Atypical femur fracture in an adolescent boy treated with bisphosphonates for X-linked osteoporosis based on PLS3 mutation

Denise M. van de Laarschot BSc[1], M. Carola Zillikens MD PhD [1]

[1] Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands
Corresponding author at: Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands.

Abstract

Long-term use of bisphosphonates has raised concerns about the association with Atypical Femur Fractures (AFFs) that have been reported mainly in postmenopausal women. We report a case of an 18-year-old patient with juvenile osteoporosis based on X-linked osteoporosis due to a PLS3 mutation who developed a low trauma femoral fracture after seven years of intravenous and two years of oral bisphosphonate use, fulfilling the revised ASBMR diagnostic criteria of an AFF. The occurrence of AFFs has not been described previously in children or adolescents. The underlying monogenetic bone disease in our case strengthens the possibility of a genetic predisposition at least in some cases of AFF. We cannot exclude that a transverse fracture of the tibia that also occurred after a minor trauma at age 16 might be part of the same spectrum of atypical fractures related to the use of bisphosphonates. In retrospect our patient experienced prodromal pain prior to both the tibia and the femur fracture. Case reports of atypical fractures in children with a monogenetic bone disease such as Osteogenesis Imperfecta (OI) or juvenile osteoporosis are important to consider in the discussion about optimal duration of bisphosphonate therapy in growing children.

In conclusion, this case report 1) highlights that AFFs also occur in adolescents treated with bisphosphonates during childhood and pain in weight-bearing bones can point towards this diagnosis 2) supports other reports suggesting that low trauma fractures of other long bones besides the femur may be related to long-term use of bisphosphonates 3) strengthens the concept of an underlying genetic predisposition in some cases of AFF, now for the first time reported in X-linked osteoporosis due to a mutation in PLS3 and 4) should be considered in decisions about the duration of bisphosphonate therapy in children with congenital bone disorders.

Key words: Osteoporosis, Osteogenesis imperfecta, X-linked osteoporosis, Bisphosphonates, Atypical femur fracture

1. Introduction

Atypical Femur Fractures (AFFs) are considered a rare but severe adverse effect of bisphosphonate use. AFFs resemble stress fractures and occur at the lateral cortex of the subtrochanteric femur after no or minimal trauma. The incidence rates for an AFF increase with longer duration of bisphosphonate use. According to Dell et al. these rates range from 1.78/100,000 persons per year with bisphosphonate exposure under 2 years to 113.1/100,000 per year amongst patients with long-term bisphosphonate use over 8 years(1). Typically, AFFs have been reported in postmenopausal women on prolonged treatment of bisphosphonates with a median duration of seven years. Also men may be affected. To the best of our knowledge, AFFs have never been documented in children or adolescents. Pediatric patients with fragility fractures, mainly due to Osteogenesis Imperfecta (OI), are extensively treated with bisphosphonates. Although it appears that bisphosphonates improve bone density in children with OI, the evidence on beneficial effects on fracture rates and clinical functional improvement is still inconclusive(2,3).

There is uncertainty about the optimal duration of bisphosphonate treatment as well as the dose and type of bisphosphonates in children. In adults it is usually advised to reevaluate the necessity of continued use after five years of treatment. For children on bisphosphonates it is unclear at what point these drugs should be discontinued. It has been suggested that termination of antiresorptive drugs in growing children leads to zones of localized bone fragility at the junction of older, denser bone and new bone(4,5). Based on these findings continued bisphosphonate therapy in younger patients with OI or persistent risk factors for compromised bone health has been suggested until growth is fully or nearly completed(6,7).

2. Case description

A boy born in 1996 has sustained multiple fractures since 2002, usually after mild trauma. In total he has experienced approximately 14 fractures until the age of 16, e.g. fingers, wrist, shoulder and arm. In 2006 a DXA-scan showed severe osteoporosis with Z-score -3.7 SD of L2-L4 and -4.6 SD of total body. His family history was positive for osteoporosis and his brother similarly presented with numerous fractures at a young age. Initially, a presumptive diagnosis of OI was made, but could not be confirmed through mutation analysis of *COL1A1* and *COL1A2* genes. In 2013 he was diagnosed with X-linked osteoporosis due to a mutation in PLS3, a gene coding for Plastin 3, an F-actin bundling protein, described as a novel monogenic cause of familial osteoporosis and by some seen as a novel form of OI(8,9).

At age nine, in 2006, he was started on pamidronate intravenously 1.0 mg/kg every four and later every six months during three days. In total he received intermittent pamidronate intravenously for seven years with a cumulative dose of 2107 mg. During this time his Bone Mineral Density (BMD) improved. A DXA-scan in 2010 showed a Z-score of L2-L4 +0.7 SD and of total body -1.1 SD. Several small fractures of the fingers and a shoulder fracture occurred after relatively minor traumas during bisphosphonate treatment.

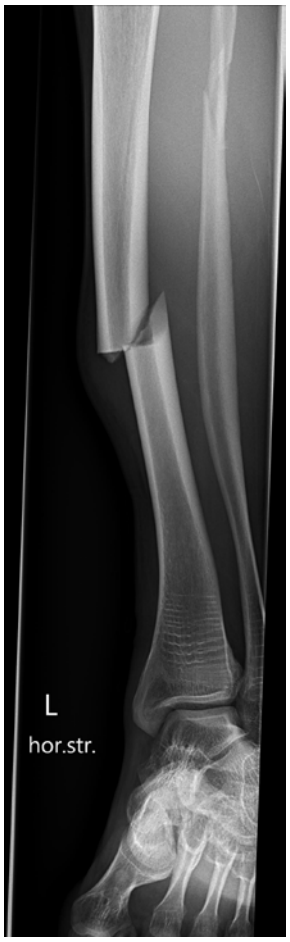
At the age of 16, he broke his tibia and fibula of the left leg after a low-impact fall when he slipped during walking (**Figure 1)**. He had complained of pain in this lower leg for several weeks before. He underwent surgery with placement of intramedullary pins. He was then switched to risedronate orally 35 mg once per week. Two months afterwards, he sustained a spontaneous fracture just above the intramedullary nail of the lower leg after a very soft fall from standing height. When he was 18 years old, he complained of pain in his upper right leg for several weeks. Just before a scheduled visit to the neurologist for this pain he fractured the right femur after a slight fall during walking at a normal pace (**Figure 2**). Following intramedullary fixation, he was referred to the Bone Centre of our hospital. Under suspicion of an AFF of the right femur, bisphosphonate therapy was discontinued and the patient was started on calcium and vitamin D supplementation. There was no delayed healing of the AFF. His BMD Z-score remained stable. A timeline of this case is shown in Figure 3.

3. Discussion

We present an 18-year-old patient with juvenile osteoporosis based on a PLS3 mutation and a spontaneous fracture of the right femur. AFFs have mostly been described in postmenopausal women but also in men. Our case meets all diagnostic criteria for an AFF. It concerns a 1) subtrochanteric fracture with minimal prior trauma, 2) is transverse in orientation whilst the fracture line becomes more oblique as it progresses, 3) extends through both cortices and 4) is not comminuted. He also presented with prodromal pain(10).

To our knowledge, this is the first documentation of an AFF in an adolescent and furthermore the first report of such a fracture in a patient with juvenile osteoporosis based on a PLS3 mutation.

The fracture of the lower leg preceded by prodromal pain and a trivial trauma, shows a predominantly transverse fracture line of the tibial shaft. We cannot exclude that the tibia fracture in our patient may be considered an atypical fracture as well.



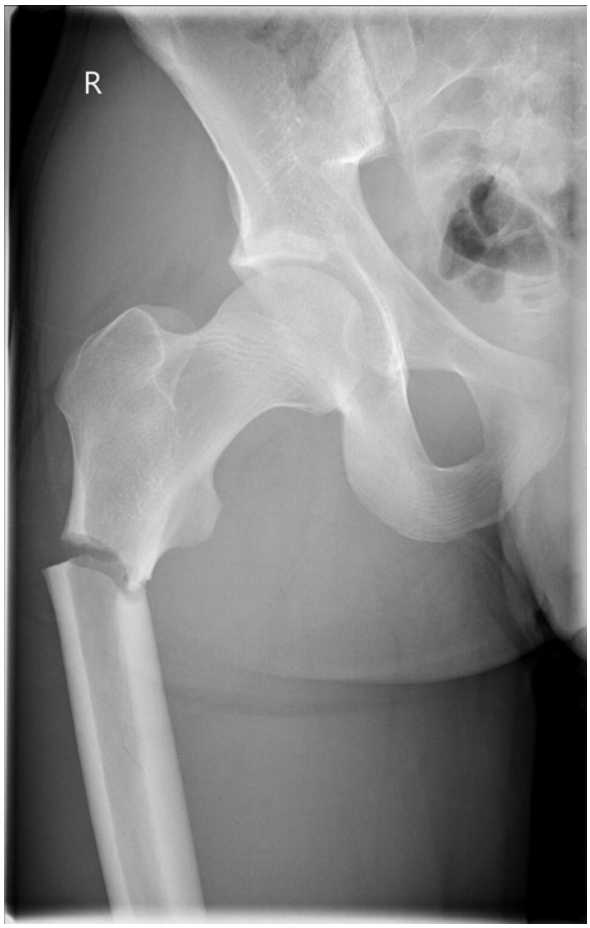


Figure 1 **Figure 2**

Figure 1: *X-ray showing tibia and fibula fracture after low-energetic trauma. Transverse sclerotic bands are visible in the metaphysis of the distal tibia, induced by intermittent pamidronate infusions. Note the predominantly transverse fracture line of the tibial shaft.*
Figure 2: *X-ray showing subtrochanteric non-comminuted femoral fracture with transverse orientation after minimal trauma, fulfilling all diagnostic criteria of an AFF.*

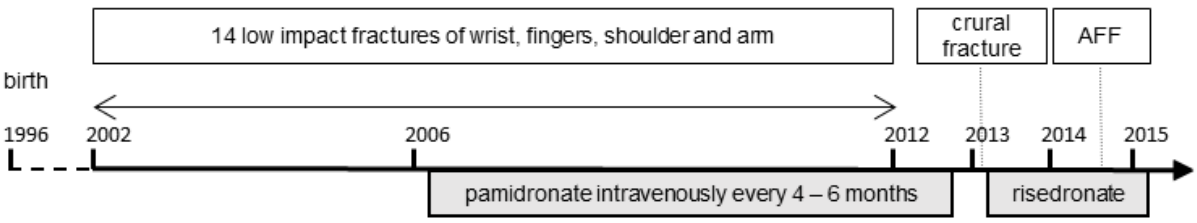


Figure 3

Figure 3: *Horizontal diagram describing the timing of fractures and bisphosphonate use.*

Several previous studies point out the actuality of atypical fractures in patients with OI treated with bisphosphonates. In a retrospective study amongst 176 bisphosphonate-treated patients with OI compared to a historic group without bisphosphonate treatment, an apparent change in pattern of fracture was observed. In the bisphosphonate-treated group proximal, subtrochanteric fractures without any history of trauma were more frequently observed compared to the control group(11). In case reports, AFFs have been described in adults with OI and bisphosphonate treatment(12,13), where a possible synergistic relationship between atypical fractures associated with bisphosphonate use and OI was suggested by the authors(13).

Recently a manuscript was published describing six children with OI who had sustained unusual subtrochanteric femoral fractures located over pre-existing intramedullary rods. Although these fractures do not fit the definition of an AFF because of the presence of the intramedullary nails, the authors proposed the possibility of a pediatric variant of the AFF associated with prolonged bisphosphonate use (14). Similarly, these children also displayed atypical fractures without prior trauma in other bones, such as the humeri.

A potential underlying genetic susceptibility for AFFs has been advocated occasionally by the manifestation of these fractures in various monogenetic bone disease other than OI with or without prior use of bisphosphonates like hypophosphatemia, hypophosphatasia, osteopetrosis and pycnodysostosis(15–21). Our finding of AFF in an adolescent boy who was treated long-term with bisphosphonates intravenously for X-linked osteoporosis contributes to the hypothesis that these rare fractures may have an underlying genetic predisposition a least in some cases.

Our patient has received a cumulative dose of pamidronate infusions of 2107mg and 3500mg of risedronate orally. We propose that children and adolescents who are extensively treated with bisphosphonates for conditions such as OI, juvenile familial osteoporosis or secondary osteoporosis are at risk of an AFF. We underline that in previous studies atypical, low-energetic stress fractures appear to occur in other weight-bearing bones as well, such as the tibia fracture in our case(22,23).

The possibility of the occurrence of AFFs in children treated with bisphosphonates should be considered in decision-making about the duration of therapy. Our case is important to view in light of the current tendency to continue bisphosphonates in children until growth is fully or nearly complete. In conclusion, we report for the first time an adolescent boy with X-linked osteoporosis due to a PLS3 mutation who developed a classical AFF after seven years of

intravenous and two years of oral bisphosphonate use. Furthermore, he experienced an unusual fracture of the lower leg after a minor trauma two years earlier. These findings highlight that AFFs also occur in adolescents treated with bisphosphonates during childhood and suggest that similarly low trauma fractures of other bones may be related to long-term use of bisphosphonates. Moreover, this case supports the concept of an underlying genetic predisposition in some cases of AFF. The possibility of AFFs in children with bisphosphonate therapy for OI or other bone disorders at risk for fragility fractures should be taken into account when deciding upon the continuation of antiresorptive drugs. Pain in weight-bearing bones amongst these patients should prompt investigation for an incomplete AFF.

Disclosure summary

All authors have no conflicts of interest.

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Authors' roles: Study design: DvdL and MCZ. Data collection: DvdL and MCZ
Patient evaluation: MCZ. Drafting manuscript: DvdL and MCZ. Revising manuscript content: DvdL and MCZ. Approving final version of manuscript: DvdL and MCZ. DvdL and MCZ take responsibility for the integrity of the data analysis.

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