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REVIEW ARTICLE

Osteogenesis imperfecta type V: About a clinical case

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Abstract Osteogenesis imperfecta (OI) is a rare inherited connective tissue disorder. It is characterized by short stature, fragility and decreased bone mass, which leads to multiple and recurrent fractures after low-energy trauma, which generates susceptibility to long bone deformity and vertebral compression. There are several types of OI, with types I to IV, in which the *COL1A1* and *COL1A2* genes are affected, being the most frequent. In recent years, the discovery of new forms of OI has led to research into the pathways critical aspects of bone metabolism, with new genes involved being identified. The mutation in *IFITM5* has been identified as the cause of OI type V, of autosomal dominant inheritance. OI type V has distinctive clinical features including the development of hypertrophic callus after fracture, early calcification of the interosseous membrane in the forearm, and the presence of hyperdense metaphyseal bands.

The case of a patient with a novo mutation in *IFITM5* is presented.

PALABRAS CLAVE
Osteogénesis imperfecta;
Displasia esquelética;
Mutación;
IFITM5;
Densidad mineral ósea;
Bifosfonatos

Osteogénesis imperfecta tipo V: a propósito de un caso clínico

Resumen La osteogénesis imperfecta (OI), es un trastorno hereditario del tejido conectivo poco frecuente. Se caracteriza por talla baja, fragilidad y disminución de la masa ósea, lo que conlleva fracturas múltiples y recurrentes después de traumatismos de baja energía, que genera susceptibilidad a la deformidad de huesos largos y compresión vertebral. Existen varios tipos de OI, siendo los tipo I a IV, en los que se afectan los genes *COL1A1 y COL1A2*, los más frecuentes. En los últimos años, el descubrimiento de nuevas formas de OI, ha llevado a investigar las vías críticas del metabolismo óseo, siendo identificados nuevos genes involucrados. La mutación

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en *IFITM5* se ha identificado como la causa de la OI tipo V, de herencia autosómica dominante. La OI tipo V presenta características clínicas distintivas, entre las que se incluyen el desarrollo de callos hipertróficos después de una fractura, la calcificación temprana de la membrana interósea en el antebrazo y la presencia de bandas metafisarias hiperdensas.

Se presenta el caso de una paciente con mutación de novo en *IFITM5*.

Introduction

Osteogenesis imperfecta (OI) is a phenotypically and genetically heterogeneous skeletal dysplasia, characterized by bone fragility, growth deficiency, and skeletal deformities. It is caused by genetic defects that result in alterations not only in collagen structure but also in its folding, modification, post-translational processing, bone mineralization, and osteoblast differentiation. In OI, the function of other connective tissues is also affected, causing imperfect dentinogenesis, hearing loss, joint hyperlaxity, blue sclerae, basilar invagination, and cardiorespiratory defects.

The classical types I to IV of OI, which are autosomal dominant in inheritance, are the most common and are caused by structural or quantitative defects in the genes that code for the α1 and α2 chains of type 1 collagen. In recent years, the discovery of new forms of OI has led to the investigation of critical pathways involved in bone metabolism. Two of these recently identified causal genes are responsible for other inherited forms of OI in an autosomal dominant manner: *IFITM5* (type V) and *WNT1* (type XV).[1]

Type V OI is a non-lethal skeletal dysplasia with various clinical presentations. Its severity is highly variable, even within the same family. It is caused by a pathogenic point mutation (c.-14C > T) in the 5′ UTR of the *IFITM5* gene, an autosomal dominant mutation that results in the addition of five amino acids (Met-Ala-Leu-Glu-Pro: MALEP) to the N-terminal of the protein.[2]

IFITM5 is a transmembrane protein whose production is induced by interferon, also known as BRIL (Bone-restricted IFITM-like), which is osteoblast-specific and plays a role in matrix mineralization, osteoblast maturation, and prenatal bone formation.[2,4]

The change in the protein structure leads to altered osteoblastic function in the bone with ectopic ossification in the interosseous membrane and the formation of hyperplastic bone calluses at the bone healing site, with the phenotype being a combination of osteoporosis and exuberant bone formation.[5]

To date, nearly 200 cases have been reported worldwide.[3,4]

Case report

A 38-year-old woman, clinically diagnosed with OI since 1987 at the age of 18 months, presented with radiological characteristics such as wormian bones in the skull (small accessory bones located in the sutures of the skull) and a left radius fracture after a low-impact fall. There was no family history of the disease.

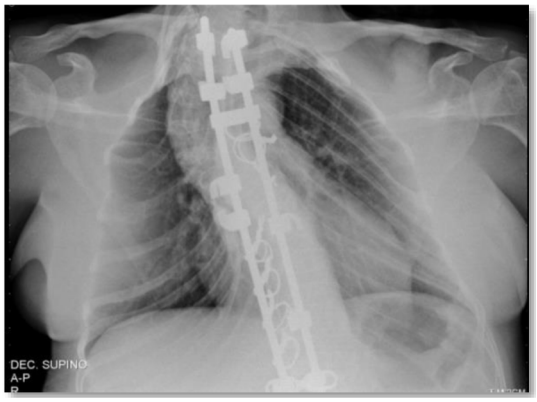

Figure 1 Surgical correction of severe scoliosis.

She was previously followed by the pediatric service of another hospital until 2007. The initial genetic study did not show any mutations in the *COL1A1* and *COL1A2* genes.

At the age of 11, she had been diagnosed with severe respiratory restriction related to severe scoliosis, which required surgical correction (Fig. 1). She had a past medical history of multiple fractures requiring surgery up to 6 times, all due to low-impact trauma and falls.

During her childhood, she received growth hormone treatment and, later, between the ages of 17 and 21 (2002–2006), she had been treated with cycles of IV pamidronate, which resulted in improved bone mineral density.

She was referred to the Endocrinology Service at the Osteogenesis Imperfecta Unit of the *Hospital Universitario de Getafe* (HUGF; Madrid, Spain) in 2007 at the age of 22.

Upon physical examination, the patient's weight was 43.9 kg, height 136.5 cm, BMI 23 kg/m^2, with blue sclerae, no imperfect dentinogenesis, narrow thorax with severe scoliosis, ligamentous hyperlaxity in extremities, and left elbow deformity.

Upon initial evaluation in our unit, there was evidence of worsening bone mineral density (BMD) and femur fracture with bone pain after discontinuation of treatment in 2006, prompting initiation of treatment with strontium ranelate in 2007. Although this treatment improved BMD, in 2011, it

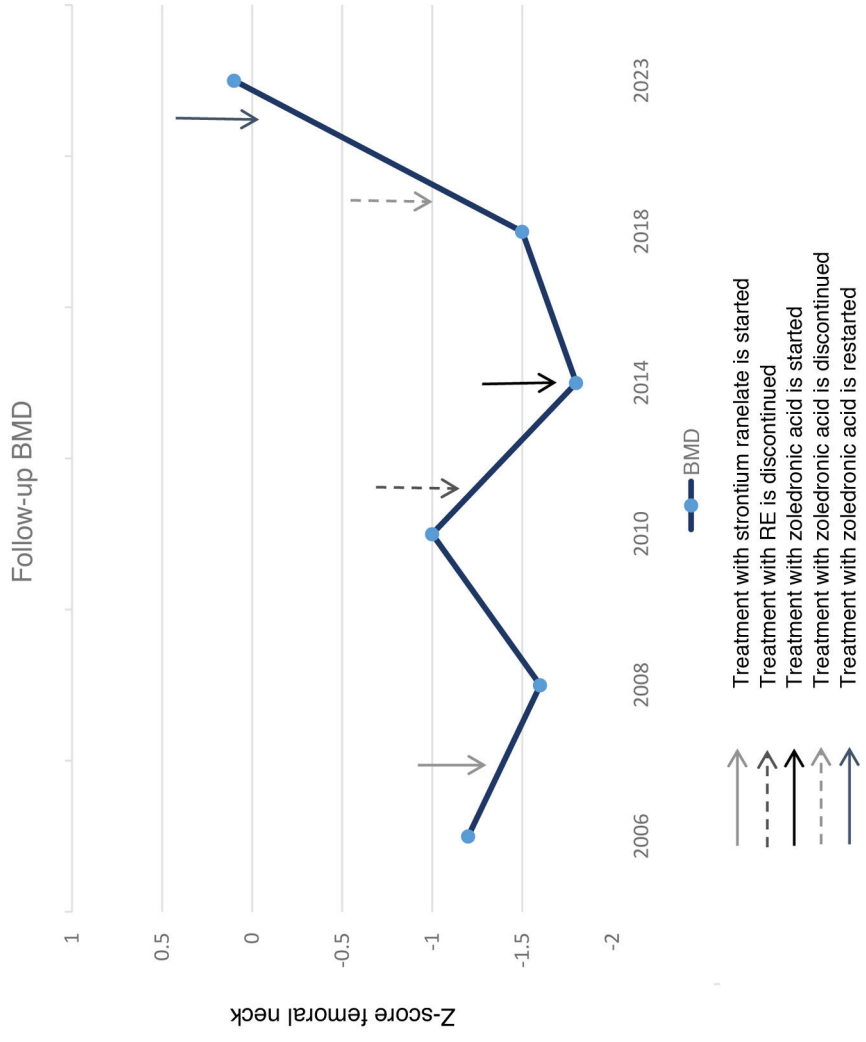

Figure 2 Progression of BMD, measured as Z-score in the femoral neck. *Due to metal fixations in the spine, BMD cannot be measured at this location.

Figure 3 Calcification of the interosseous membrane.

was discontinued due to health alerts associating it with an increased risk of myocardial infarction (Fig. 2).

In March 2014, at the age of 29, treatment with zoledronic acid was initiated due to worsening BMD, new fractures of the left femur, tibia, and fibula, which showed consolidation issues, and generalized bone pain. This treatment improved pain but with minimal densitometric improvement (Fig. 2).

Despite active treatment, in 2017, the patient suffered a new right femoral shaft fracture (from a fall) requiring surgery for intramedullary nailing, with significant consolidation problems. In 2018, she suffered another fall, with a fracture of the right radial head and a fracture in the left proximal ulna, which were managed conservatively (Fig. 3).

In 2019, at 34 years old and after 5 years on zoledronic acid therapy, a therapeutic break was agreed upon, and zoledronate was discontinued after 7 doses of 4 mg (Fig. 2).

In 2021, a new genetic study was requested because the previous analysis only examined *COL1A1* and *COL1A2* genes. As new genetic variants involved in the pathogenesis of this disease had been identified, and since new variants are described annually, the genetic study was expanded through next-generation sequencing of the entire exome (xgen exome panel v1.0). The analysis, filtered for genes included in the OI panel, identified the pathogenic *c.-14C > T* variant in the *IFITM5* gene, in heterozygosis. Given the absence of parental involvement, this was considered a de novo mutation, confirming the diagnosis of type V OI.

In June 2022, zoledronic acid treatment was resumed due to symptoms of asthenia and generalized bone pain, continuing until present time (Fig. 2).

Discussion

Type V OI was first clinically described in 2000 as a condition unrelated to pathogenic variants in the type 1 collagen genes (*COL1A1, COL1A2*).

This form of OI is caused by a recurrent autosomal dominant pathogenic variant in the 5'-UTR region of the interferon-induced transmembrane protein 5 (*IFITM5*) gene, which encodes the BRIL (Bone-restricted IFITM-like) protein, a transmembrane protein induced by interferon and restricted to bone, playing a positive role in osteoblast mineralization. The reported pathogenic variant is almost invariably *c.-14C > T* in heterozygosis; however, a recent case with the *c.119C > T* variant has been documented, associated with a severe form of the disease.[6]

Type V OI accounts for approximately 5% of OI diagnoses. Although it shows significant clinical heterogeneity, most patients present with moderate-to-severe forms of OI.

Type V OI presents clinical and radiological characteristics that distinguish it from the classic OI variants (types I–IV). Although all forms share a predisposition to frequent bone fractures occurring with minimal trauma, they differ in key characteristics.

Types I and IV are typically associated with blue sclerae and imperfect dentinogenesis. Type V, however, is characterized by normal sclerae and generally does not present dental involvement.[7]

In type V OI, radiological signs such as interosseous membrane calcification (Fig. 3) are common, which appear as a hyperdense metaphyseal band in the forearm, severely limiting pronation-supination,[5,6,8] and hyperplastic callus formation after fractures or surgical procedures. Radial head luxations are a common finding, and scoliosis is present in about two-thirds of cases. Additionally, bone mineralization may be excessive, affecting bone shape and strength, leading to atypical fractures that are less predictable and often more resistant than conventional therapies.

Before the nature of this form of OI was understood, some patients were misdiagnosed with osteosarcomas.[7]

Our patient presents blue sclerae, normal dentin, and no radial head luxations. As mentioned earlier, while patients with this type of OI typically have normal or slightly colored sclerae, it is important to recognize that in many genetic conditions, individual variability in clinical presentation can occur, which explains why some individuals with type V OI may display this unusual trait.

Of note, symptoms and disease severity can vary significantly across patients, even within the same family. While OI is often diagnosed in childhood due to frequent fractures and features such as blue sclerae, some forms of OI may manifest later in life, even in adults, where symptoms may be subtle and overlooked. This variability can include recurrent fractures, bone pain, and dental issues that may not initially be associated with OI. Recognizing these presentations in adults is crucial, as it helps identify undiagnosed cases and provide an accurate diagnosis, which, in turn, allows for better management and treatment of the disease.[9]

Regarding pharmacological therapy, while there is no specific treatment, bisphosphonates (BP) have been the most widely used drugs to counteract the systemic effects of OI. Their beneficial effect on bone mineral density in these patients is well-established. The effect of BPs on the incidence rate of fractures is more controversial, although there is agreement on a likely beneficial effect in reducing the number of fractures per patient (it should be assumed that patients will continue to fracture). IV BPs have positive effects on pain and quality of life.[9–13]

However, BPs do not improve bone tissue connectivity, have a long half-life in bone, and the effects of prolonged use throughout time are not well understood.

Currently, there are no data on the use of BPs in patients with type V OI, and their effect on hyperplastic bone cal-

luses is still to be elucidated.[14,15] It has been speculated that the response to BPs in these patients may be worse than expected because their pathogenesis differs from that of other types.[15]

Other drugs studied in OI, such as teriparatide, have shown positive effects only in patients with type I OI.[16–18]

On the other hand, rehabilitation and physical therapy have been considered part of the treatment for type V OI, as they improve quality of life and functionality by strengthening muscles and protecting joints, thereby reducing the risk of fracture. These programs help maintain the range of motion, especially in limbs affected by calcification, and help prevent deformities and improve posture. Moreover, physical therapy promotes functional independence through exercises that improve coordination and balance, thus facilitating safe completion of daily tasks. It also provides emotional benefits, as progress in treatment increases self-esteem and motivation.[19]

A rehabilitation and physical therapy program, along with multidisciplinary care, not only minimizes physical complications but also enables a more active and fulfilling life. It can help manage pain and functional independence, improve strength and endurance, prevent deformities, and enhance the patient's quality of life.[20]

Therefore, diagnosing OI type V and differentiating it from other variants is crucial to provide appropriate clinical management, as this form presents unique characteristics, such as abnormal calcifications and hypertrophic calluses, requiring specialized management, especially in surgical procedures. Moreover, OI type V is linked to a mutation in the IFITM5 gene, distinct from the mutations in the type 1 collagen genes present in types I-IV, which affects the response to treatments like BP. A precise diagnosis avoids confusion with other conditions, such as osteosarcoma, and enables adequate follow-up, genetic counseling, and personalized treatment, thus optimizing the patient's prognosis and quality of life.

Conclusions

OI type V is a distinctive and complex form of skeletal dysplasia characterized by bone fragility and clinical variability in its presentation. Unlike the classic types of OI, OI type V is caused by a mutation in the *IFITM5* gene, highlighting the genetic heterogeneity of the disorder. This type of OI not only affects collagen structure but also bone metabolism, resulting in unique clinical signs, such as calcification of the interosseous membrane and formation of hypertrophic bone calluses.

Timely diagnosis is crucial, especially in adults who may have been misdiagnosed or previously undiagnosed. The identification of the pathogenic mutation through genetic studies allows for the establishment of appropriate management, which includes pharmacological treatments, such as bisphosphonates, and a multidisciplinary approach integrating rehabilitation and physical therapy. These treatments are essential not only to improve bone density and prevent fractures but also to optimize the patient's quality of life and functionality.

As understanding of this condition advances, it is vital to increase awareness of the clinical characteristics of OI type V and the importance of an individual therapies. With appropriate management, patients can lead more active lives with better quality of life, despite the challenges this disease presents. In conclusion, OI type V illustrates the need for a precise diagnosis and comprehensive treatment to improve the overall well-being of those affected.

Declaration of competing interest

None declared.

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