Natural History of Hyperplastic Callus Formation in Osteogenesis Imperfecta Type V

Moira S Cheung, Francis H Glorieux, and Frank Rauch

ABSTRACT: Hyperplastic callus formation was assessed in 23 patients with osteogenesis imperfecta type V. Hyperplastic callus mostly affected long bones in the lower extremities and occurred predominantly during phases of rapid growth.

Introduction: Hyperplastic callus (HPC) formation is one of the most conspicuous features of osteogenesis imperfecta (OI) type V, but the natural history of HPC has not been well characterized.

Materials and Methods: In this retrospective single-center study, we assessed HPC in 23 OI type V patients (9 females and 14 males).

Results: Fifteen patients (65%) had HPC at 48 skeletal sites, 30 of which affected the lower limbs. The number of HPC sites per patient ranged from 0 to 7, with an average of 2.6 for men and 1.1 for women (p = 0.047 for this sex difference; t-test). New HPC formation was observed both after fractures and outside of the context of fractures. Only a minority of lower limb fractures (26%) precipitated HPC formation. After an initial enlargement phase, HPC lesions usually stabilized, but could also resolve completely (n = 2) or progress and lead to bone deformation. The most common complication of HPC was a fracture through the lesion (n = 7). Neither pamidronate nor indomethacin seemed to influence the course of HPC.

Conclusions: HPC is a potentially serious complication of OI type V. Given the rarity of the disorder, treatment studies will require multicenter collaborations.


Key words: children, fractures, genetic disorder, hyperplastic callus, osteogenesis imperfecta

INTRODUCTION

OSTEGENESIS IMPERFECTA (OI) is a heritable disorder characterized by brittle bones. Frequently, extraskeletal features such as dentinogenesis imperfecta and blue sclera are associated. The most widely used disease classification divides OI into four types, OI types I to IV, according to clinical phenotype. In the last decade, three distinct entities were identified from within the heterogeneous group of OI type IV patients and have been named OI types V to VII. In the large majority of patients with OI types I to IV, the disease is caused by mutations in the two genes that encode collagen type I α chains. Such mutations are absent in OI types V to VII. OI type VII is caused by mutations in a gene that plays an important role in the post-translational modification of collagen type I, but the genetic defects underlying OI types V and VI are unknown at present.

OI type V is characterized radiologically by interosseous membrane calcification of the forearms and a radiodense band visualized at the growth plate. Patients with OI type V do not have blue sclera or dentinogenesis imperfecta. They have a typical histological appearance on bone biopsy with a mesh-like lamellation that is not seen in other types of OI. The clinically and radiologically most conspicuous feature of OI type V patients is that they can form hyperplastic callus (HPC).

Exuberant callus formation in OI patients has been long described in the literature dating back to 1908. Histopathologic analyses of rapidly growing HPC have shown distinctive zones with the outer regions of callus containing edematous tissue with a loose collagenous network to the innermost region showing hypercellular trabeculae of woven bone and small cartilaginous islands. Until now, the main focus of much of the literature on HPC has been to differentiate it from osteosarcoma. Isolated case reports and small case series have aimed at describing the evolution and progression of HPC.

In this study, we examined the natural history of hyperplastic callus formation in a retrospective review of clinical and radiological data from 23 patients with OI type V.

MATERIALS AND METHODS

The study population was made up of 23 subjects (9 females and 14 males; age at last follow-up, 4–66 yr) with a...
diagnosis of OI type V who were seen at least once at the
Shriners Hospital for Children in Montreal (Table 1). This
cohort included children and adolescents who were re-
ferral for their bone fragility disorder (*n*/*H11505* 19), as well as
affected family members who consented to be examined at
the Shriners Hospital (*n*/*H11505* 4).

The diagnosis of OI type V was based on the criteria as
described (3): calcification of the interosseous forearm mem-
brane, presence of HPC, and mesh-like pattern of lamella-
tion under polarized light microscopy of iliac bone samples.
The defining feature of OI type V is the abnormal pattern
of lamellation on bone histology, which was observed in the
17 patients who had undergone bone biopsy. Of the six
patients where bone histology was not available, five had a
family history of OI type V and a history of bone fragility.
In the sixth patient, the diagnosis was based on typical clini-
cal and radiological findings (interosseous membrane calci-
fication, bone fragility) alone. Three patients were exam-
ined only once. The length of the follow-up time in the
other patients ranged from 18 mo to 20 yr. Fourteen pa-
tients were tested for mutations affecting collagen type I,
but no sequence abnormalities were detected in any of
these patients. In five of the families with more than one
affected member, an autosomal dominant pattern of inher-
ance was suggested. The OI type V patients of the sixth
family, patients 15 and 16, were male twins and a product of
a consanguineous union, suggesting an autosomal recessive
mode of inheritance.

All available radiographs were assessed for the presence
of HPC. HPC was defined as a radio-opaque lesion that
originated from the surface of the bone and that was large
relative to the size of the unaffected bone and showed un-
usual features such as sun ray spicules and butterfly-like
appearance. Normal callus formation after a fracture was
excluded.

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<th>Patient</th>
<th>Age at last X-ray (yr)</th>
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M, male; F, female; LA, left arm; RA, right arm; LL, left leg; RL, right leg.

![Anatomic distribution of sites of HPC formation.](image)
RESULTS

HPC was found in 15 of the 23 (65%) OI type V patients who were examined in this study (Table 1). These patients had a total of 48 HPC sites. The number of HPC sites per patient ranged from 0 to 7, with an average of 2.6 for males and 1.1 for females ($p = 0.047$ for this sex difference; $t$-test). Eight patients, 4–18 yr of age, were negative for HPC, but had other typical findings of OI type V (Table 1).

The earliest occurrence of HPC was documented in a 9-mo-old girl who had a lesion in the left femur. Development of the first HPC was only observed in patients who were under the age of 5 yr and between 13 and 15 yr of age.

HPCs were found predominantly in long bones (Fig. 1). None of the patients had radiographic evidence of HPCs in the thoracic cage, vertebral bodies, hand or foot bones. However, iliac involvement was present in five male patients (Fig. 2). In two of these patients, only the right iliac bone was affected; the other three had bilateral iliac HPCs. All patients with iliac involvement suffered from severe bone fragility and had extensive deformities of one or both femurs.

The relationship between fractures and subsequent HPC formation was assessed in the tibias and femurs, where documentation was best. A total of 35 lower limb fractures were documented in the entire cohort. HPCs developed after nine (26%) of these fractures, but normal bone healing was observed after the other fractures. Conversely, of the 48 HPCs examined in this study, 10 occurred at sites where no fracture had been documented before. HPC formation was not observed after osteotomy procedures, even though five patients had intramedullary rods placed at eight sites (Fig. 3).

The evolution of HPC was variable. In the majority of cases, there was an initial enlargement phase that could last from months to several years. After lesion size had stabilized, internal reorganization made the HPC tissue less radiopaque than in actively enlarging lesions. Although HPC size then often remained stable for years, reactivation of new HPC formation at the same site was also observed. In a few cases, HPC took the opposite course and decreased in size. Complete resolution of HPC was noted in two lesions.

In six patients, all male, a HPC was so large that it seemed to envelope the entire bone, ultimately leading to a loss of the original cortical architecture. Such extensive involvement was only observed in the femur. In two patients, both femurs were affected in such a dramatic fashion. Even though extensive HPC formation could lead to the dissolution of normal bone architecture, there was no evidence that HPC lesions grew in an invasive manner. Nevertheless, HPCs from adjacent bones could become confluent (Fig. 4).

The most common complication of HPCs was a fracture through the lesion, which was observed in seven cases. In one patient, HPC led to the destruction of the hip joint,
necessitating total hip replacement. Malignancy did not occur in any patient.

Thirteen patients of this series received 1.5–7.9 yr of intravenous pamidronate therapy at a yearly dose of 9 mg/kg body weight to treat severe bone fragility.\(^{(13)}\) Eight of these patients were affected by HPCs. At the start of pamidronate treatment, these eight patients had HPCs in a total of 14 sites. Five of these patients developed nine new HPC lesions while receiving pamidronate. Four patients had six new HPC sites after pamidronate therapy had been stopped.

Because the initial phase of active HPC formation resembles an inflammatory reaction and can be associated with pyrexia and soft tissue swelling, seven patients received indomethacin to try to limit the size of HPC. No obvious treatment effect on HPC evolution could be observed.

Other radiographic abnormalities were found in the patients of this study. Apart from the calcified interosseous membrane of the forearm (Table 1), these included an undulating aspect of cortical surfaces or cortical thickening, which was observed in 15 patients. These abnormalities did not have an obvious relationship with bone deformities or fracture repair and were also observed in OI type V patients who did not have HPC. The fibula was the most frequently affected bone, but similar observations were also made in other long bones (Fig. 5). In one child 3 mo of age, abnormal focal lesions could be identified in the cortex of the proximal femur. These lesions could be clearly seen throughout childhood and later went on to become sites of HPC formation (Fig. 6).

**DISCUSSION**

In this study, we found that HPCs mostly affect long bones and are more frequently detected in the lower than in the upper extremities. New HPC formation seems to occur predominantly during phases of rapid growth. The evolution of HPC lesions is very variable, ranging from radiographic resolution of all signs of HPC to the destruction of normal bone anatomy. These observations confirm and extend the findings described in case reports and small case series.\(^{(10)}\)

As reported before, not all OI type V patients have HPC, but in our experience, all patients with HPC have OI type V.\(^{(3)}\) Among the close to 500 OI patients who have been assessed at our institution over the past decade, HPC was found only in the patients with OI type V that are described in this report. We use the term “hyperplastic callus” in line with previous reports. The justification for this terminology is that most cases of HPC arise after a fracture. Nevertheless, the relationship between HPC and fractures is not
straightforward. On one hand, the majority of fractures in OI type V patients heal without HPC formation. On the other hand, our observations and other reports suggest that HPC can form at sites where no radiologically detectable fracture has occurred before. The most obvious difference to regular callus formation is that HPC tissue seems to proliferate exuberantly and does not remain confined to the site of the insult but can take up considerable space along the shaft of a long bone.

The etiology of HPC is unclear at present. However, radiological and histological evidence suggests that HPC starts with a proliferation of soft tissue that has its origin at the level of the periosteum. The observations that new HPC formation is largely confined to the growth period and predominantly affects the largest bones in the body may also be relevant in this context. It seems that HPC mainly form at times and sites of rapid periosteal apposition, suggesting that HPC is caused by some dysregulation of periosteal bone growth. A problem with periosteal osteogenesis is also suggested by the finding that the cortices of many OI type V patients have an undulating appearance.

After HPC mineralizes, it usually remains stable for some years. Smaller lesions can resolve without leaving a trace, whereas larger lesions can bring about the destruction of normal bone anatomy. This variable course resembles that of infantile cortical hyperostosis, where an initial localized bout of new bone formation on the outer cortical surface is followed by remodeling and resorption either at the external surface or the endocortical surface. Infantile cortical hyperostosis and OI type V certainly differ in many respects, but the two disorders may nevertheless share some common pathogenetic features.

Another new finding of this study is the observation that male OI type V patients had more sites with HPC than female patients. In addition, the more severe phenotypes were also seen predominantly in males, such as total involvement of the femoral bone and iliac bone involvement. If iliac bone HPC was present in a child-bearing female, obstetric complications might result. It may therefore be useful to assess female OI type V patients with childbearing potential for the presence of iliac HPC.

The most common complications of HPCs are fractures through the site and bone deformation. Osteosarcoma needs to be considered in the differential diagnosis because, albeit extremely rare, it has been described in children with OI. MRI and CT can be useful to distinguish hyperplastic callus from osteosarcoma in unclear cases.

This study is a retrospective review of radiographs, a study design that is not particularly well suited to elucidate the effects of therapeutic intervention. Nevertheless, it may be useful to point out that neither intravenous pamidronate nor oral indomethacin prevented the formation of HPCs. Earlier authors have attempted to treat HPCs with immobilization, steroids, or radiotherapy at the early stage of development, but none of these approaches have been tested in a systematic fashion. Thus, it is unclear at present whether any medical intervention changes the natural history of HPC.

In summary, this study shows that HPCs occur predominantly in the long bones of OI type V patients. Lesions can be precipitated by fractures, arise spontaneously and can become very large, altering the architecture of the bone. Although the pathophysiology of HPC remains unclear, several lines of evidence are compatible with the hypothesis that dysregulated periosteal osteogenesis is one of the factors involved. At present, there is no evidence that HPC formation can be influenced by medical treatment approaches. Given the rarity of the disorder, treatment studies will require multicenter collaborations.

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REFERENCES


FIG. 6. Series of femur radiographs of patient 1. Focal lesions can be noted (A) at the child’s first skeletal survey at the age of 3.5 mo. These lesions are present throughout childhood (B and C). On fracture, HPC formed at these sites bilaterally (D).

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