Multiple osteonecrosis as a form of presentation of osteogenesis imperfecta

Summary
The case of a woman diagnosed with osteogenesis imperfecta, who presented with multiple osteonecrosis, is described. To our knowledge, this is the first reported case of such a clinical presentation. The therapy, as well as the outcome for the patient, is also analysed.

Keywords: osteogenesis imperfecta, osteonecrosis, teriparatide, denosumab.
Introduction

Osteogenesis imperfecta (OI) is a congenital disease of the connective tissues, of autosomal dominant inheritance, which affects the gene for collagen type I, present in many tissues such as bone, tendons, ligaments and scera. The disease is classified in various types, from type I (the most frequent and lightest) and type II (lethal at birth), to types III, IV, V, VI and VII which present phenotypes of varying intensity from moderate to severe.

The principal clinical manifestations of OI are recurrent fractures and secondary bone deformities. Dentinogenesis imperfecta and a blue colouration of the scera are also common characteristics of this disease. Its diagnosis is based on its clinical manifestations and on the presence of family antecedents. The administration of calcium and vitamin D, and the bisphosphonates, are the basis of treatment.

On the other hand, primary or idiopathic osteonecrosis has been related with fractures due to an insufficiency in the chondral bone. Unlike the secondary form, there are usually no predisposing factors and the disease is associated with the female sex, advanced age and obesity. The diagnostic text of choice is nuclear magnetic resonance (NMR), with a hypersignal in the bone marrow at T sequences and a hypersignal in the STIR sequences or for fat saturation T2.

We present the case of a patient with osteogenesis imperfecta, which made its first appearance as multiple osteonecrosis. To our knowledge, this is the first case described in the literature of this form of presentation of the disease. The treatment administered and the development of the patient are analysed.

Presentation of Case

A woman of 47 years of age without toxic habits, known drug allergies, or relevant medical conditions. She attended hospital in January 2010 due to the presence of pain in the right ankle over the previous year, which increased with load and which was accompanied by flogotic signs. A bone gammagrapy was carried out, as well as an NMR which showed an intense bone oedema with severe loss of mineral density, suggestive of osteonecrosis of the astragalus bone with associated articular leaking (Figure 1A). Treatment with intravenous pamidronate was initiated, but the patient presented high fever following the infusion, for which reason the administration was halted.

Tramadol, diclofenac and rehabilitation treatment were prescribed, without evident easing of the pain. In September 2010 she reported intense pain in the right inguinal region, which increased when walking. An NMR scan was performed in both hips with avascular necrosis being observed in the right femoral head, stage I-II in the FICAT classification (Figure 1C). Treatment was initiated with oral gabapentin (600mg/8 hours), and she was referred to a bone metabolism unit. In the physical examination in our clinic what drew our attention was the presence of blue scerae (Figure 2). On questioning the patient again, she indicated that her mother had had multiple fractures from the age of 49, which immobilised her. A brother and two maternal aunts had suffered early hip fractures. The densitometer showed serious osteoporosis in the three usual locations (lumbar spine: T-score=-3, Z-score=-1.8; femoral neck: T-score=-3.1, Z-score=-2.3 and total hip: T-score=-2.7, Z-score=-2.0). The calcium was 336 mg/dl, levels of 25(OH) vitamin D 11 ng/ml and intact PTH, 49 pg/ml. The markers for bone remodelling were clearly high (CTX: 1.036 ng/ml). Given the clinical findings and the family history, the diagnosis of osteogenesis imperfecta type I was established.

The audiometry showed a minimal fall in the acute tones. Treatment was initiated with calcium (1,000 mg/day), vitamin D (800 UI/day) and risedronate (35 mg/week), in January 2011. In March of that year the risedronate was changed for subcutaneous teriparatide (20 mcg/day) due to digestive intolerance. In May 2011 an NMR check showed a clear reduction in the bone oedema and in the articular leaking in the ankle, as well as in the oedema in the bone marrow of the right hip (Figures 1B and 1 D). The patient completed 24 months with teriparatide without complications and with progressive clinical improvement. The markers for bone formation remained high during the treatment (aminoterminal propeptide of procollagen type 1 –PINP–: 45 ng/ml; osteocalcin: >100 ng/ml), as did the levels of 25 (OH) vitamin D. In March 2013 treatment was initiated with denosumab (60 mg/6 months), the patient presenting satisfactory clinical and radiological development. In the last consultation, in January 2015, the markers for remodelling were suppressed (PINP: 5.8 ng/ml; carboxy-terminal telopeptide of collagen type 1–CTX–: <0.030 ng/ml) and levels of 25 (OH) vitamin D of 31 ng/ml. The bone mineral density (BMD) level was not significantly reduced with respect to the baseline figure (lumbar spine: T-score=-3.1 and Z-score=-1.5; femoral neck: T-score=-3.2 and Z-score=-2; total hip: T-score=-3 and Z-score=-2), but the patient had suffered no fractures or osteoporosis in the follow up period.

Discussion

Osteogenesis imperfecta is the most common congenital disease of bone tissue. We believe that our case has special interest due both to the unusual form of presentation (osteonecrosis of ankle and hip) and the clinical and radiological response to the treatment received.

The osteonecrosis was interpreted as being primary, given that the patient did not have any predisposing factors and had not received any treatment which might impact on the bone. We are not able to discount, as a hypothesis, the possibility that the osteonecrosis may have been secondary to the patient’s OI, taking into account the fact that the microscopic alterations in the trabecular bone characteristic of this genetic disease may be associated with lesions of ischemic origin typical of osteonecrosis.
In our patient, due to her serious necrosis, treatment was initiated with bisphosphonates, which were withdrawn due to an adverse reaction (pamidronate) or digestive intolerance (risedronate). For this reason, a sequential combination of teriparatide and denosumab were administered, with an excellent clinical and radiological response in the patient’s osteonecrosis.

The bisphosphonates are the first option for treatment of OI and, although its efficacy has been demonstrated in children, studies in adults are scarce. In general terms, the treatment is the same as that for osteoporosis, even though the fact that the physiopathology of the two diseases is different needs to be taken into account. While in osteoporosis a loss of bone mass predominates, in OI an alteration in the bone matrix is prevalent, which could explain that lack of efficacy of these drugs in the prevention of fractures in some cases of OI.

In this respect, the therapeutic alternatives available to us are few. The use of teriparatide in light forms of OI has been suggested in some works, but without conclusive data. Thus, Orwol et al. analysed the efficacy of this drug in adults with OI type I, observing a significant increase in BMD in the lumbar spine and hip, although no differences were observed in the risk of fracture compared with the group which received the placebo. Gatti et al., studied 13 postmenopausal women with OI who had received treatment with neridronate over two years and had suffered a fracture during this period. Teriparatide was administered to them for 18 months with a significant increase being observed compared with the base-
line value in the lumbar spine but not in the hip, data similar to those found in our patient. The authors suggest the possibility that the treatment with teriparatide is not that effective in terms of increasing the BMD, as is the case in postmenopausal or senile osteoporosis8.

At the present time, biological drugs are being evaluated for the treatment of OI, such as denosumab or anti-sclerostin antibodies, as well as gene therapies based on mother cells9.

With respect to treatment with denosumab, there are studies which have been carried out in children with OI type VI. This condition is characterised by an autosomal recessive mutation in the SERPINF1 gene, which leads to the activation of the osteoclasts through the RANK/RANKL pathway, which has resulted in the use of denosumab as an alternative to treatment with bisphosphonates in those patients who have a poor response to them10. Our patient presented a good clinical development, with stability in BMD and a congruent response in the markers for bone remodelling, after the prescription of teriparatide and, subsequently, denosumab. Furthermore, the osteonecrosis in the hip improved in the radiological checks which were carried out.

In the light of this case, and the literature review, the use of teriparatide, followed by denosumab in patients with OI and intolerance to, or adverse effects with, the bisphosphonates, could be taken into consideration.

**Bibliography**