (64 to 92) and more socially active than the others who were not using alendronate (7).

Odvina et al. (10). for the first time in 2005, have determined 9 patients with spontaneous non-pathological fractures after long-term alendronate use. These fractures developed during daily life activities such as walking, standing, etc. Fracture areas were pubic arms, femur shaft, ischium, costas and sacrum. Histomorphometrical analysis of the trabecular bone in these patients indicated that the bone formation was suppressed; osteoblastic and osteoclastic surfaces decreased or disappeared and matrix synthesis decreased. They concluded that strong suppression in bone turnover may develop during long-term alendronate treatment and that, non-spinal, especially femur body fractures may occur. In our patient, multiple fractures were determined in ischium, pubic arms and left femur diaphysis.

Fractures in women receiving alendronate are usually subtrochanteric fractures at the metaphysis-diaphysis junction and mostly occur after minimal trauma. Most of these patients report prodromal pain in the affected hip in months prior to fall (7). Our patient also had left femoral pain before the diagnosis of the fracture in the left femur and her pain did not respond to analgesics, besides, no pathologies were determined in X rays. However, after the MRI performed because of the intractable pain, a fracture line in the left femur diaphysis was determined.

Kwek et al. (8) reported formation of a transverse pattern of the fracture line in the lateral femur, which leads to possibility of deficiency and stress fracture, and a formation of radiographic fracture configuration which was characterized by hypertrophy in the medial cortex. The femur diaphysis fracture in our patient was also formed with transverse pattern. Hypertrophic cortex detected on MRI was also compatible with the stress fracture. Drug compliance of patients

Table 1. Atypical femoral fracture: Major and minor features[a]

Major features[b]
• Located anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar şare
• Associated with no trauma or minimal trauma, as in a fall from a standing height or less
• Transverse or short oblique conŞguration
• Noncomminuted
• Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.
Minor features
• Localized periosteal reaction of the lateral cortex[c]
• Generalized increase in cortical thickness of the diaphysis
• Prodromal symptoms such as dull or aching pain in the groin or thigh
• Bilateral fractures and symptoms
• Delayed healing
• Comorbid conditions (eg, vitamin D deŞciency, RA, hypophosphatasia)
• Use of pharmaceutical agents (eg, bisphosphonates; glucocorticoids, proton pump inhibitors)

a: Specifically excluded are fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, pathologic fractures associated with primary or metastatic bone tumors, and periprosthetic fractures.
b: All major features are required to satisfy the case definition of atypical femoral fracture. None of the minor features are required but sometimes have been associated with these fractures.
c: Often referred to in the literature as breaking or flaring.

is not mentioned in the literature, whereas it was good for our patient.

Transverse pattern, cortical hypertrophy and prodromal pain of all reported patients indicated that these fractures occurred as a result of a stress fracture. As a result of supressed microdamage repair and delay in bone improvement, low energy traumas were become enough to transform the stress fracture to a complete fracture (5). However, the actual relationship of these fractures with biophosphonates and the underlying pathogenesis still has not been clearly identified.

Incidence of atypical subtrochanteric fractures were reported to be 78/100000 patient-years in a study from California and the highest estimated rate of atypical subtrochanteric diaphysial fractures in long-term bisphosphonates users were reported as 100/100000 patient-years in Denmark. Fracture intervention trial (FIT) study showed that about 700 nonvertebral and 1000 clinical vertebral fractures would be avoided per 100000 person-years in women using alendronate without baseline vertebral fractures. In women with prior vertebral fractures, the corresponding numbers are found to be 1000 and 2300. Thus the risk-benefit ratio favors biphosphonate treatment (9).

Despite there are some opinion about harmful effects of long term bone turnover supression, bisphosphonates are highly effective in reducing risk of spine and non-spine fractures and they are the first line therapy for the prevention of osteoporotic fractures. Therefore, use of these agents should not be avoided whenever necessary.

Conflict of Interest:

Authors reported no conflicts of interest.

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