CASE REPORT

Worsening of Callus Hyperplasia after Bisphosphonate Treatment in Type V Osteogenesis Imperfecta

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Background: Type V osteogenesis imperfecta is characterized by hyperplastic callus formation and interosseus membrane calcification. **Case characteristics:** A 16-year-old boy who presented with history of recurrent fractures, had hard persistent swellings at fracture sites, and had radiographic features of hyperplastic callus and interosseus membrane calcification. **Outcome:** Sequence analysis of the *IFITM5* gene revealed the c.-14 C>T mutation. The patient had significant exacerbation of callus hyperplasia after initiation of bisphosphonate therapy, which reversed following cessation of the treatment. **Message:** Bisphosphonates may exacerbate callus hyperplasia, and may therefore have to be used with caution in patients with type V osteogenesis imperfecta.

Keywords: *Bisphosphonates, Fractures, Osteogenesis imperfecta.*

Osteogenesis imperfecta (OI) is a clinically and genetically heterogeneous group of disorders characterized by bone fragility and increased susceptibility to fractures. Around 15 different types are known, with significant phenotypic overlap amongst the different types making clinical differentiation difficult [1,2]. Type V OI has distinct clinical and radiological features, and is associated with a specific mutation in the *IFITM5* (Interferon-induced transmembrane protein 5; OMIM *614757) gene, which make it relatively easy to diagnose [3,4].

While bisphosphonate therapy is the standard of care for most forms of OI, literature pertaining to its use in Type V OI is limited [5,6]. We report a patient of type V OI, who had exacerbation of callus hyperplasia on treatment with bisphosphonates.

CASE REPORT

A 16-year-old boy, the first offspring of non-consanguineous parents, presented with a history of recurrent (five) fractures following minimal trauma since three years of age, and hard persistent non-tender swellings at the fracture sites. There was no history of hearing loss. There were no symptoms suggestive of any other chronic systemic disease. His developmental milestones and cognitive functions were normal. There was no significant family history.

The anthropometric measurements were as follows: height 154 cm (3rd centile for age), weight 40 kgs (5th centile for age) and head circumference 51 cm. Clinical examination revealed a diffuse, ill-defined, hard swelling over the upper lateral aspect of the left thigh. There was no other obvious bone deformity. The sclerae were white and the teeth were normal. Hearing assessment was normal in both the ears. The patient had limitation in the range of pronation and supination in both forearms, with a greater degree of impairment in the right forearm. Systemic examination was normal. Both parents were normal on clinical evaluation.

Skeletal radiographs revealed hyperplastic callus in the upper lateral part of the left femur (extending from the greater trochanter to the upper thirds of the femur) (***Fig.* 1a**), radiodense metaphyseal bands in the distal femora, proximal tibias and distal radii, and compression of the lower thoracic vertebral bodies. Interosseous membrane calcification was present in both upper and lower limbs (***Fig.* 1b**). Bone mineral density measured through dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femoral necks bilaterally was found to be low (T score ranging from -3.5 to -3.9).

Type V OI was suspected based on the clinical and radiological features. Sequence analysis of the first exon and the flanking 5′-untranslated region of the *IFITM5* gene revealed the c.-14C>T mutation, thereby confirming the diagnosis.

The patient was started on bisphosphonate therapy (oral alendronate 1 mg/kg/week) with calcium supplementation and was followed up on a monthly basis.

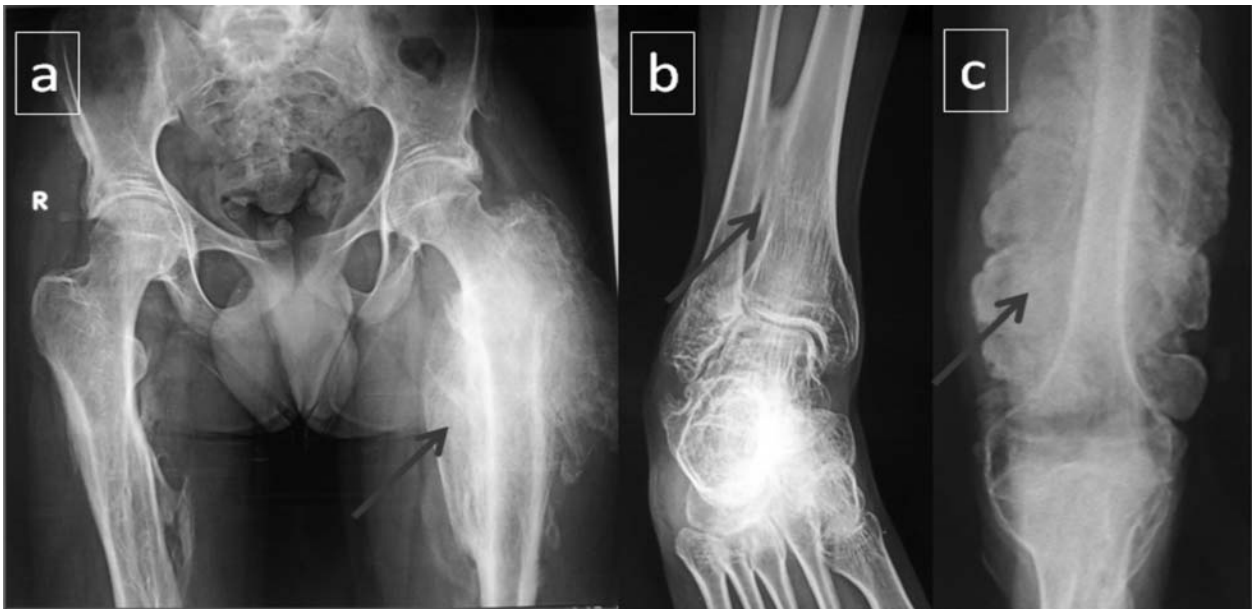

***Fig.* 1** *(a) Hyperplastic callus seen in the proximal part of the left femur before the initiation of bisphosphonate therapy; (b) calcification of the interosseus membrane seen between the distal parts of the tibia and fibula; (c) extensive callus formation along the left femur following initiation of bisphosphonate therapy in the patient.*

Over the next 10 months, he did not develop any fractures but there was a progressive increase in callus formation with extension of the callus from the proximal to the distal end of the left femur on both the medial and lateral aspects (***Fig.* 1c**), and new callus formation on the right femur and upper and lower parts of the left tibia and left fibula. As this exacerbation of callus formation appeared to be chronologically related to the bisphosphonate therapy, oral alendronate was discontinued. Following cessation of bisphosphonates, the patient has been on follow-up for three months, during which time there has been no further increase in the callus formation, and slight resolution of the callus around the left femur.

DISCUSSION

Type V OI, first described by Glorieux, *et al*. [3], is a distinct entity characterized radiologically by calcification of the interosseous membrane and hyperplastic callus formation, and histopathologically by a mesh-like appearance of the bone lamellae [3]. It is an autosomal dominant disorder and majority of cases occur sporadically due to a *de novo* mutation. As per the recently proposed nomenclature for OIs, type V OI is now referred to as OI with calcification in interosseous membranes [1]. The c.-14C>T mutation, which is till date the only mutation reported to cause type V OI, occurs in the 5′-untranslated region of the *IFITM5* gene, 14 bp upstream of the annotated translation initiation codon [4].

As for other forms of OI, management of type V OI involves supportive therapy to minimize fractures and maximize function, and orthopaedic intervention for fractures and spinal compression/deformity. Bisphosphonates (intravenous pamidronate and zolendronate, and oral alendronate and risedronate), which act by decreasing bone resorption, are being used for almost two decades in the management of all forms of OI [7]. There is limited information regarding the effects of the therapy on callus hyperplasia, which is an integral component of Type V OI. In a study by Cheung, *et al*. [5] in 23 patients with type V OI, pamidronate therapy was not found to influence the course of hyperplastic callus formation. In another study of 11 patients with type V OI, the response to pamidronate treatment was found to be the same as in other types of OI [6]. In our patient, the exacerbation in callus formation appeared to be chronologically related to, and thus attributable to the initiation of bisphosphonate therapy. Treatment with bisphosphonates in experimental models of osteoporosis has been found to be associated with increased callus size and mineralization and reduced callus remodelling [8]. Pathogenesis of type V OI is different from that of the other OI types in that the mutant allele appears to have a differential tissue-specific and chronology-specific expression (as suggested by the contradictory components of osteopenia *versus* ectopic calcification and hyperplastic callus), and this may lead to a deviant

response to bisphosphonate therapy in some cases with this OI type [9].

At present, no drug has been found to be beneficial in reducing callus hyperplasia or interosseous membrane calcification in Type V OI. Thus, although type V OI is relatively easy to diagnose, it remains a difficult condition to treat.

Contributors: PR: Clinical evaluation, diagnosis and management of patient, review of literature, preparation of manuscript; JS: Molecular genetic analysis of patient, inputs for manuscript preparation; RI: Clinical evaluation of patient, inputs for manuscript preparation; SRP: Genetic evaluation of patient, preparation and review of manuscript.

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