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CASE REPORT

Do femoral fractures in adult patients with osteogenesis imperfecta imitate atypical femoral fractures? A case series

J. D. Andersen[1] · M. H. Bünger[2] · O. Rahbek[2] · J. D. Hald[1] · T. Harsløf[1] · B. L. Langdahl[1]

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Abstract

Atypical femoral fractures (AFFs) are low-energy femoral fractures with characteristic radiological features and a suspected relation to treatment with bisphosphonate (BP) or denosumab. In osteogenesis imperfecta (OI), BP is currently the drug of choice when medical treatment is indicated. Due to bone deformities, the radiologic appearance of femoral fractures may be different in patients with OI and patients with osteoporosis. We investigated the prevalence and appearance of femoral fractures in a cohort of adult patients with confirmed OI (55 patients, age range 19–69 years, 26 women (47%) and 35 patients (64%) had received BP treatment), who attended the outpatient clinic at Aarhus University Hospital. The fractures were evaluated according to major and minor AFF criteria. In our OI cohort, we found that eight out of 55 patients had suffered a femoral fracture in adult year: five women and three men, aged 25 to 54 years. One patient had OI type I, two had OI type III, four had OI type IV, and one had OI type V. All fractures were associated with no or minimal trauma. Four patients had fractures that fulfilled the criteria of AFFs. Two of the four patients had received long-term BP treatment prior to the fracture and three patients had severe deformities of the femur. Femoral fractures in OI imitate AFFs. This suggests that bone deformity, collagen deficiencies, and alterations in mineralization of bone may cause femoral fractures that imitate AFFs even in the absence of antiresorptive treatment. Bone deformities should be monitored as part of the management of adult patients with OI. Continuous dull or aching pain in the groin or thigh should lead to radiographic examination. The radiologic appearance of femoral fractures may be different in patients with osteogenesis imperfecta (OI) and patients with osteoporosis, thus imitate atypical femoral fractures (AFF). We found that bone deformity, collagen deficiencies, and alterations in bone mineralization may cause femoral fractures that imitate AFFs even in the absence of antiresorptive treatment.

Keywords Adult · Atypical femoral fractures · Bisphosphonate · Bone deformity · Osteogenesis imperfecta

Introduction

Atypical femoral fractures (AFFs) are low-energy fractures with characteristic radiological features including a transverse fracture pattern [1]. During the last decade, increasing amount of evidence suggests that AFFs are associated with long-term bisphosphonate (BP) or denosumab treatment in patients with osteoporosis, although other factors such as bone quality and bone deformities may also be of importance [2].

✉ J. D. Andersen
Jane.Dahl.Andersen@auh.rm.dk

M. H. Bünger
mathbung@rm.dk

O. Rahbek
olerahbe@rm.dk

J. D. Hald
jannhald@rm.dk

T. Harsløf
torbhars@rm.dk

B. L. Langdahl
bente.langdahl@aarhus.rm.dk

[1] Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Palle Juul-Jensens Boulevard 165, Aarhus N, 8200 Aarhus, Denmark

[2] Department of Pediatric Orthopedics, Aarhus University Hospital, Palle Juul-Jensens Boulevard 165, Aarhus N, 8200 Aarhus, Denmark

Osteogenesis imperfecta (OI) is a hereditary disease caused by collagen type I deficiency, predominantly due to mutations in *COL1A1* or *COL1A2* genes. Manifestations include low-energy fractures caused by severe skeletal fragility and pronounced bone deformities [3, 4]. BPs are widely used in the treatment of severe OI. In patients with osteoporosis, BP treatment decreases fracture risk [5–7]. The fracture preventing effect of BPs in adult patients with OI is debated, and the evidence is sparse [8].

In the first case in this case series, a 54-year-old woman with OI type I, who suffered a femoral fracture with a radiological appearance that fulfills the AFF criteria after receiving only two infusions of zoledronic acid, prompted us to investigate AFFs in patients with OI. Case reports suggest that BPs may cause AFFs in OI [9–11]. However, due to the underlying defects in bone quality as well as the bone deformities in OI, femoral fractures may have a different appearance due to the underlying disease itself.

Here we present a case series of adult patients with OI who suffered low-energy femoral fractures in order to investigate whether femoral fractures in adult OI resemble AFFs and if bone deformities might play a role for development of femoral fractures with an AFF appearance in patients with OI.

Materials and methods

We investigated the prevalence of femoral fractures in adult patients with confirmed OI in a cohort of adult patients who attend the outpatient clinics at Aarhus University Hospital. This cohort included 55 patients, of whom 26 were women (47%) age range 19–69 years and the majority had received BP treatment (64%). In eight patients, femoral fractures were evaluated against the major and minor criteria of AFF [1]. In six of the eight patients, a molecular diagnosis had previously been confirmed. The patients presented in the case series have given informed consent to participation.

Results

Eight of the 55 adult patients with OI followed at the outpatient clinics at Aarhus University Hospital patients had suffered a femoral fracture. The patient characteristics are summarized in Table 1. All fractures were associated with no or minimal trauma and were non-comminuted. Three patients had fractures with a transverse configuration—one patient had fracture with oblique configuration, located distal to the lesser trochanter. These four fractures fulfilled the criteria of AFF. Three of the four patients with AFF-like fractures had severe varus deformity of the femur. Two had received long-term BP treatment prior to the fracture, whereas one patient had not received BPs for more than 10 years and one patient had received oral BPs for a few years with poor compliance (Table 1).

Case by case description:

1) A 54-year-old female, OI type I, walking independently. She presented with acute pain in the right thigh after moving between chairs. Radiographs displayed a complete diaphyseal femoral fracture with a transverse fracture line (Fig. 1, 1) consistent with AFF. However, the images also displayed a pre-existing varus deformity of the femur. BP treatment had been initiated recently and she had received two infusions with zoledronic acid 5 mg.
2) A 44-year-old female, OI type III, assisted walking. She presented with bilateral transverse subtrochanteric femoral fractures with no or minimal trauma prior to the event. The fractures were consistent with AFF, but she also had severe bilateral varus deformities of her femurs (Fig. 1, 2). She had been treated with BPs for two to three decades.
3) A 27-year-old male, OI type III, wheelchair user. He had three displaced femoral fractures presenting after falling out of his wheelchair (Fig. 1, 3A–3C). The fractures included two femoral fractures over existing intramedullary nails and one beneath a nail. This patient had received intravenous BP for two decades, and one year of teriparatide treatment prior to this event. The bones have a pathological appearance typical for OI with a small diameter of the diaphysis, varus, and bulky epiphysis. Due to the rod, the fracture cannot be classified as an AFF even though the appearance looks like AFF.
4) A 47-year-old male, OI type IV. He presented with pain in his right groin, thigh, and knee, above the region where he previously had a fracture that was treated with a retrograde intramedullary nail. Radiographs showed a small fissure lateral in his right femoral neck in addition to coxa vara and acetabular protrusion (Fig. 1, 4). This patient had received BP for more than a decade. The fracture is located at the collum and therefore does not fulfill the AFF criteria.
5) A 26-year-old female, OI type IV. She presented with diffuse pain of the right thigh and groin over two months. Radiographs showed a severe varus and a small fissure in the lateral cortex just below the trochanter, with callus. While awaiting surgery, she suffered a complete femoral fracture with a transverse and then oblique fracture pattern (Fig. 1, 5). In her childhood and early teens, she had been treated with BPs, but had not received any OI treatment for ten years at the time of the fracture. The fracture fulfilled the AFF criteria.
6) A 40-year-old female, OI type IV. She presented with increasing pain over five months at her left thigh and hip. Initial radiographs showed an incomplete fracture of the femoral neck and acetabular protrusion; however, shortly hereafter, she suffered a complete dislocated

Table 1 Patient characteristics

Patient	OI type	Genetics	Age	Gender	BP treatment	Femoral fracture location	Pre-existing deformities	AFF: Y/N
1	I	–	54	Female	2 years, i.v.	Transverse, complete, diaphyseal	Varus deformity of femur	Y
2	III	–	44	Female	2–3 decades, i.v.	Bilateral, transverse, subtrochanteric	Varus deformity of femur	Y
3	III	*COL1A1*: c.3226G>A	27	Male	> 25 years, i.v.	Femoral fractures over existing intramedullary nails	Varus deformity of femur, bulky epiphyses, and small diaphysis diameter	N
4	IV	*COL1A1*: c.1845_1847delGGC	47	Male	> 10 years, i.v.	The fracture is located at the collum.	Coxae vara, protrusion of acetabulum	N
5	IV	*COL1A2*: c.2314G>A	26	Female	Childhood*	Transverse and then oblique, complete, subtrochanteric	Varus deformity of femur	Y
6	IV	*COL1A1*: c.1845_1847delGGC	40	Female	6 years, i.v.	Transverse, femoral neck	Coxae vara	N
7	IV	*COL1A1*: c.3235G>A	47	Female	> 10 years, i.v.	Dislocated midshaft femoral fracture, transverse at the lateral cortex and oblique as it progresses	–	Y
8	V	*IFITM5*: c.-14C>T	25	Male	Few years, oral with poor compliance	Transverse, intertrochanteric	–	N

*Treatment during childhood, no treatment for > 10 years

femoral neck fracture (see Fig. 1, 6), when moving from a chair to her bed. Prior to her fracture, she had received BP for six years. The fracture does not fulfill the criteria for AFF.

7) A 47-year-old female, OI type IV, tripped and fell down on her left side. Radiographs revealed a dislocated midshaft femoral fracture, transverse at the lateral cortex, and oblique as it progresses. The femur is without significant bone deformity (Fig. 1, 7). She had received BP treatment for at least ten years prior to the event. The fracture has an AFF appearance.
8) A 25-year-old male, OI type V characterized by excessive callus formation and interosseous membrane calcification. He fell and suffered an intertrochanteric femoral fracture just above a region of interosseous membrane calcification (Fig. 1, 8). He had received a few years of weekly oral BP with poor compliance. The fracture does not fulfill the AFF criteria.

Discussion

In our cohort, four of eight femoral fractures in OI patients fulfilled the AFF criteria, illustrating that femoral fractures in OI often imitate AFFs. Only half of AFF cases had BP treatment for decades; this suggests that the bone deformities and impaired bone quality that are hallmarks of OI may by themselves, or in combination with BP treatment, play a significant role in causing femoral fractures to imitate AFFs.

Bone mass is often reduced in patients with OI, but not in all cases [12, 13]. The reduced bone mass will contribute to the increased fracture risk seen in patients with OI; however, in most cases, the impaired bone quality is probably the more important factor. Bone quality in OI is affected by alterations of least two of the components of bone: collagen and mineralization. The collagen component is affected either quantitatively or qualitatively. Patients with type I OI have haploinsufficiency leading to a reduced quantity of structurally normal collagen. Patients with type III or IV have mutations generating structurally abnormal collagen. The altered collagen structure makes the bone less compressive and leads to hypermineralization [14, 15]. Hypermineralized bone is less capable of deformation and may fracture at a lower force. Increased mineralization is seen in normal bone with low remodeling activity, for example, long-term antiresorptive therapy or in patients with pycnodysostosis [16]. Regarding AFFs in osteoporosis patients treated with BPs, the pathogenesis is probably multifactorial and may include the accumulation of advanced glycation end products [17] and alterations in collagen structure [18]. In addition, Lloyd et al. [19] found that cortical bone adjacent to the fracture site is more mineralized in patients treated with BPs who suffered AFFs compared to

Fig. 1 Case X-rays

patients treated with BPs who suffered classical osteoporotic fractures. The hypermineralization seen in OI may therefore be partly responsible for the femoral fractures imitating AFFs.

Configuration of the femur and deformities has been shown to be important for the risk of AFFs. Several authors have underlined the fact that lateral bowing and femoral diameter were of importance for the risk of AFFs using a computer-based modeling analysis [20–22].

BP has been the only drug of choice in patients with OI for decades despite limited evidence for the antifracture efficacy in adults [8]. More case reports suggest that long-term BP usage is associated with AFF. More research is needed to investigate if femoral fractures in patients with OI resemble AFFs because of bone material properties, lower limb geometry, BP treatment, or a combination of the three.

Although the present case series of eight adult patients with femoral fractures of which four imitates AFFs to the best of our knowledge is the largest case series presented, there are limitations to consider. OI is a rare disease, and despite an increased fracture risk, femoral fractures are rare. Due to the low number of fractures in patients with different OI types, we cannot conclude on any difference between femoral fractures in patients with different OI types. Unfortunately, we do not have pre-fracture radiographs in all patients, which would have allowed us to identify areas of bone with thinning or sclerosis, another theoretical cause of fracture.

Severe bone deformities should be recognized in the long-term management of adult patients with OI. Continuous dull or aching pain in the groin or thigh requires immediate attention. The indication for bisphosphonate treatment and the duration of treatment should be carefully considered and the benefits weighed against the risks. Prophylactic intramedullary nailing and deformity correction must be considered in preventing debilitating spontaneous femoral fractures.

Compliance with ethical standards

Conflicts of interest None.

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