Etiological Analysis and Treatment Principles of Atypical Femur Fracture

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Research article

Keywords: Atypical femur fracture, Bisphosphonates, Severe osteoporosis, Coxa vara, Lateral femur bowing angle

Posted Date: July 19th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-705219/v1>

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Abstract

Purpose: To discuss the etiology and clinical characteristics of atypical femur fracture (AFF) and to improve AFF recognition.

Methods: The clinical data of AFF patients treated in our hospital from January 2007 to June 2020 were retrospectively analyzed, and the clinical characteristics of AFF were summarized.

Results: Sixteen patients (24 femurs, eight bilateral femurs), including 14 females, with a median age of 73 years (53-85 years old), were included in this study. The etiological factors were divided into four categories: (1) administration of bisphosphonates (BPs), (2) severe osteoporosis, (3) hip joint dysfunction, and (4) structural abnormality of the femur. Six femurs with incomplete fractures received conservative treatment. Three femurs with incomplete fractures and 13 femurs with complete fractures received intramedullary nail treatment, and one patient (bilateral femurs) underwent plate fixation. All patients were followed up until fracture union; the follow-up time was 3-14 months.

Conclusions: For high-risk patients, if there are prodromal symptoms or a simple transverse fracture of the femur, the possibility of AFF should be considered. At the same time, imaging examinations should be performed to exclude the presence of AFF on the contralateral side.

Introduction

Atypical femur fracture (AFF) is a rare low-energy injury with periosteal reactions in the lateral cortex^[1, 2]. In 2005, Odvina et al. proposed that the severe inhibition of bone turnover after the long-term use of bisphosphonates (BPs) was the main cause of AFF^[3, 4]. Other studies have also found that proton pump inhibitors (PPIs) and glucocorticoids (GCs) may cause AFF^[5, 6]. To further improve the recognition of AFF, the clinical data of AFF patients in our hospital were collected and summarized, with the purpose of analyzing the etiology and treatment principles of AFF.

Methods

The clinical data of patients with femoral fractures treated in our hospital from January 2007 to June 2020 were collected. Among those patients, 16 patients met the AFF diagnostic criteria^[5] published by the American Society of Bone and Mineral Research (ASBMR) in 2013. Based on the etiological factors, the clinical characteristics, treatments and clinical effects for each patient were analyzed.

The AFF diagnostic criteria are as follows: the fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. In addition, at least four of five major features must be present. None of the minor features is required but have been sometimes associated with these fractures. Major features: 1. No or minor trauma-related fractures, such as falling from standing position or a low position; 2. The fracture line originates at the lateral cortex and is generally transverse in its orientation; when extending to the medial femur, it may become oblique; 3. Complete fracture passes through both cortices, may be associated with a medial spike; incomplete fracture involves only lateral cortex; 4. The fracture is non-comminuted or minimally comminuted; and 5. Local periosteal reaction or endosteal thickening ("beaking" or "flaring") in the lateral cortex is present at the fracture site. The minor features are as follows: 1. Generalized increase in cortical thickness of the femoral diaphyses; 2. unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh; 3. bilateral complete or incomplete femoral shaft fractures; and 4. delayed fracture healing.

Excludes fractures of the femoral neck, intertrochanteric fractures with spiral subtrochanteric extension, peri-prosthetic fractures and pathological fractures associated with primary or metastatic bone tumors and miscellaneous bone diseases (e.g., Paget's Disease, fibrous dysplasia).

Results

All patients were hospitalized. There were 16 patients (24 femurs, eight bilateral femurs), of whom 14 were female and two were male, with a median age of 73 years (53–85 years old). Six femurs with incomplete fractures were received conservative treatment. Three femurs with incomplete fractures and 13 femurs with complete fractures were received intramedullary nail treatment, and one patient (complete fracture of the left femur and incomplete fracture of the right femur) underwent plate fixation. All patients were followed up until fracture union, ranging from 3–14 months. Based on fracture location, AFF can be divided into subtrochanteric fractures and femoral isthmus fractures. The pathogenic factors of AFF were divided into four categories, i.e., administration of BPs, severe osteoporosis, hip joint dysfunction, and structural abnormality of the femur. The detailed information of each patient is shown in Table 1.

Table 1
Detailed information of 16 AFF patients

No.	pathogenic factors	sex	age	prodromal symptoms	GCs	BMD	location		type		Treat-ment		healing(months)	
							L	R	L	R	L	R	L	R
1	BPs	F	70	No	No	-0.5	sub	sub	CF	CF	IM	IM	10	11
2	BPs	F	74	No	No	-0.6	sub	sub	ICF	CF	CT	IM	11	8
3	BPs	F	61	No	Yes	-0.9	-	sub		CF	CT	IM	-	5
4	BPs	F	53	Yes	Yes	-3.1	ist	ist	ICF	CF	CT	IM	14	12
5	BPs	F	77	Yes	No	-2.5	-	ist	-	CF	-	IM	-	3
6	BPs	F	66	No	No	-2.1	-	sub	-	CF	-	IM	-	8
7	BPs	M	65	Yes	No	-3.4	-	ist	-	ICF	-	CT	-	4
8	SO	F	78	Yes	No	-5.2	sub	-	ICF	-	CT	-	6	-
9	SO	F	85	No	No	-3.2	sub	sub	CF	CF	IM	IM	7	8
10	SO	F	80	Yes	Yes	-3.7	sub	-	ICF	-	IM	-	9	-
11	SO	F	76	No	No	-4.4	-	sub	-	CF	-	IM	-	9
12	SO	F	65	Yes	No	-3.4	sub	sub	ICF	CF	CT	IM	8	9
13	HJD	M	74	Yes	No	-4.1	-	sub	-	ICF	-	IM	-	7
14	HJD	F	54	No	No	-4.3	sub	sub	ICF	CF	CT	IM	4	8
15	FSA	F	72	Yes	No	-2.7	ist	sub	CF	ICF	IM	IM	14	8
16	FSA	F	76	Yes	No	-5.2	sub	ist	CF	ICF	PF	PF	8	8
pathogenic factors: BPs, bisphosphonates; SO, severe osteoporosis; HJD, hip joint dysfunction; FSA, femur structural abnormality;														
Sex: F, female; M, male;														
GCs: glucocorticoids;														
BMD: the lowest T value for hip BMD;														
Location: L, left; R, right; Sub, subtrochanteric; Ist, isthmus;														
Type: CF, complete fracture; ICF, incomplete fracture;														
Treatment: IM, Intramedullary nail; PF, plate fixation; CT, conservative treatment														

There were seven patients (six females and one male; median age, 65 years (53–77 years old)) with AFF (10 femurs, three bilateral femurs) caused by the administration of BPs. For cases 1 (Fig. 1) and 2, due to multiple bone metastasis of breast cancer, zoledronic acid was intravenously administered for 10 and 20 years, respectively. The lowest T values for hip bone mineral density (BMD) were $-0.5SD$ and $-0.6SD$, respectively, and both were bilateral AFF. Moreover, for case 3, nuclide abnormal concentration were found at the right subtrochanteric by radionuclide bone scan at six months before the injury, and misdiagnosed as bone metastasis of breast cancer. For cases 4 and 5 have taken glucocorticoids for for a long time, to treat severe osteoporosis, they were treated with Fosamax for four years and 10 years, respectively, the lowest T values for hip BMD were $-3.1SD$ and $-0.9SD$, respectively. At the same time, case 6 manifested as subtrochanteric localized periosteal thickening of the left femur. The other three patients were treated with oral Fosamax to treat severe osteoporosis for five years, three years and six months; the lowest T values for hip BMD were $-2.5SD$, $-2.1SD$ and $-3.4SD$, respectively. Three patients had prodromal symptoms, such as thigh pain before finding the fracture. In this BP group, three incomplete fractures and one case of periosteal thickening were received conservative treatment, and the other seven complete fractures were treated with intramedullary nails.

There were five patients (all female; median age 78 years (65–85 years old)) with AFF (seven femurs and two bilateral femurs) caused by severe osteoporosis, with no history of BPs using. The average of lowest T values for hip BMD were $-3.98 \pm 0.82 SD$. For cases 7, 8, 9, the patients had no long-term history of using various drugs, and their medical records indicated severe osteoporosis. For cases 10 manifested as anterolateral pain in the left thigh before finding incomplete fracture at the left subtrochanteric. Both cases 11 and 12, were found completely AFF after minor trauma. Cases 13 and 14 involved primary and secondary osteoporosis. The patient information of case 15 was described in Fig. 2. The patient associated with case 16 was treated with Aromasin for 20 years after breast cancer surgery and presented with anterolateral pain in both thighs. X-ray examination revealed subtrochanteric fractures of the bilateral femurs. The fracture in the right femur was complete and was treated with an intramedullary nail, while the fracture in the left femur was incomplete and was treated conservatively.

There were two patients with AFF caused by hip joint dysfunction. Details about the case 17 was described in Fig. 3. Case 18 was found incompletely AFF and completely AFF in the left and right femur respectively, resulting from slight trauma. She suffered from a thoracic spinal cord injury caused by decompression surgery for thoracic spinal stenosis before two and a half years. After thoracic surgery, she walked unsteadily and had a duck-like gait. The lowest T value for hip BMD was $-4.3SD$. Other details are shown in Table 1

There were two patients with AFF caused by structural abnormality of the femur. For case 19 (Fig. 4), with coxa vara, she had intermittent pain in the right thigh for five years. X-ray examination revealed a subtrochanteric incomplete fracture of the right femur. The lowest T value for hip BMD was $-2.7SD$.

The lateral femur bowing angle (FBA) is defined as the angle made by the mid-diaphyseal lines of the proximal and distal parts of the femur^[7]; In a standing anteroposterior radiograph of the entire femur, the lateral FBA was calculated as follows: A line that best described the midpoint of the endosteal canal of the femoral diaphysis was drawn in the proximal and distal quarters. The degree of bowing was defined as the angulation between the two lines. Case 20 (Fig. 5) manifested as an increase in the lateral FBA. The patient was a 76-year-old female with double knee varus deformity and an increase in the lateral FBA of the bilateral femurs for many years, and walking difficulties gradually occurred. Bilateral total knee arthroplasty was performed 2.5 years ago, and daily walking was recovered after surgery. Anterolateral pain in both thighs occurred before 1 year. Severe pain in the left thigh occurred when turning over in bed three days before admission. X-ray revealed a left subtrochanteric completely AFF and incompletely AFF in the right femoral isthmus. The lowest T value for the hip BMD was $-5.2SD$.

Discussion

AFFs are insufficiency fractures in stress fractures and typically characterized by prodromal symptoms^[8], i.e., symptoms of pain, discomfort, weakness in the groin area or on the thigh during weight bearing in the weeks or months prior to the

fracture^[1, 6, 2]. In this study, 9 (9/16) patients had prodromal symptoms, mainly manifesting as pain, weakness during movement or inability to stand on one leg, and fracture(s) were discovered after seeing a doctor. AFF occurred with minor or no trauma; for case 8, the fracture occurred when turning over in bed.

On X-ray, the simple transverse fracture line was revealed. When the fracture line extends to the medial femur, it may become inclined. Complete AFF passes through two layers of cortex, potentially with small tips on the medial side. For incomplete AFF, local periosteal reactions or periosteal thickening of the lateral femoral cortex is often observed^[4, 9–11]. In this study, 14 completely AFFs and 10 incompletely AFFs were involved.

Studies have shown that bilateral femoral fractures occur in 40% of AFF patients but in only 2% of patients with common fractures, and another 21% of AFF patients present with focal cortical thickening of the contralateral femur^[5, 12, 13]. Eight patients (8/16) in this study had bilateral AFFs; therefore, bilateral femoral X-rays, MRI or bone scans are recommended in unilateral AFF patients.

I. BPs and AFF

BPs mainly inhibit the function of osteoclasts. The long-term administration of BPs excessively inhibits bone turnover, increases bone mineral content, decreases the toughness and energy absorption capacity of bone tissue^[16, 17], increases bone fragility, and decreases fracture resistance; therefore, fractures may occur even after no or minor trauma, resulting in transverse fractures^[18]. In this study, there were three patients with a history of BP use for more than 10 years. The lowest T values for their hip BMD were -0.5SD, -0.6SD and -0.9SD, and AFF occurred when falling from a standing position. Another three patients had a history of Fosamax use for six months, four years and five years. They had no definite history of trauma and only showed anterolateral pain in the thigh. AFF was found during examinations.

When bone turnover is severely inhibited, the mechanisms involved in fracture union may be dysfunctional, leading to delayed union^[14]. Bone turnover markers, iliac crest biopsy and fracture site biopsy have confirmed that bone remodeling is inhibited in typical BP-related AFFs^[1, 5, 15]. After fracture occurs, osteoclasts cannot participate in bone remodeling, and delay fracture union. In this study, the patient in case 8 took oral Fosamax for four years and continued to take it after surgical treatment of AFF on the left side, and there was no sign of fracture union last 11 months after surgery. When Fosamax was stopped, teriparatide was administered for three months, and the fracture healed.

For patients with a long-term history of BPs using, when injuries are caused by slight violence, the fracture site often involves the subtrochanteric femur (6/10), considered a violence action point; when patients report chronic pain, fractures often involve the femoral isthmus (4/10), related to femur anatomical morphology.

BPs can reduce the risk of hip, spine and other fractures by 50–70% and are the main drugs for treating osteoporosis^[19, 20]. However, in patients receiving BPs, the exposure time is directly related to AFF risk^[5, 21, 22], and the long-term use of BPs (more than five years) has been listed as an independent risk factor for AFF^[23]. Multinational guidelines recommend that after oral BPs for five years and intravenous BPs for three years, drug holidays can be considered^[24–26, 27]. Our recommendation is regularly monitoring bone metabolism markers and conducting femoral MRI or bone scans during BPs treatment, allowing for the early detection and treatment of incomplete AFF^[28].

II. Severe osteoporosis and AFF

Neviaser AS and Hyodo K reported AFFs, that unrelated to BPs^[4, 29]. Lim^[30] et al. studied 6644 hip fractures and found that the incidence of AFF was 2.95%, of which 24.5% did not involve a history of BPs administration. Kim^[31] studied 147 patients with AFF and found that 22% of the patients had no history of BPs using. They both found that severe osteoporosis is an independent risk factor for AFFs.

The lowest T value for hip BMD in this group of patients with severe osteoporosis was $-3.98SD$, and three patients had primary osteoporosis. Among the two patients with primary and secondary osteoporosis, one patient received oral glucocorticoids for seven years to treat rheumatoid. X-ray examination revealed subtrochanteric localized periosteal thickening of the left femur due to anterolateral pain in the thigh. After conservative treatment for three months, incomplete AFF was found. Localized periosteal thickening, i.e., “beaking” or “flaring”, is one of the characteristics of AFFs, often appearing one year before the onset of AFFs^[32, 33]. Therefore, the presence of “beaking” or “flaring” is indicative of the early stage of AFFs. For the combined administration of glucocorticoids and BPs, 8–10% of patients with periosteal thickening may develop AFF within two years, thus indicating that “beaking” or “flaring” is an important predictor of AFFs^[32–35]. Therefore, for patients with severe osteoporosis who receive glucocorticoids long term for other disease, regular imaging examinations of the femur should be carried out to detect the occurrence of “beaking” or “flaring”, especially for those who use BPs concurrently.

Another patient with primary and secondary severe osteoporosis was treated long term with Exemestane after breast cancer surgery. This drug inhibits the conversion of androgen to estrogen, and a side effect is severe osteoporosis. For AFF patients with severe osteoporosis, when a low-energy injury occurs, the fracture site is located in the femoral isthmus, which may be related to the lateral force on the femur when falling; when there is no obvious history of trauma, the fracture site is located in the subtrochanteric region of the femur. We speculate that the stress in the subtrochanteric region of the femur is concentrated and that long-term repeated stimulation eventually leads to fracture, similar to the characteristics of stress fractures.

III. Hip joint dysfunction and AFF

In this study, the AFFs in two patients were caused by hip joint dysfunction. The fracture site was in the subtrochanteric region of the femur. One patient had severe hip OA with limited motion, and the other patient had a thoracic spinal cord injury, leading to a duck-like gait when walking. Abnormal hip function, which affects the stress distribution in the proximal femur, and severe osteoporosis may have been the causes of AFF. At present, there is no literature report on AFF caused by hip joint dysfunction, and more clinical cases are needed for analysis.

IV. Structural abnormality of the femur and AFF

This study found that when abnormal femoral structure (coxa vara or abnormal the lateral FBA) is combined with severe osteoporosis, AFF can occur. David P Taormina reported that there is an obvious relationship between the cervical shaft angle and the development of AFF^[36]. Using a computed tomography (CT)-based nonlinear finite element analysis model, Oh Y et al. showed that with a decrease in the cervical shaft angle, the tensile stress in the lateral cortex of the subtrochanteric region increased, eventually resulting in AFF^[37]. The patient in case 2 had AFF in the subtrochanteric region of the left femur nine years prior, and intramedullary fixation was performed. After surgery, dynamization was performed due to nonunion of the fracture, and the Intramedullary nail was removed until the fracture was completely healed. After surgery, the left cervical shaft angle was 118.1° . The patient was admitted to our hospital due to pain in the right thigh. The lowest T value for hip BMD was $-2.7SD$, and the right cervical shaft angle was 103.7° . X-ray revealed a right subtrochanteric incomplete AFF. A new type of interlocking intramedullary nail was used, and the fracture healed three months after surgery.

Many studies report that AFF is a stress fracture related to tension failure of the lateral femoral cortex caused by biomechanical effects over time^[5, 38, 39]. Yoo H et al. measured the femurs of 56 individuals and suggested that the lateral FBA threshold should be 5.25° based on the receiver operating characteristic (ROC) curve. In other words, if the lateral FBA is greater than 5.25° , femoral shaft fracture is more likely to occur^[40]. The case 2 in this group, underwent bilateral total knee arthroplasty, the lateral FBAs of the left and right lateral femurs were 34.7° and 38° , respectively. Anterolateral pain in both thighs occurred during walking one year prior, and X-ray revealed bilateral periosteal thickening of the lateral cortex at the femoral isthmus. Three days before admission, severe pain in the middle and upper part of the left thigh, with limited motion, occurred when turning over in bed, and X-ray revealed a completely AFF at the left subtrochanteric and an incomplete AFF at

the right femoral isthmus. A possible mechanism is as follows: when the lateral FBA increases, the tensile force on the lateral cortex and the compressive stress on the medial cortex increases accordingly. Daily loads first lead to the destruction and opening of the lateral cortex, subsequently leading to a complete fracture.

If osteoporosis evaluations and treatment are provided to such patients, it is recommended to perform imaging evaluations and measured the lateral FBA and the cervical shaft angle on the bilateral femur. If the lateral FBA increases or the cervical shaft angle is too small, drug administration is recommended to promote bone formation. If drugs that inhibit bone resorption (such as BPs or denosumab) are selected, the patients should be followed up regularly, and bone metabolic markers should be examined. In particular, if prodromal symptoms occur, femoral imaging examinations should be performed promptly, including X-ray, femoral MRI or bone scans.

Conclusions

In short, AFF is an insufficiency fracture one of which stress fracture. For a patient who has a history of BPs using, severe osteoporosis, hip joint dysfunction or structural abnormality of the femur, if there are prodromal symptoms or simple transverse fractures caused by low-energy injuries, the possibility of AFF should be considered. At the meantime, to exclude the presence of AFF on the contralateral side, imaging examinations should be performed. For the long-term administration of antiosteoporosis drugs (BPs or denosumab) that inhibit bone resorption, attention should be paid to the possibility of AFF. For the intravenous administration of BPs, the recommended administration time should not exceed three years, and oral administration should not exceed five years. Bone metabolism markers in patients should be evaluated regularly. If prodromal symptoms occur, the possibility of AFF should be considered, and femoral imaging examinations (including X-ray, MRI, and bone scans) should be performed. If bone scans show local nuclide abnormal concentration in the femur, care should be taken to distinguish between metastasis of local tumor foci and AFF. The etiological analysis of 16 patients with AFF (24 femurs) in this study aimed to improve the understanding of the etiology of AFF, which should not be limited to BPs.

Abbreviations

AFF: atypical femur fracture; BPs: bisphosphonates; PPIs: proton pump inhibitors; GCs: glucocorticoids; ASBMR: American Society of Bone and Mineral Research; BMD: bone mineral density; FBA: femur bowing angle; SO: severe osteoporosis; HJD: hip joint dysfunction; FSA: femur structural abnormality; F: female; M: male; L: left; R: right; Sub: subtrochanteric; Ist: isthmus; CF: complete fracture; ICF: incomplete fracture; IM: Intramedullary nail; PF: plate fixation; CT: conservative treatment

Declarations

Ethics approval and consent to participate

This study was conducted according to the Declaration of Helsinki and approved by the Peking University Third Hospital Medical Science Research Ethics Committee. The written informed consent was waived by the Peking University Third Hospital Medical Science Research Ethics Committee due to the retrospective nature of the review, and the data was anonymized.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare they have no competing or conflict of interest.

Funding

National Key R&D Program of China (No. 2018YFF0301103) (awarded to zhishan zhang). The authors have no other conflict of interest.

Authors' contributions

All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were performed by Zhishan Zhang and Hongqing Wang. The data were evaluated by Zhishan Zhang, Fang Zhou and Yun Tian. Follow-up were performed by Zhongwei Yang and Guojin Hou. Zhishan Zhang and Hongqing Wang wrote the first draft of the manuscript, and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank Kaifeng Ye for language editing, and Xiaoyan Niu for her help in collecting the clinical materials in our hospital.

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Figures

Figure 1

Case █ A 70-year-old woman was treated with zoledronic acid for 10 years after bone metastases secondary to breast cancer, and a subtrochanteric AFF occurred after a fall from a standing height (A and B). Radionuclide bone scan showed a right subtrochanteric nuclide abnormal concentration (C). The fracture healed 11 months after the operation. Three years ago, the left subtrochanteric AFF was completely healed after intramedullary nailing (D).

Figure 2

Case █ An 80-year-old woman, who took oral prednisone for chronic rheumatoid arthritis. The X-ray showed local periosteum thickening at the left subtrochanteric region (A). After antiosteoporosis treatment for three months, an incomplete AFF was found (B), and intramedullary nailing was performed. Nine months after the operation, fracture healing was observed at the fracture site (C and D).

Figure 3

Case 1 A 74-year-old man with proximal right thigh pain for half a year, has severe hip osteoarthritis with limited hip movement and severe osteoporosis, which the lowest T value for hip BMD was -4.1SD, and a right subtrochanteric incomplete AFF (A and B). After 7 months of intramedullary nail fixation, the fracture healed (C and D).

Figure 4

Case 1 A 72-year-old woman with an X-ray showing an incomplete right subtrochanteric AFF. The right neck shaft angle was 103.7° (A, B, and C). The new interlocking intramedullary nail fixation was performed (D and E). Five years ago, an X-ray showed a right lateral cortical periosteal reaction (F), and an MRI showed right subtrochanteric hyperintensity (G) but no treatment was provided. Nine years ago, an AFF at the left isthmus was treated with intramedullary nailing (H). One year after the operation, the fracture had healed poorly (J). The intramedullary nail was dynamized (K). It was removed 2.5 years after the operation (L). The left neck shaft angle was 118.1° (M).

Figure 5

Case 1 A 76-year-old woman with severe “O-shaped legs” and bilateral severe OA of knee who was unable to walk properly for five years due to pain (A and B). Bilateral total knee arthroplasty was performed 2.5 years ago (C and D). The left and right lateral FBAs were 34.7° and 38° (E and F). One year ago, there was anterolateral pain in both thighs when ambulation, and an X-ray showed that the periosteum of the lateral cortex of both femoral isthmi were thickened (G and H). Three days ago, the patient experienced severe pain in the middle and upper left thigh with limited movement when turning over. An X-ray showed a left subtrochanteric fracture (K), and the periosteum thickening in the isthmus of the right femur was more obvious than before (J). Because the lateral FBAs were too large to intramedullary nailing, bilateral plates were used (M and N).