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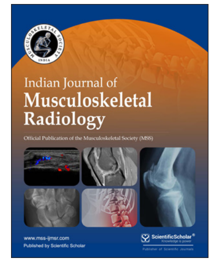

Case Report

Navigating the radiological landmarks in a rare case of osteogenesis imperfecta type V – A case report

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ABSTRACT

Osteogenesis imperfecta (OI) is a rare genetic disorder characterized by bone fragility due to defects in type I collagen. Among its subtypes, OI type V is distinct, presenting with hyperplastic callus formation, interosseous membrane ossification, and characteristic metaphyseal bands while lacking dentinogenesis imperfecta and blue sclera. This case report describes an 18-year-old male with a history of multiple fractures following minor trauma. Radiographic and clinical findings were consistent with OI type V. Genetic analysis confirmed a mutation in the interferon-induced transmembrane protein 5 gene. We discuss the unique radiological features, clinical presentation, and management strategies for this rare subtype, emphasizing the role of imaging in diagnosis and differentiation from other OI types.

Keywords: Hyperplastic callus, Interosseous membrane ossification, Multiple fractures, Osteogenesis imperfecta, Skeletal dysplasia

INTRODUCTION

Osteogenesis imperfecta (OI), also known as “brittle bone disease” or “fragilitas ossium,” is an inherited genetic disease characterized by abnormalities in the quantity and/or quality of type I collagen, which results in diminished bone density and increased bone fragility. OI occurs in a variety of forms, ranging from mild to severe clinical presentations. It can cause skeletal deformities, multiple fractures, short stature, and even death.[1]

While milder cases are significantly harder to diagnose and can occasionally be mistaken for non-accidental injury or “child abuse” in young children, severe cases are typically diagnosed before birth. Conventional radiography is still the gold standard for diagnosing OI, regardless of its severity.[1]

Although some cases are linked to autosomal recessive features or spontaneous mutation, it is typically described by an autosomal dominant mode of inheritance (95% of cases).[1]

OI affects about 1 in 10,000–20,000 newborns, making it uncommon but by no means extraordinary.[1] The collagen type I alpha 1 *(COL1A1)* or collagen type I alpha 2 *(COL1A2)* genes, which encode the pro-alpha 1 and pro-alpha 2 chains, respectively, are mutated in the great majority of cases. Intracellular type I procollagen, the precursor to extracellular type I collagen, is made up of these polypeptide chains arranged in a triple helix. The latter is a constituent of numerous tissues, including skin, tendons, ligaments, eye sclera, dental enamel, and bone.

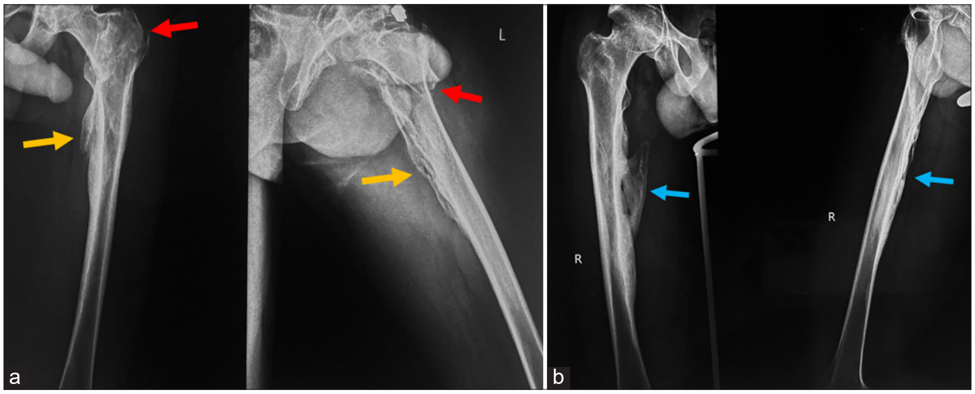

Figure 1: (a) Frontal and lateral radiographs of the left femur show healed old fracture of the proximal shaft with hyperplastic callus formation (orange arrows) and a displaced subtrochanteric fracture (red arrows). (b) Frontal and lateral radiographs of the right femur show healed old fracture of the midshaft with hyperplastic callus formation (blue arrows).

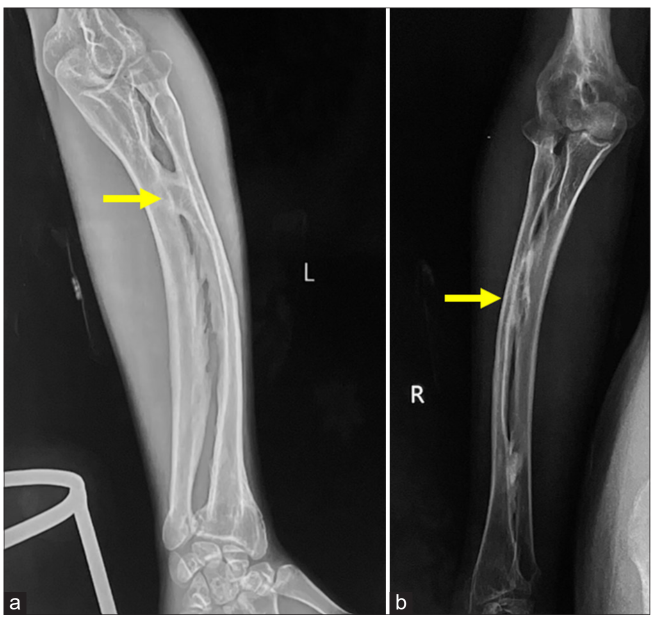

Figure 2: (a) Frontal radiograph of the left forearm shows ossification of the radioulnar interosseous membrane (yellow arrow). (b) Frontal radiograph of the right forearm shows ossification of the radioulnar interosseous membrane (yellow arrow).

Genetic mutations change the biomechanical characteristics of type I collagen, especially its resistance to stretching, by altering the spatial arrangement of the polypeptide chains. Therefore, bone fragility and other connective-tissue symptoms, with a wide range of phenotypes, are the hallmarks of OI.[2]

Patients with type V OI have moderate to severe bone fragility and moderate deformation. There is no dentinogenesis imperfecta or blue sclera. Three characteristics set it apart: Hypertrophic calluses at fracture locations, the existence of a radio-opaque metaphyseal band on radiographs adjacent to the growth plates, and the calcification of the interosseous membranes between the forearm bones. Histological analysis reveals that the bone organization differs significantly from the typical lamellar pattern, resembling an uneven mesh.[3]

CASE REPORT

An 18-year-old boy, born of a non-consanguineous marriage, presented with a fracture of the left proximal femur (subtrochanteric fracture) following a slip and fall on level ground. There is a similar history of multiple fractures and limb deformities from early childhood following trivial trauma which were managed conservatively. On clinical examination, his height for age was decreased. There was a scoliotic deformity of the spine. There was no blue sclera or dental abnormalities. There was no hearing loss or hyperlaxity of joints. There was no significant family history or similar history in his siblings.

Radiographs of the lower limbs and upper limbs were obtained. The bone density was not decreased. There was a mildly displaced subtrochanteric fracture of the left femur with adjacent cortical thickening and hyperplastic callus (HPC) formation along the medial aspect of the proximal meta-diaphyseal region [Figure 1a]. There was a healed old fracture of the midshaft of the right femur with similar HPC formation along the medial aspect [Figure 1b]. The proximal diaphysis of the left fibula showed cortical thickening along the lateral aspect. There was deformity with bowing of the shafts of the radius and ulna on both sides with calcification of the interosseous ligament [Figure 2a and b]. The radiograph of the thoracic spine showed scoliotic deformity with convexity to the right [Figure 3]. Radiograph of the skull showed basilar invagination and Wormian bones.

Computed tomography (CT) scan of the craniovertebral junction showed the tip of the dens projecting 15.1 mm above the Chamberlain line, suggestive of basilar invagination [Figure 4]. The Welcher's basal angle was increased (145°), suggestive of platybasia [Figure 5]. The finding of Wormian bones on the skull radiograph was confirmed on CT [Figure 6].

Figure 3: Frontal radiograph of the dorsal spine shows scoliotic deformity with convexity to the right.

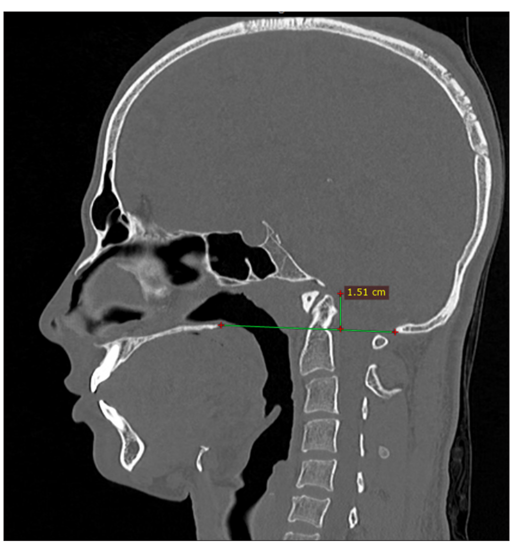

Figure 4: Sagittal computed tomography image of the skull with the craniovertebral junction shows the tip of the dens projecting 15.1 mm above the Chamberlain line, suggestive of basilar invagination.

Biochemical markers including vitamin D, calcium, phosphorus, and parathyroid hormones were within normal limits. Alkaline phosphatase levels were elevated (360 U/L).

A genetic workup was advised which revealed a mutation of the interferon-induced transmembrane protein 5 (*IFITM5*) gene, confirming the diagnosis of OI type V.

The patient underwent open reduction and internal fixation of the left subtrochanteric femur fracture [Figure 7] and was started on injection of zoledronate along with calcium supplementation.

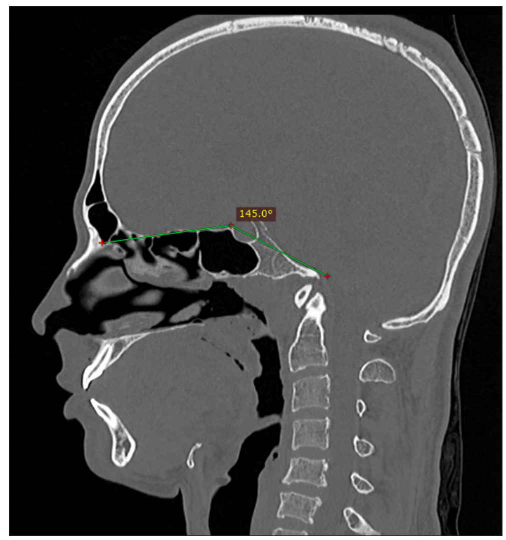

Figure 5: Sagittal computed tomography image of the skull with the craniovertebral junction shows the Welcher's basal angle to be 145°, suggestive of platybasia.

Figure 6: 3D volume rendered computed tomography image of the skull (posterior aspect) shows Wormian bones along the lambdoid suture.

Figure 7: Post-operative radiograph of the pelvis.

DISCUSSION

OI exhibits various subtypes, ranging from mild (type I) to fatal (type II), with types III and IV being severe, and types V-VIII showing mild to moderate severity. The initial Sillence classification of OI Types I-IV was linked to mutations in *COL1A1* or *COL1A2* genes, resulting in defective collagen type I biosynthesis. These types typically present with blue sclera, dentinogenesis imperfecta, joint hypermobility, skeletal abnormalities, and increased fracture risk.

Glorieux[3] introduced three kinds of OI that do not have type I collagen mutations but have phenotypes similar to other types of OI [Table 1]. The original classification system has been expanded to include types V, VII, and VII which have abnormal bone on microscopy and comparable phenotype, but no type I collagen mutation.[4,5]

OI Type V has been identified as a distinct entity according to this new classification, distinguishable by its unique clinical, histological, and radiological features. While it shares the characteristic of increased bone fragility with other subtypes, OI type V notably lacks blue sclera and dentinogenesis imperfecta. Some dental irregularities observed include missing premolars, ectopic molar eruption, and shortened molar roots. HPC formation, though characteristic of OI type V, is not always present. During active HPC formation, elevated levels of alkaline phosphatase are observed, with the femur being a frequent site for this occurrence as in our patient. Microscopically, there is an overproduction of poorly mineralized and disorganized extracellular matrix.[6,7]

Additional radiological findings in OI type V include interosseous membrane calcification, enlarged olecranon/coronoid process, radial head dislocation, Wormian bones in the skull, scoliosis, and heterotopic calcification. The specific genetic cause of OI type V is a mutation in the *IFITM5* gene, though the underlying mechanism for HPC and interosseous membrane calcification remains unclear. It has been proposed that excessive mineralization is the result of the mutant *IFITM5* gene product, which is related to the development of HPC or calcification of the interosseous membranes.[8] Bisphosphonates are considered a standard treatment for OI, as they help reduce fracture risks.

Extra-skeletal symptoms can vary and include blue sclera (mostly in type I OI) or yellowish or gray tooth surfaces (dentinogenesis imperfecta, primarily in type III OI), skin brittleness, hyperlaxity of joints and ligaments, premature hearing loss, and cardiovascular anomalies including aortic valve disease. These extra-skeletal manifestations are absent in type V OI as in our patient. Neurologic disorders involving direct involvement of neurovascular structures or basilar impression and platybasia (mostly in type IV OI) are less common. However, there were findings of basilar invagination and platybasia in our patient though he was asymptomatic with no neurological deficits at presentation.[4] Based on their experience with three cases and a review of seven examples from the literature, Pozo *et al*.[9] proposed that patients with OI who undergo basilar invagination only show moderate versions of the disease (Sillence type I and IV). Harkey *et al*.[10] observed basilar impression in two patients (half of their series) with the more severe type III OI. Thus, with the exception of the deadly perinatal (type II) variation, basilar invagination has been documented in all clinical subtypes of OI. There was no published literature citing the presence of basilar invagination in type V OI and this makes our case unique.

A study by Kim *et al*. on 16 genetically proven patients with type V OI showed HPC in 75% of the patients with the femur being the most common site of fracture. 100% of the patients showed interosseous membrane calcification with none of the patients having blue sclera of dentinogenesis imperfecta. There was also a high prevalence of Wormian bones, about 94%. These were all similar to the findings in our patient. However, in their study, there was a higher prevalence of other dental anomalies such as hypodontia, short molars, and ectopic eruptions which were not seen in our patient.[11]

The long-term outcomes of managing OI type V involve a multidisciplinary approach, including bisphosphonates to increase bone mineral density and reduce fracture risk, though their efficacy in fracture prevention remains uncertain. Surgical interventions, such as intramedullary nailing, are used to correct deformities and stabilize bones, but high revision rates and complications like non-union are common. Despite these treatments, OI type V remains challenging due to persistent bone fragility and the need for ongoing care to optimize function and quality of life.[12-14]

Table 1: Adapted from references 1, 2, 4.

Type of OI	Genetic mutation	Clinical and radiological features
Type I OI (mild)	COL1A1, COL1A2	Fractures; minor deformities Almost normal stature Blue sclerae "Dentinogenesis imperfecta" may be present
Type II OI (lethal)	COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, BMP1	Death before birth (respiratory deficiency) Multiple fractures in utero
Type III OI (severe)	COL1A1, COL1A2, CRTAP, LEPRE1, PPIB, FKBP10, SERPINH1, SERINF1, WNT1	Fractures; kyphoscoliosis; major deformities Very small stature Triangular face; variable colour of sclerae "Dentinogenesis imperfecta" is frequent
Type IV OI (moderate)	COL1A1, COL1A2, CRTAP, FKBP10, SP7, SERPINF1, WNT1, TMEM38B	Fractures Small stature Variable colour of sclerae "Dentinogenesis imperfecta" may be present
Type V OI	IFITM5	Fractures; hyperplastic callus; interosseous membrane ossification; metaphyseal dense lines Normal colour of sclerae No "dentinogenesis imperfecta"
Type VI OI	SERPINF1	Looser striations mimicking fractures No wormian bones
Type VII OI	CRTAP	Fractures; coxa vara Normal colour of sclerae No "dentinogenesis imperfecta" Rhizomelia

CONCLUSION

All children who exhibit increased bone fragility, including fractures that occur with little to no trauma, should be suspected of having OI. Radiography, physical, personal, and family medical history, and in certain situations, supplementary tests such as bone densitometry, biochemical testing, or DNA-based sequencing are used to make a positive diagnosis. Although OI does not exhibit any pathognomonic features on radiographs, some of them can be indicative of the diagnosis.

OI type V remains a challenging diagnosis due to its rarity and overlapping features with other OI subtypes. This case highlights the importance of recognizing its hallmark radiological findings, including HPC formation and interosseous membrane calcification. Genetic confirmation aids in definitive diagnosis, guiding treatment approaches such as bisphosphonates to reduce fracture risk. Early diagnosis and multidisciplinary management are essential in improving patient outcomes. Patients with OI Type V face a guarded long-term prognosis with a significant lifelong risk of recurrent fractures, hardware failure, and the development of debilitating HPC formation, a hallmark complication of this subtype. Mandatory long-term management involves rigorous multidisciplinary follow-up and long-term bisphosphonate therapy. Orthopedic and radiological surveillance with regular radiographs is essential for early detection of complications, particularly HPC and hardware failure. Future research must be directed toward finding a cure for the underlying genetic abnormality. Further research is needed to elucidate the underlying mechanisms of OI type V and optimize therapeutic strategies directed toward the underlying genetic abnormality.

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