ORIGINAL ARTICLE

Atypical femoral fractures related to bisphosphonate use: A comprehensive review of 19 patients

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ABSTRACT

BACKGROUND: Atypical femur fracture is a rare complication of bisphosphonate treatment, which is widely used for the prevention of osteoporotic fractures. This study aims to report clinical and radiological features and outcomes of surgically treated atypical femur fractures related to bisphosphonates.

METHODS: We retrospectively reviewed patients with the diagnosis of atypical femur fracture who were under bisphosphonate treatment and who were surgically treated in our clinic between January 2009 and December 2017. Patients who met the atypical femur fracture criteria defined by the American Society for Bone and Mineral Research were included in this study. Radiological features of the fractures, bisphosphonate treatment and duration, prodromal clinical and radiological findings were evaluated. Outcome measures included perioperative results, clinical and radiological outcomes and mobilization status.

RESULTS: In this study, 19 patients were enrolled. Mean age of the patients was 69.6 years (range: 60.8-85.1) and the mean follow-up was 33.8 months (range: 13-104). Mean bisphosphonate use duration was 8.65 years (range: 3-18). Four patients had bilateral fractures. Eight of 23 fractures were subtrochanteric and 15 were diaphyseal. Twenty-one fractures were treated with an intramedullary nail, one fracture with a locked compression plate and one fracture with cephalomedullary nail. Union was observed in 15 fractures within the first six months. There was a delayed union in four fractures and non-union in four fractures. Mean union time was 5.1 months (range: 2-9). While seven patients preserved their preoperative mobilization status, 12 patients showed regression after the fracture.

CONCLUSION: This study suggests that atypical femur fractures may have prodromal signs and that their management is complex due to high complication and nonunion rates.

Keywords: Bisphosphonates; femur fracture; fragility fracture; hip fracture; osteoporosis; stress fracture.

INTRODUCTION

Osteoporosis is a chronic and progressive pathology that causes impairment of bone formation, leading to the deterioration of the bone structure and may result in fractures.[1] As the incidence of osteoporosis increases due to prolonged life expectancy, the prevention of osteoporosis-related fractures has become an important problem for the physicians. Bisphosphonates (BP) are the most preferred drugs in this field today. BPs, which are antiresorptive agents, provide this effect by decreasing bone turnover and increasing bone mineral density.[2–4] However, studies have shown that long-term use of BPs may result in atypical femur fractures (AFF).[5–7]

The definition of an AFF suggested by the American Society for Bone and Mineral Research (ASBMR) task force in 2010 was revised in 2013. According to this, AFFs were defined as fractures located in femoral diaphysis between the distal part of the lesser trochanter and the proximal part of the supracondylar region and that meet at least four of the five major criteria (Table 1).[8] Radiologically, it can be seen that these fractures start from the lateral cortex and have transverse - oblique orientation may cause spike formation in the medial cortex, or cortical thickening and periosteal reaction.[8,9]

Although previous studies have reported that AFFs are associated with high complication, delayed union, and high revision

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surgery rates[10, 11] because of their rarity, the number of comprehensive studies on BP related AFF in the literature is limited and information on the outcome of these fractures is insufficient, which remained under-researched. The present study aims to report the radiological and clinical outcomes of the patients who were operated with the diagnosis of BP related AFF.

MATERIALS AND METHODS

Between January 2009 and December 2017, the patients who were operated in our clinic with the diagnosis of AFF in the subtrochanteric or diaphyseal region were retrospectively reviewed. Patients who had at least four of the criteria defined by ASBMR and who had a history of BP use were included in this study.[8] (Table 1) Tumor-related pathological fractures and fractures that did not meet the criteria were excluded from this study. Demographic data of the patients, type of BP used and treatment duration, radiological features of fractures, duration of hospitalization, and union time of fractures and mobilization status of patients were evaluated. Institutional review board approval was obtained before the formation of this study.

Preoperative clinical evaluation of patients, comorbidities and drug use that affect bone metabolism were noted. The patients who had prodromal pain were identified. The BP used by the patients and its duration and the changes in their medications after fracture treatment were noted. In perioperative clinical evaluation, complications, such as wound problem, infection, intraoperative fracture development, pulmonary embolism, anesthesia-related conditions and duration of hospitalization, were determined. The implant used for surgical treatment was also noted for each patient.

The mobilization of the patients was divided into five separate categories: mobilized without aid, mobilized with a single crutch, mobilized with double crutches, mobilized with a walker and immobilized. Pre-fracture and the last follow-up mobilization status were noted for each patient. Radiological evaluation of the patients was performed with X-rays of first admission, postoperative 1st day and postoperative 1st, 2nd, 4th, 6th, 12th, 24th month X-rays. All evaluations were performed on both anteroposterior (AP) and lateral radiographs. The fractures located in the area up to 5 cm distal to the lesser trochanter were evaluated as subtrochanteric fractures and the fractures in the region extending from this point to the supracondylar area were evaluated as diaphyseal. All patients had x-rays of the contralateral side at the time of admission and the presence of radiological findings, such as cortical thickening and periosteal reaction, were noted on these radiographs. The fractures extending up to the medial cortex were defined as complete, non-extending fractures were defined as incomplete fractures. Union was defined as the formation of bridge callus in at least three cortices in postoperative AP and lateral X-rays. Absence of radiological signs of the union until postoperative 6th month and postoperative 1st year were defined as delayed union and non-union, respectively. All radiological evaluations were performed by the first author, and then, the consistency of the measurements was confirmed by the other authors.

RESULTS

In this study, 19 female patients who had 23 AFFs were included. The mean age of the patients was 69.6 years (range: 60.8-85.1). Four patients had bilateral fractures. In three of these four patients, bilateral fractures were detected at the time of admission and both femurs were treated at the same session. One of them was operated for a new fracture on the contralateral femur four years after the first fracture. Of the 15 patients with unilateral fractures, six patients had right femur fracture and nine patients had left femur fracture. The

Table 1. ASBMR Task Force 2013 revised case definition of AFFs

The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare

Major features	**Minor features**
Associated with no trauma or minimal trauma, as in a fall from a standing height or less	Generalized increase in cortical thickness of the femoral diaphysis
The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur.	Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh
Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex	Bilateral incomplete or complete femoral diaphysis fracture
The fracture is noncomminuted or minimally comminuted	Delayed fracture healing
Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (“beaking” or “flaring”)	

mean body mass index (BMI) of the patients was 27.40 (range: 20.28-34.13). The mean follow-up duration was 33.8 months (range: 13-104). The mean hospital stay was 11.6 days (range: 6-21 days) (Table 2).

Seven out of 19 patients had a comorbidity (hypothyroidism, rheumatoid arthritis, Hashimoto's thyroiditis), which could affect bone metabolism. In the medical records of three patients, the use of drugs (corticosteroids), which could adversely affect bone metabolism, was noted. The anamnesis of the patients revealed that 12 patients had prodromal symptoms, such as thigh, groin, or hip pain before the fracture (Table 2).

In the radiographs of the patients, eight of 23 fractures were subtrochanteric and 15 were diaphyseal. Of the four patients with bilateral fractures, two had bilateral subtrochanteric and the other two patients had bilateral diaphyseal fractures (Fig. 1, 2). Five of 23 fractures were incomplete (three diaphyseal, two subtrochanteric) and 18 of them were complete fractures. At the time of presentation, four patients had radiographic findings, such as cortical thickening and periosteal reaction on the contralateral side (Fig. 3).

The mean duration of BP treatment before fracture was 8,65 years (range: 3-18). Zoledronate (ZOL) was used in three patients. Alendronate (ALE) was used in 13 patients and ibandronate (IBA) was used in three patients. BP treatment was continued in four patients and discontinued in 15 patients af-

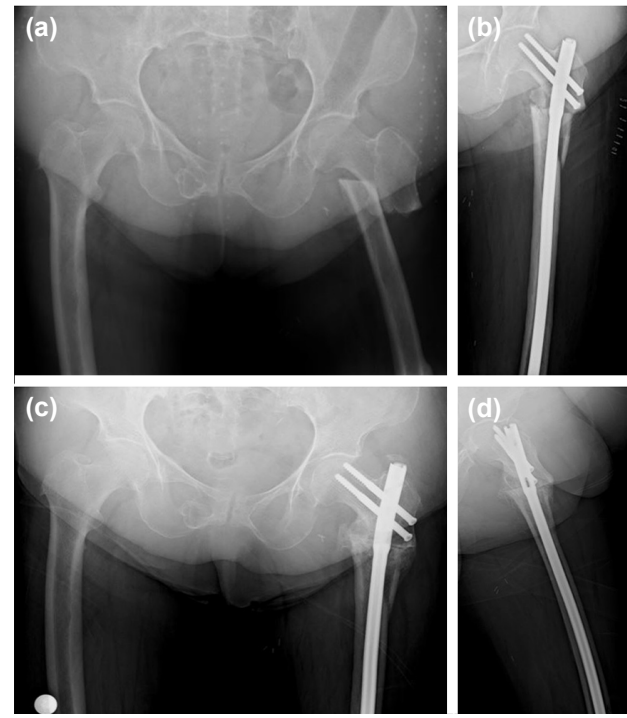

Figure 1. Admission radiograph of a patient with a subtrochanteric transverse atypical femur fracture on the left femur **(a)**. Early post-operative radiograph showing fixation with an intramedullary nail. A peri-operative lateral cortex fracture in the subtrochanteric region can be seen **(b)**. Post-operative 4th month anteroposterior and lateral radiographs show a complete union **(c, d).**

Table 2. Demographic data and clinical features of the patients

Patient no	Age (years)	Fracture side	Body mass index	Hospitalization duration (days)	Prodromal symptom	Metabolic disorder	Corticosteroids use
1	76,0	Left	22.06	11	-	-	-
2	66.5	Left	34.13	10	+	-	-
3	66.1	Bilateral	27.43	12	-	-	-
4	74.8	Left	31.11	6	+	-	-
5	60.8	Bilateral	26.57	6/20	+	Hypothyroidism	-
6	61.9	Left	27.76	12	+	Hypothyroidism	-
7	70.0	Right	27.37	9	-	-	-
8	77.4	Left	26.21	14	-	-	-
9	63.7	Right	31.57	12	+	Hypothyroidism	-
10	69.1	Left	33.29	15	-	-	-
11	80.1	Left	29.90	19	+	-	-
12	75.9	Right	34.37	21	+	Hypothyroidism	-
13	85.1	Right	29.24	8	+	-	-
14	76.4	Right	24.44	14	-	Hashimoto's thyroiditis	+
15	69.0	Left	23.12	7	-	-	-
16	69.8	Right	30.91	6	+	Rheumatoid arthritis	+
17	69.6	Left	26.17	7	+	-	-
18	62.4	Bilateral	24.97	12	+	Rheumatoid arthritis	+
19	68.6	Bilateral	20.28	11	+	-	-

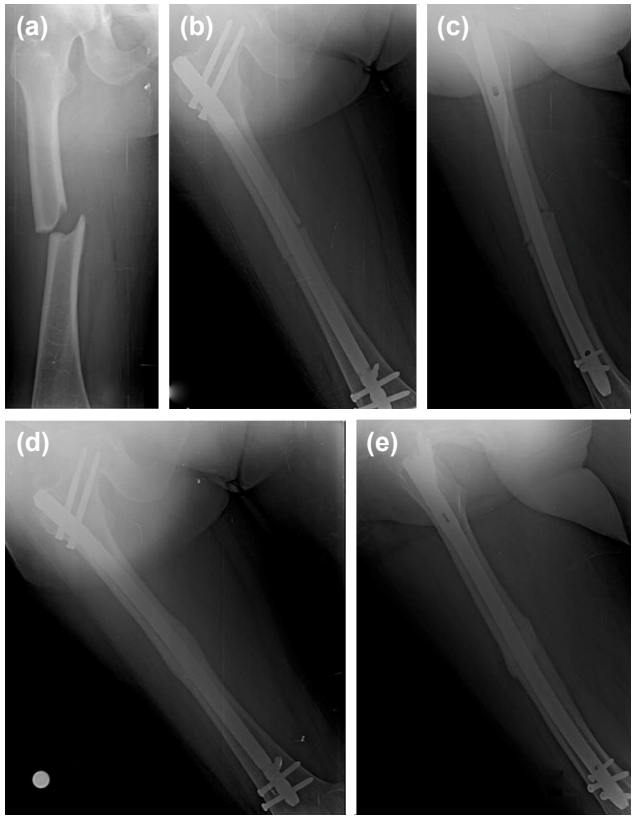

Figure 2. Admission radiograph of a patient with a diaphyseal atypical femur fracture of the right femur. A spike formation can be seen in the medial cortex **(a)**. Early postoperative anteroposterior and lateral radiographs showing fixation with an intramedullary nail **(b, c)**. Post-operative 4th month anteroposterior and lateral radiographs show a complete union **(d, e)**.

ter a fracture. In the postoperative period, teriparatide (TPT) treatment was started on one patient due to nonunion and 10 patients started to have calcium (CA) and vitamin D (D3) supplementation (Table 3).

Before the fracture, only two patients were mobilized with a single crutch and the other patients did not need any support. In the post-operative period, seven patients needed a single crutch and five patients needed walkers. While seven patients preserved their preoperative mobilization status, 12 patients showed regression after fracture (Table 3).

In this study, 21 of the 23 fractures were treated with intramedullary nail (IMN), one fracture with a locked compression plate (LCP), and one fracture with cephalomedullary nail (CMN) (Table 3). Fifteen fractures were observed to unite in the first six months. Delayed union was observed in four fractures with complete union achieved after six months postoperatively. No signs of the union were detected in four fractures until the end of the follow-up period of this study and considered as nonunion. The mean union time of the fractures was 5.1 months (range: 2-9) (Table 3).

Two of the four non-united fractures belonged to a patient with bilateral subtrochanteric fractures. The patient had undergone IMN operation on the left femur and LCP operation on the right femur and died on postoperative 13th month due to congestive heart failure and pneumonia. Two other fractures with nonunion were seen in a patient with bilateral diaphyseal fractures. IMN was applied bilaterally to this patient. The patient had a perioperative subtrochanteric femur fracture on the left side and had an infection that was followed-up with serial debridement. On the right side, implant failure and femoral neck fracture had developed due to a fall and the patient was treated with a long-stemmed total hip arthroplasty on postoperative 15th month (Fig. 4). One patient who was treated with IMN surgery had implant failure on 9th month and underwent revision surgery. In another patient who had undergone an IMN operation, cemented total hip arthroplasty was applied on the postoperative 4th year when a collum femoris fracture developed. However, the patient died on the 3rd postoperative day due to pulmonary embolism. In addition, two patients who had undergone IMN had perioperative lateral cortical propagation of the index fractures and two patients had irritation around the area of the distal locking screws. In another patient with IMN, acute renal failure developed in the early postoperative period, which healed without a need for dialysis (Table 3).

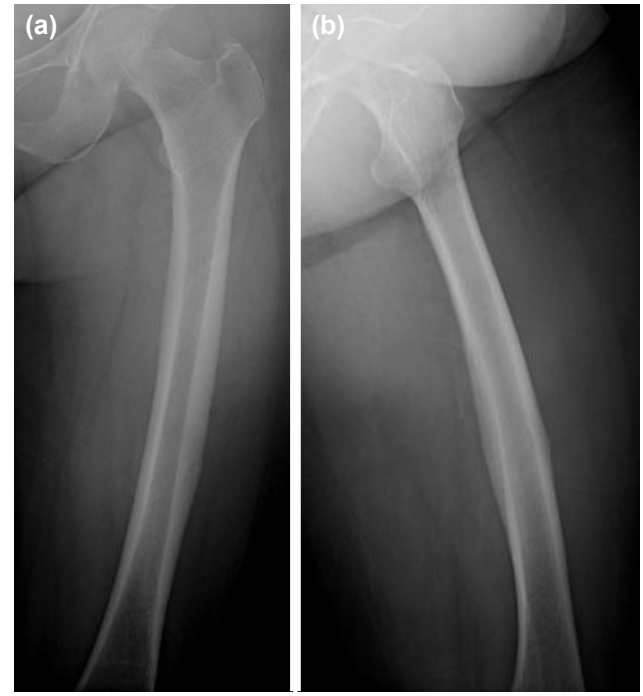

Figure 3. Admission anteroposterior **(a)** and lateral **(b)** left femur radiographs of a patient showing cortical thickening in the diaphyseal region, which can be considered as a radiological sign of a stress reaction.

DISCUSSION

Although BP-related AFF is a frequent subject of studies, there is a lack of prospective studies with high cohort numbers on this subject in the literature because of its rarity. Therefore, a clear-cut causality relationship between BP use

Table 3. Union status and duration, bisphosphonates used and treatment duration, used implants and complications

Patient no	Union	Radiological union time (months) (years)	Used BP and treatment duration the fracture	Osteoporosis treatment after	Used implant	Complication
1	+	3	ZOL / 5	D3	IMN	-
2	+	5	ZOL / 15	ZOL	IMN	Implant failure on 9th month, revision surgery
3 R/L	-/-	-/-	ALE / 6	-	LCP/IMN	-
4	+	2	İBA / 10	-	IMN	-
5 R/L	+	4/6	ALE / 3	ALE	IMN/IMN	-
6	+	6	ALE / 10	CA + D3	IMN	-
7	+	3	ALE / 4	-	IMN	Collum femoris fracture on 4th year. Revision surgery (Cemented total hip arthroplasty). Pulmonary embolism and death.
8	+	5	ALE / 6	CA + D3	IMN	Perioperative fracture
9	+	5	ALE / 10	D3	IMN	-
10	+	3	ALE / 6	CA + D3	IMN	Perioperative fracture
11	+	6	İBA / 6	-	IMN	-
12	+	9	ALE / 7	CA+D3	CMN	-
13	+	6	ALE / 5	-	IMN	Postoperative acute kidney failure
14	+	4	ALE / 15	ALE	IMN	Skin irritation of distal locking screw
15	+	3	ALE / 17	ALE	IMN	-
16	+	9	ALE / 7	-	IMN	-
17	+	8	ALE / 4	D3	IMN	-
18 R/L	+	7/4	İBA / 9	D3	IMN/IMN	Skin irritation of distal locking screw in the right femur
19 R/L	-/-	-/-	ZOL / 18	CA + D3 + TPT	IMN/IMN	Implant failure and collum femoris fracture of the right femur. Revision surgery (total hip arthroplasty). Perioperative fracture and infection in the left femur.

BP: bisphosphonate; R: right; L: left; ZOL: zoledronate; ALE: alendronate; IBA: ibandronate; IMN: intramedullary nail; LCP: locked compression plate; CMN: cephalomedullary nail.

and AFFs has not been established yet. However, the risk of AFF is higher in the population using BP and the risk is increased in direct proportion to the duration of use.[8,12] The ASBMR task force states that the risk of development of AFF in BP users with a duration of fewer than five years is reported to be 3.2-50 per 100000 cases per year, although this risk has been shown to increase with longer use.[8] AFFs are thought to be stress fractures or insufficiency fractures. It is normally expected that the micro-fracture regions formed as a result of recurrent loading in the femoral cortex will be resorbed by osteoclasts in normal individuals and then repaired. However, by the suppression of osteoclasts by BP, resorption is not possible in these micro-fracture areas, and as a result of suppressed bone turn-over and remodeling, these micro-fractures are thought to accumulate and spread to cause AFFs.[6–8,13,14]

Figure 4. Pelvis **(a)** and right femur **(b)** radiographs of a patient who was treated with intramedullary nail because of bilateral atypical femur fracture. A femoral neck fracture is seen in the right hip. The patient was treated with nail removal and long-stemmed total hip arthroplasty **(c)**. Left femur radiographs of the same patient show a nonunion in the diaphyseal region **(d).**

BP-associated AFFs usually arise from minimal or no trauma. In the majority of cases, thigh, hip or groin pain is present for some time before fracture.[8] In a study that retrospectively evaluated 12 BP-related AFFs, nine patients (75%) were reported to have prodromal pain symptoms.[15] In another multicenter retrospective study, it was reported that 34% of the patients had previously reported prodromal pain on the fracture site.[10] In our study, 12 of 19 of the patients (63%) had prodromal pain, consistent with the rates reported in the literature.

Although it is still controversial, there are some opinions that metabolic disorders and corticosteroids facilitate the development of AFF in BP users.[7,10] In a study published by Phillips et al.,[15] six out of 12 patients (50%) with BP-related AFF had a metabolic disorder (polymyalgia, rheumatica, hypothyroidism, nephritic syndrome), and two of these six patients were under corticosteroid treatment. In another case series, 25% of the patients were reported to have a metabolic disorder (rheumatoid arthritis, Addison's disease) and corticosteroid use.[16] In our series, 36% (7/19) of the patients had a metabolic disorder (hypothyroidism, rheumatoid arthritis, Hashimoto's thyroiditis). Three of these patients were under corticosteroid therapy.

As stated by ASBMR, AFFs can be seen bilaterally.[8] Even if it is not bilateral, the risk of developing AFF in the contralateral side should be known. Therefore, the contralateral femurs of all patients should be examined from the time of the first admission. In radiological imaging, even if no complete fracture is seen, stress reactions that may be considered as the precursors of fracture can be detected and preventive measures can be taken. Of the 19 patients in our study, four (21%) patients had bilateral fractures. In three of these four patients, bilateral fractures were present at the first admission and in one of the patients, a fracture developed on the contralateral side during follow-up. Excluding three patients with bilateral fractures on admission, four of the remaining 16 patients (25%) had radiological findings, such as cortical thickening and periosteal reaction on the contralateral side in X-rays. The findings in other studies also support our results. In one study, 40% of the patients with AFF have been reported to have radiological signs of stress reaction on the contralateral side.[17] In another study, this rate was 59% in the pre-fracture radiographs of the contralateral femurs.[10]

IMN is the recommended treatment method for AFFs in many studies. IMN is biomechanically superior in the treatment of AFF because it provides a better load distribution compared to osteosynthesis with plate-screw and causes less bending movement in the fracture area.[18] Besides, there are some opinions that IMN is more advantageous in a biological sense, as well.[19] The authors base this view on the biological basis of fracture healing. BPs do not prevent callus formation; they inhibit osteoclasts and suppress remodelling of callus to bone tissue.[20,21] Therefore, the use of BPs is thought to adversely affect bone healing in plate-screw osteosynthesis in which primary bone healing is observed. Regardless of the surgical technique used, there are studies reporting that BP-related AFFs have a high rate of nonunion, delayed union, and these fractures are associated with higher complication and revision surgery rates than typical femoral fractures.[7,8,10,15,22–24] In a retrospective study, the mean union time was reported to be 24 weeks and the authors stated that union time reached up to 56 weeks for some patients.[15] In another study, it was reported that 46% of the patients with AFF who were treated with IMN had additional interventions due to lack of union.[24] The findings in our study are consistent with these results. In 23 fractures, nonunion was observed in four (17%) and delayed union was observed in four (17%) and the mean union time was 5.1 months. 17% of the fractures (4/23) required revision surgery or debridement due to various complications (collum femoris fracture, implant failure, infection). In 22% of the fractures (5/23), minor complications not requiring further interventions (intraoperative fracture, locking screw irritation) developed.

Although they increase the risk of AFF, BPs are the preferred drugs for fracture prevention in osteoporosis. Edward et al.[25] reported that the benefits of BPs were 100 times greater than AFF development risk. In the studies, it was shown that the risk of AFF is directly proportional to the duration of BP use and the risk decreases with the cessation of treatment.[12,26] BP treatment is a low-risk and advantageous treatment in the initial years in correctly selected patients. However, it is reported that BP treatment may increase the risk of AFF without additional benefit on the prevention of osteoporotic fractures with prolonged treatments.[27]

In conclusion, AFFs may develop due to prolonged use of BPs and they are prone to high complication, nonunion, delayed union and revision surgery rates. The important point is to keep patients taking BPs under close and cooperated follow up by an endocrinologist and orthopedist to take advantage of this treatment while avoiding the risk of AFF.

The retrospective nature of the presented study and the evaluation of a small group of patients constitute the weak aspects of this study, as in the majority of the studies on this subject in the literature. It is, therefore, difficult to conclude a cause-effect relationship. However, due to the comprehensive evaluation of the patients both clinically and radiologically, we believe that this study makes an important contribution to the current literature on the rarely seen AFF.

Conflict of interest: None declared.

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ORİJİNAL ÇALIŞMA - *ÖZET*

Bifosfonat kullanımı ile ilişkili atipik femur kırıkları: 19 hastanın kapsamlı değerlendirmesi

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AMAÇ: Bifosfonatlar osteoporozlu hastalarda kırık gelişimini önlemek için sıklıkla kullanılan ilaçlardır. Ancak bifosfonat kullanımı nadiren de olsa atipik femur kırıklarına yol açabilir. Sunulan çalışma cerrahi olarak tedavi edilen bifosfonatla ilişkili atipik femur kırıklarının klinik ve radyolojik özellikleri ile tedavi sonuçlarını sunmayı amaçlamaktadır.

GEREÇ VE YÖNTEM: Kliniğimizde Ocak 2009 ile Aralık 2017 tarihleri arasında atipik femur kırığı tanısıyla ameliyat edilmiş olan ve bifosfonat kullanma öyküsü olan hastalar geriye dönük olarak incelendi. Çalışmaya Amerikan Kemik ve Mineral Araştırma Topluluğu (American Society for Bone and Mineral Research) tarafınca tanımlanmış olan atipik femur kırığı kriterlerini karşılayan hastalar dahil edildi. Dahil edilen hastaların kırıklarının radyolojik özellikleri, kullanılan bifosfonat ve kullanım süresi, prodromal klinik ve radyolojik bulguların varlığı değerlendirildi. Tedavi sonrası sonuç değerlendirmesi ise klinik değerlendirme, radyolojik kaynama durumu ve mobilizasyon durumuna göre gerçekleştirildi.

BULGULAR: Çalışmaya 19 hasta dahil edildi. Hastaların ortalama yaşı 69.6 yıl (aralık: 60.8-85.1) ve ortalama takip süresi 33.8 yıldı (aralık: 13-104). Ortalama bifosfonat kullanım süresi 8.65 yıl (aralık: 3-18) yıl olarak bulundu. 4 hastada bilateral kırık mevcuttu. Çalışmada incelenen 23 kırıktan 8 tanesi subtrokanterik, 15 tanesi ise diafizer yerleşimliydi. 21 kırık intramedüller çivi ile, 1 kırık kilitli kompresyon plağı ile ve 1 kırık da proksimal femur çivisi ile tedavi edilmişti. 15 kırıkta ilk 6 ay içinde kaynama gözlendi. 4 kırıkta kaynama gecikmesi ve 4 kırıkta kaynamama tespit edildi. Ortalama kaynama süresi 5.1 ay (aralık: 2-9) olarak bulundu. Toplam 7 hastanın operasyon sonrasında preoperatif mobilizasyon durumunu koruğu gözlenirken 12 hastanın mobilizasyon durumunda kırık sonrasında gerileme olduğu görüldü.

TARTIŞMA: Bu çalışmanın bulguları atipik femur kırıklarının prodromal bulguları olabileceğini ve bu kırıkların yüksek komplikasyon ve kaynamama oranları ile ilişkili olduğunu göstermektedir.

Anahtar sözcükler: Bifosfonat; femur kırığı; osteoporoz, kalça kırığı; stres kırığı; yetmezlik kırığı.

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