Case report

Atypical femoral fracture in a 51-year-old woman: Revealing a hypophosphatasia

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A B S T R A C T

We report a 51-year-old woman who suffered 2 atypical subtrochanteric femoral fractures (AFFs). She had a history of several metatarsal fractures. She had a normal bone densitometry. An adult form of hypophosphatasia (HPP) was diagnosed from low serum alkaline phosphatase (ALP), and tissue nonspecific isoenzyme of ALP (TNSALP) mutation analysis revealing 2 heterozygous mutations: c.299C>T (p. T100M) and c.571G>A (p. E191K). Low ALP is the hallmark of the diagnosis of HPP; which is associated in adults with premature loss of deciduous teeth, recurrent metatarsal stress fractures, and joints and tendons disorders. The incidence of AFFs in the population is 5.9 per 100,000 person-years. Physicians and patients with bone fragility must pay attention to prodromal pain, which require urgent radiographic evaluation of both femurs. Rheumatoid arthritis, use of glucocorticoids, and proton pump inhibitors have been associated with an excess risk of AFFs. Healthy subjects carrying a TNSALP mutation with low ALP value may be exposed to develop AFF spontaneously or while receiving potent anti-resorptive drugs. Low ALP must be checked as a cause of bone fragility.

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1. Introduction

Atypical subtrochanteric femoral fractures (AFFs) have been reported in patients using bisphosphonates or denosumab as anti-resorptive therapy for osteoporosis. AFFs are located below the lesser trochanter to the supracondylar flare, occur with no or low trauma, and have a transverse or short oblique morphology [1]. In a study of 12,777 women 55 years and older who sustained a subtrochanteric femoral fracture, 59 were considered as atypical; among them 13 occurred in subjects who never received bisphosphonate [2]. Thus, other risk factors can be related to these atypical fractures. We describe a middle-aged woman who sustained such a fracture, revealing an unexpected bone disease.

2. Case report

A 51-year-old woman was referred for medical treatment after surgery for a fracture of the left femoral diaphysis, related to a fall from a standing position. Major criteria of diagnosis of AFF, as defined by the American Society for Bone and Mineral Research [1] were fulfilled. The fracture was subtrochanteric, related to a fall from a standing height, has a transverse and non-communited configuration, and associated with a medical spike (Fig. 1). The patient had no prodromal pain of the thighs.

This was actually the second one, as the patient reported having had a non-trauma fracture of the right femoral diaphysis 3 years before with a delay of healing of about 2 years. Retrospective analysis of the X-rays confirmed that this fracture had also diagnostic criteria of AFF. The patient recalled having had 6 or 7 metatarsal fractures, with healing delay, since the age of 15 years (Fig. 2). Moreover she reported early teeth loss. She never received any anti-osteoporotic treatment and had no family history of low trauma fractures. Bone mineral density was measured by dual-energy X-ray absorptiometry; T score were +2.9 and +0.6 at the lumbar spine and femur, respectively.

In view of this medical history, the diagnosis of hypophosphatasia (HPP) was considered and confirmed by low serum alkaline phosphatase (ALP) activity: 8 U/l (35–60 U/l). Serum calcium, phosphate, 25-hydroxyvitaminD [25(OH)D] levels were normal. Tissue nonspecific isoenzyme of ALP (TNSALP) mutation analysis revealed 2 heterozygous mutations: c.299C>T (p. T100M) and c.571G>A (p. E191K).

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Fig. 1. Atypical femoral fracture in a 51-year-old woman: subtrochanteric fracture with a transverse and non-comminuted configuration, and associated with a medical spike; in patient suffering from hypophosphatasia.

3. Discussion

AFFs have been described in monogenic disorders that cause osteomalacia: hypophosphatasia and X-linked hypophosphatemia, and heritable diseases of low bone turnover: osteoporosis and pycnodysostosis. Hypophosphatasia is an inborn loss-of-function mutation within the gene ALPL that encodes the cell surface enzyme tissue nonspecific isoenzyme of ALP. As a consequence, there is an accumulation of the substrate, inorganic pyrophosphate, which blocks the mineralization process. It is a rare disorder with an estimated prevalence between 1/100,000 and 1/300,000 in severe forms, and 1/6370 in moderate form [3,4]. Low ALP is the hallmark of the diagnosis; the prevalence of this biological abnormality has been reported to be 0.06%, in a large rural multispecialty clinic population, using a threshold of 30 U/l to define persistent low ALP [5]. We have shown that low ALP level is not recognized in a clinical setting; among 48,755 patients who had ALP assessment in a tertiary hospital over one year, 62 had persistent low ALP (below 40 U/l) and this low value was noticed in the discharge summary for 2 patients only, without any comment [6].

As the phenotype varies greatly in severity depending on the degree of residual enzyme activity, the diagnosis of adult form of HPP is a challenge. The severity of the disease is thought to be associated with the early age of onset. Patients could be in good health in early childhood, and, as our patient, considered as unaffected by any skeletal problems. However, attention must be paid on premature loss of deciduous teeth, early loss or extractions of adult teeth, recurrent metatarsal stress fractures, and some joint and tendon diseases (chondrocalcinosis, enthesopathies, calcific arthropathies), which are more frequent in subjects with low serum values of ALP [5,7]. Delay of diagnosis of adult forms is estimated to 4 and 6 years for women and men respectively [7]. In our case, the diagnosis has been made at 51 years, although symptoms as stress fractures should have alarmed before. Beyond the genetic HPP, multiple causes of hypophosphatasia should be considered: profound hypothyroidism, Cushing disease, cancer, chemotherapies... and use of any treatment decreasing bone remodeling such as bisphosphonates, being the main causes [5].

In a report of 22 cases of hypophosphatasia, diagnosed in adults (49 years old on average), 4 had subtrochanteric femoral fractures, all observed in women. In this genetic disorder, these fractures can be bilateral, beginning as pseudofractures of the lateral cortex of the diaphysis. The incidence of atypical femoral fractures in the population is low: 32 per million person-years [8] and 5.9 per 100,000 person-years in a retrospective study from 1996 to 2009 [9]. It is estimated that among non-trauma fractures of the femur, 12.5% are subtrochanteric, and among them 4% are atypical [10]. Attention must be paid in patients with bone fragility to prodromal pain such as dull or aching pain in the groin or thigh, especially in case of bilateral symptoms. Physicians and patients must be aware of these symptoms, which require urgent radiographic evaluation of both femurs (even if pain is unilateral). If plain radiographs are normal or equivocal and clinical suspicion is high, MRI or radionuclide scintigraphy should be performed. MRI can detect a stress fracture, as a cortical fracture line, associated with bone and marrow edema or hyperemia. Rheumatoid arthritis, use of glucocorticoids, and proton pump inhibitors have been associated with an excess risk of AFFs. Concomitant glucocorticoids is associated with a fivefold increased risk of subtrochanteric fractures, proton pump inhibitors use was noted in 39% of AFFs reported in patients with bisphosphate exposure [11]. Bisphosphonate use is one of the associated risk factors, with a risk increasing with duration of use [1,2].

In our case, ALP values were deeply low, although not recognized by the physicians who dealt with the repeated fractures of the patient. The primary clinical utility of ALP assessment is the diagnosis of bone disease with increased ALP value because of a high bone turnover (osteomalacia, Paget’s disease...), and little attention is paid to the low values of ALP [6]. Healthy subjects carrying a TNSALP mutation with low ALP value (including in the lower part of the normal range) [11] may be exposed to develop AFF while receiving potent anti-resorptive drugs [12,13].

The clinical lesson from the patient is that low serum alkaline phosphatase must be checked as a cause of bone fragility, even in an adult 50 years old. Diagnosis of HPP is relevant to prevent the prescription of anti-resorptive drugs.

Disclosure of interest

Esther Maman declares that she has no competing interest.
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