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Case reports in pediatric orthopedics 2022

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Editorial: Case reports in paediatric orthopaedics 2022

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Editorial on the Research Topic
Case reports in pediatric orthopedics 2022

Paediatric orthopaedics is a very fascinating branch of orthopaedics as a child's skeleton has great remodelling capabilities thanks to growth cartilage, but often this can be the cause of growth defects when damaged. Sometimes, the pathologies have a clinical manifestation that involves different systems, and often in these cases, they are rare pathologies with difficult diagnosis. The diagnosis in children is made more difficult by the complicated communication with the patients and treatment of the same pathology varies according to the patient's age. These situations are already present for well-known pathologies and become even more serious in the case of rare pathologies or for atypical manifestations where lack of diagnosis and treatment can lead to poor prognosis. The issues covered by these studies are different, all united by the fact of being unusual and rare. This topic aims to share a series of rare case reports to form an understanding of the possible expression of various conditions and their treatments for improving clinical practice, diagnostics, and therapeutics.

Physeal fractures account for 30% of all paediatric fractures, although growth plate injuries are common. Growth disturbance related to physis lesions is rare, but when it occurs, it could cause severe deformities with poor prognosis; distal physis is more frequently involved than proximal physis, and distal tibial physis is the most commonly involved type of low extremity followed by the distal femur. The literature has reported that a maximum of 30% of the bone bridge of the physis area can be successfully removed, and in cases of genu valgus of 20°, a corrective osteotomy is often necessary (1). Basiglini et al. showed that partial epiphysiodesis inserting the bone wax is possible in up to 30% of the cartilage area without osteotomy, because the cartilage around the lesion can react by hyperactivating and allow the recovery of the load axis. Ankle fractures account for about 5% of all paediatric fractures. While rare, loss of the medial malleolus is more common in children. Furthermore, it leads to a higher risk of complications such as medial physeal bar with varus angulation and leg length discrepancies (LLD) due to premature physis arrest. Medial malleolus contributes to maintaining normal tibiotalar joint characteristics, and fractures can significantly decrease contact area, increase contact pressure, and lead to ankle instability (2). Chengming Zhu et al. reported that in rare cases of open Salter–Harris type VI fractures with complete loss of the medial malleolus, there is the possibility of rebuilding it using an autologous iliac crest apophyseal graft without deformity and LLD.

Primary osseous spinal tumours are rare in children and young adults, accounting for only 1% of all spine and spinal cord tumours combined (3), but they should always be considered in the differential diagnosis of back pain in children. Despite benign bone lesions prevailing in young patients (4), some cases of malignant lesions have been reported in the literature. In general, orthopaedic surgeons use age and anatomical site to determine the histological type of tumour, but it is important not to use these as fixed rules because sometimes, in orthopaedic oncology, these are subverted, and often when it happens, they have more aggressive behaviour; the lack of diagnosis leads to a poor prognosis. Rosa M. Egea-Gámez et al. described the first published case of giant cell-rich osteosarcoma (GCRO) in the cervical spine in a paediatric patient, reporting a treatment option that showed excellent results at 3 years of follow-up; in this case report, the age, site of the lesion, and histological variant were unique.

Florio et al. reported a successful reconstruction of the metatarsal bone with fibular graft for a case of giant cell tumour (GCT) marked by an unusual location and age group. GCT develops almost exclusively in the epiphysis of long bones, and the most common location is around the knee region; only four cases of GCT on metatarsal bone have been reported in the literature (5).

Heterotopic ossification (HO) is a rare condition that is generally secondary to other conditions, particularly trauma (often repetitive microtrauma) or hereditary form; it is essential to make a differential diagnosis with oncological pathologies to better manage these conditions (6). This pathology can rarely occur without a previous condition in an atypical location. It is important to know this, especially because early HO lesions may histologically mimic a sarcoma; unlike the latter, in the case of HO, complete removal allows excellent results without recurrences. Instead, when it is secondary to a genetic condition such as fibrodysplasia ossificans progressive (FOP), the prognosis assumes an aggressive and relapsing aspect especially due to surgical treatment; it is essential in these cases to intervene surgically only when necessary. Dong Sun at al. reported a case report of FOP where the surgical choice was adequately made in respect to the affected joints essential for leading a satisfactory life (jaw, hip, and spine). This is the first case of non-traumatic massive heterotopic iliopsoas ossification described in the literature.

Kaposi haemangioendothelioma (KHE) is a rare vascular neoplasm that presents usually within the first year of life. There is often a delay in diagnosis, and this may lead to morbidity and mortality of up to 30%, mostly due to a life-threatening consumptive coagulopathy named the Kasabach–Merritt phenomenon (KMP), which occurs in 40%–70% of cases, although this is a complication. However, when present, it helps in the diagnosis (7). The treatment is still much discussed, especially from a pharmacological point of view. Qiu et al. reported a case report of KHE at a late age originating from the bone and limited inside the bone with bilateral involvement. It is important to note that when involved, only the bone without periosteal reaction KMP is not associated, and this can lead to a lack of diagnosis. This is the only case involving bilateral femur symmetry reported in the literature. In this case, sirolimus without prednisolone was effective. Given the rarity of the pathology, it may happen that despite the presence of KMP, there may be a delay in the diagnosis. In this topic, a case report of KHE with KMP in a 2-month patient has been reported; he showed symptoms from the first week of life and was treated first for urticaria, then cellulitis, and then necrotic fasciitis until the right diagnosis was made, at two months of age. He was treated with sirolimus (off-therapy because it is accepted from 2 years onwards) with excellent results 3 years after treatment.

Congenital bowing of the tibia is a rare condition (1/140.000–190.000) and is considered the precursor of congenital pseudarthrosis of the tibia; little is known about its clinical features. While the diagnosis is simple, the treatment, which varies from conservative to surgical, is not. Surgical treatment could consist of different methods, none of which have shown superiority over the other, with a 50% amputation incidence. Mastantuoni et al. reported a case of congenital bowing of the tibia treated with double osteotomy and Tens, with excellent results after 8 years of treatment. Yijun Zhou et al. conducted the only epidemiological study, which included a large sample of patients (514). The authors reported a higher incidence of Crawford IV in boys and in the middle or distal part of the tibia; most patients were less than 3 years old, and the major surgical complications were ankle valgus and limb length discrepancy.

Osteogenesis imperfecta is an autosomal dominant congenital pathology characterised by bone fragility and associated with other clinical signs. Many gene variants determine a different phenotypic expression. In their study, Dirani et al. reported the first clinical description of a patient with a splice variant in intron 34 in the COL1A1.

Scoliosis is the most common congenital pathology, which can be caused by vertebra segmentation or formation defects. Caredda et al. showed how conservative treatment in the case of lumbar hemivertebra is a good choice; it can improve the Cobb's value of the curve and maintain the long-term correction. Conservative treatment in selected patients can also change the natural history of congenital scoliosis due to the failure of formation, which permits the hypertrophy of adjacent vertebrae, thus preventing its deformation. However, the treatment should be implemented as early as possible without waiting for the evolution of the curve, in contrary to what occurs in lower idiopathic scoliosis.

Scapholunate dissociation (SLD) is a very rare condition, especially in children. When it occurs, in most cases it is post-traumatic or secondary to other conditions. If undiagnosed, it can lead to chronic pain, SL advanced collapse, and early osteoarthritis (8). In this topic, Bandinelli et al. reported the

only case known in the literature of SLD in a paediatric patient that was not secondary to trauma or other conditions. The unique symptom was a wrist extension deficit. The only alteration found in the patient was generalised hyperlaxity. Thanks to the correct diagnosis and treatment, the patient showed a complete functional recovery after 12 months. It is important to know that a trauma-free SLD can exist, probably due to hyperlaxity, which allows to treat it adequately while avoiding long-term complications.

Author contributions

MM drafted the original manuscript. AGA participated in the conception and helped to draft and review the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CASE REPORT
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Case Report: Unusual Heterotopic Ossification of the Hindfoot

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Heterotopic ossification (HO) is a pathologic condition in which aberrant lamellar bone deposits in soft tissues, outside of the normal skeleton. Pathogenesis is still unclear, but different risk factors are known. Here we report a case of a 14 year-old girl presenting with pain in the medial calcaneal region and evidence of a rapidly growing, firm and solid neoformation. The lesion was diagnosed 6 years earlier, but it was consistently smaller and asymptomatic so that the patient did not undergo any follow up. The patient had no previous trauma or surgery, no other risk factors for HO and did not show any clinically evident HO in other districts. Xray and CT showed a heterogeneous bony lesion in the context of soft tissues, isolated from the calcaneus. After complete excision, histological analysis confirmed the diagnosis of HO. In conclusion, lone non congenital HO can occur regardless of known risk factors. Small HO lesion may also enter a proliferative phase without evidence of triggering events. More studies are required to better understand etiopathogenesis of HO in these clinical settings.

Keywords: heterotopic ossification, bone, foot, case report, children

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INTRODUCTION

Heterotopic ossification (HO) is a pathologic condition in which aberrant lamellar bone deposits in soft tissues, outside of the normal skeleton. Apart from rare cases of genetic forms, the majority of HO cases are acquired and they can be either spontaneous or post-traumatic.

The early identification of patients with HO can be difficult. Clinical signs are variable and nonspecific, ranging from inflammatory signs such as pain, erythema, swelling and warmth to increased joint stiffness and limited range of motion (ROM) of the involved joint. Asymptomatic masses are not uncommon presentations, as well (1).

Here we report a case of a skeletally immature girl without any known risk factor, with a diagnosis of lone HO lesion of the calcaneal region of the right foot.

CASE DESCRIPTION

A 14-year-old girl presented to our hospital with pain and discomfort in the medial region of the right hindfoot and evidence of a solid and firm mass reported to be rapidly growing during the previous weeks.

She was evaluated six years earlier for a painless, slowly enlarging mass in the same region. Anamnestic evaluation at the time revealed no history of acute trauma or repetitive minor trauma, as well as a negative familiarity. Complete clinical examination confirmed the absence of other similar lesions.

Plain X-ray demonstrated a neoformation in the context of soft tissue with calcifications inside and undefined limits (**Figure 1A**). Ultrasound (US) had shown a poorly defined mass of mixed echogenicity measuring approximately 6 mm × 8 mm, with hyperechoic areas similar to bone signal. No cystic component or abnormal Doppler flow was found.

For approximately six years she had been completely asymptomatic and had not been doing any clinical or radiological follow up.

At the time of presentation local examination revealed moderate oedema and hyperkeratosis in the posterior-medial side of the right hindfoot with evidence of a hard, firm mass measuring about 20 mm in diameter (**Figure 1B**). No sign of local inflammation was evident and neurovascular examination was normal.

A new X-ray examination demonstrated that the lesion was enlarged and contained more areas of ossification (**Figure 1C**).

CT scan (**Figures 1D–F**) showed the mass to be made of mixed bone and non-ossified areas. The lesion was clearly separated from the calcaneal cortical bone and measured approximately 14 × 18 mm in its maximum diameter.

A complete excision of the mass was performed through a small lesion-centered incision (**Figures 2A,B**). The mass was clearly separated from calcaneal periosteum and macroscopic radical excision was achieved. Histopathological examination confirmed the lesion to be made of "multiple foci of stromal osseous metaplasia.", thus supporting the diagnosis of HO (**Figure 2C**).

Radical excision of the mass was demonstrated with Xray and confirmed during follow up (**Figure 3**).

No perioperative and postoperative, confirmed or suspected adverse events were recorded.

The patient was discharged without other treatments but with a strict clinical and radiological follow up, to detect early eventual local relapses or secondary lesions. During the programmed follow up the patient did not complain about

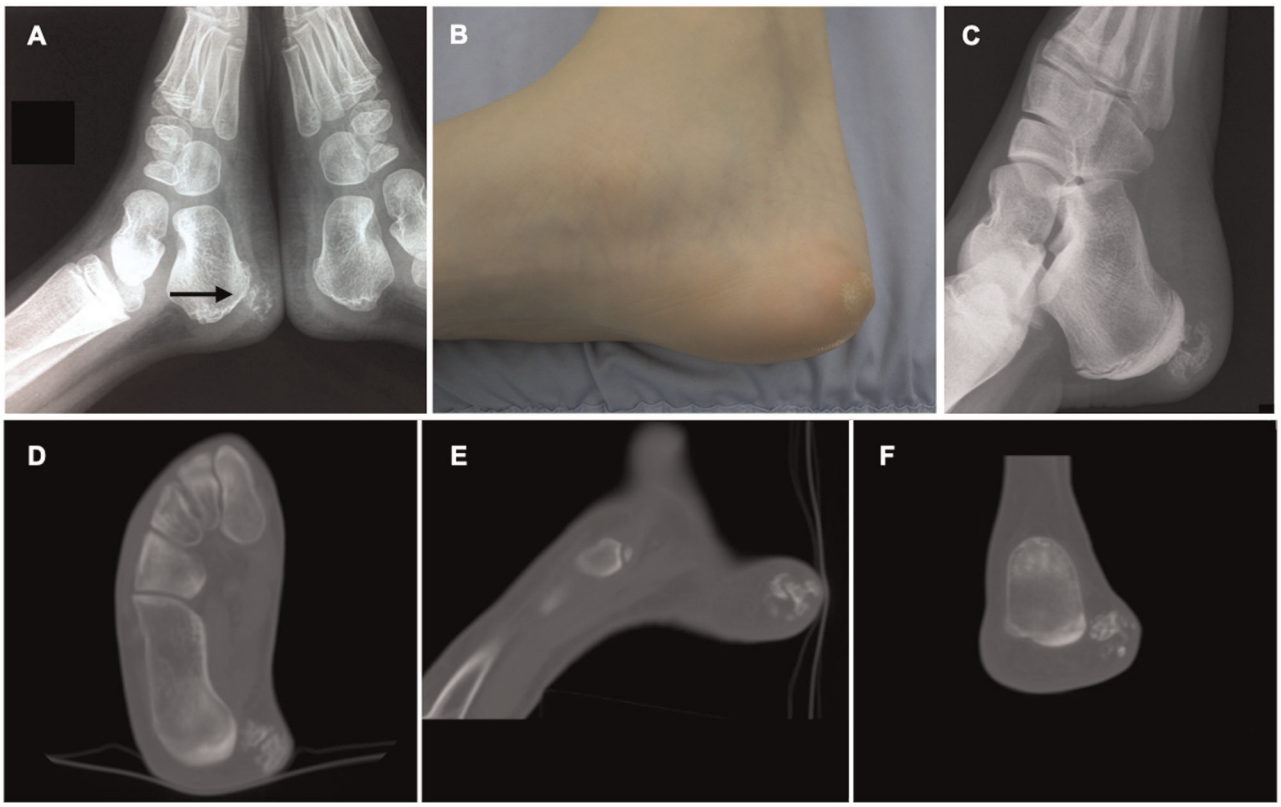

FIGURE 1 | (**A**) Old X-ray showing the clinically silent lesion at the age of 6 years. (**B**) Clinical picture showing the mass covered with areas of hyperkeratosis. (**C**) New X-ray at time of presentation showed increased size of the lesion. (**D–F**) Preoperative CT section of the lesion.

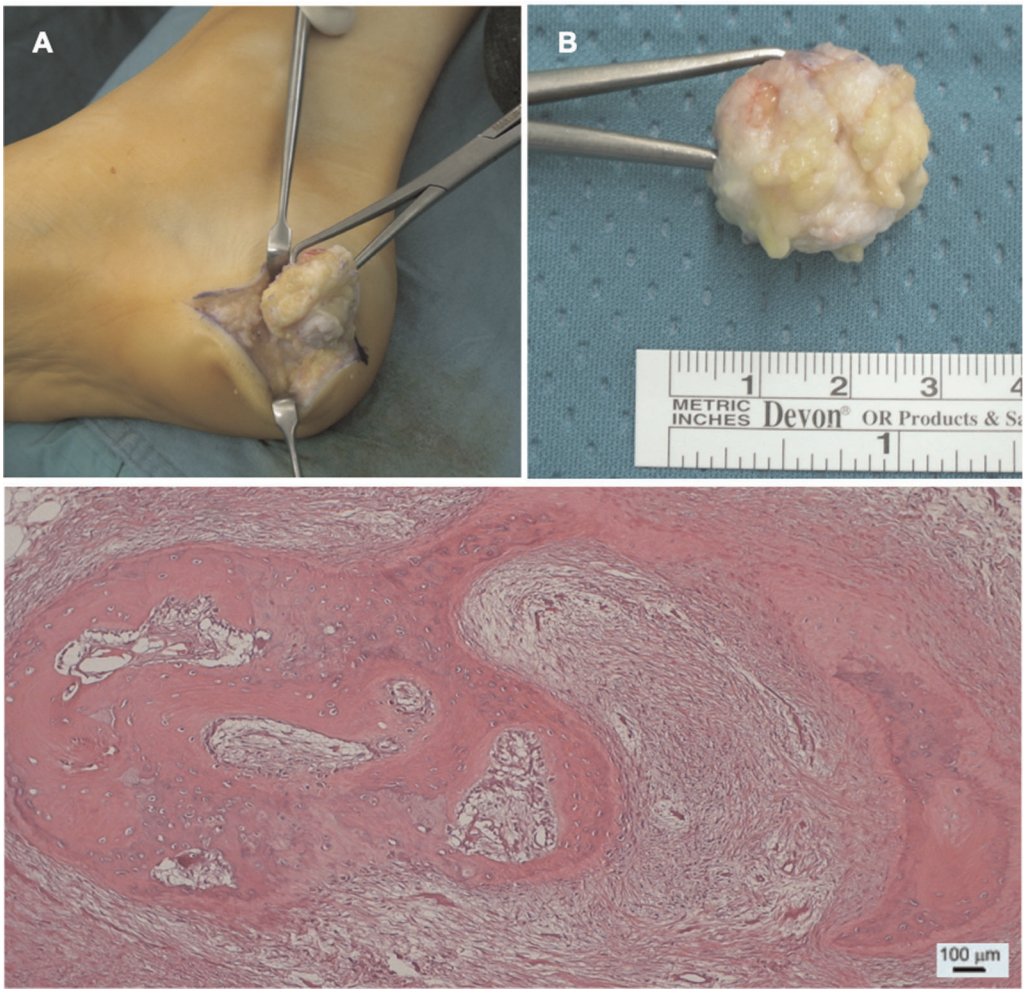

FIGURE 2 | (**A**) Intraoperative image of the excision of the mass. (**B**) Picture of the sample measuring approximately 2.5 × 1.5 × 2 cm. (**C**) Section of the lesion as seen with optic microscopy and Hematoxylin & Eosin staining. The specimen shows "*mixed fibrous-adipose dermo-epidermal tissue with foci of stromal osseous metaplasia*", as confirmed also by pathology report.

local al distant symptoms in any way potentially related with relapses or secondary lesions. Thus, given the absence of secondary lesions and family history, the patient was still excluded from whole exome sequencing protocol.

Moreover, after 6 years of follow up, the patient is still asymptomatic and has experienced no signs or symptoms suggestive of local relapses or distant secondary lesions. (**Figure 4** - Timetable).

DISCUSSION

Heterotopic ossification (HO) is a pathological condition in which qualitatively normal bone tissue aberrantly forms in extra-skeletal tissues. The ultimate pathogenetic cause is the alteration of the usual process that regulates the timing and location of bone formation. This aberrant growth takes place not within the muscle fibers, but between muscle planes. Furthermore, these lesions are isolated from the skeletal bone, and even if in contact they do not interfere with the periosteal anatomy.

The most common clinical presentation is an acquired singular neoformation in a young adult. In approximately 75% of the cases a local trauma can be identified as the triggering event and repetitive microtrauma are highly suspected in the remaining (2). The other predisposing conditions are: surgical exposures in orthopedic surgery (3), fractures or dislocations (4), spinal cord injury and other neurological and metabolic disorders (2, 5).

Rare hereditary forms include Fibrodysplasia Ossificans Progressiva (FOP) and Progressive Osseous Heteroplasia (POH), with different genetical backgrounds and pathological appearances.

African-American ethnicity was clearly recognized as an independent risk factor for development of HO after total hip arthroplasty (THA). Male sex was also suggested as an

independent risk factor but in this case evidence is conflicting (6, 7).

Beyond these few known risk factors and epidemiological notes, the exact pathogenesis of heterotopic ossification is still unclear. Chalmers et al. (8) described three conditions necessary to HO formation: the recruitment of osteogenic precursor cells (9), an event that triggers the differentiation of mesenchymal cells into bone-forming cells and a suitable tissue microenvironment that supports bone formation.

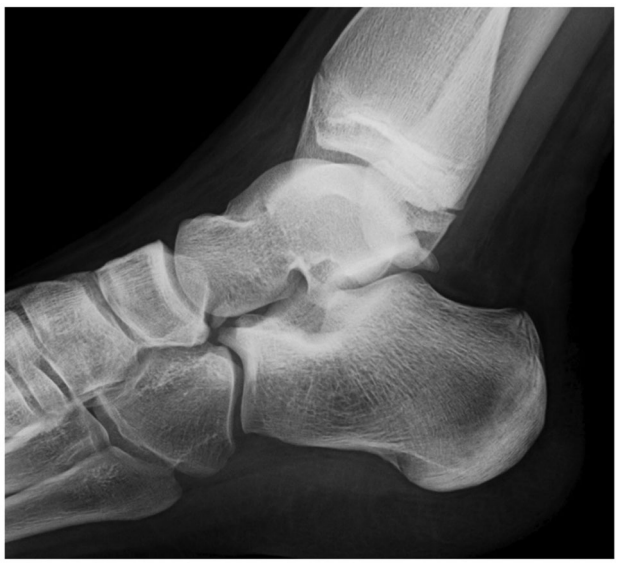

FIGURE 3 | Xray 6 months after surgery confirming complete excision of the lesion without residual pathology.

Different studies have demonstrated that an insufficient inhibitory response that causes overexpression of BMP signaling (7, 8) may play a role in eliciting the differentiation of osteogenic cells. Many other cytokines have also been claimed to play a role, even though no definitive mechanisms have been identified, yet (12).

A predisposing local environment may be induced by inflammation (13), tissue hypoxia (14), alteration in peripheral nerve system (PNS) activity and neuro-inflammation (15), prolonged immobilization (16), PTH or calcitonin alterations and mismatch in Ca/P ratio (17).

Histologically, early HO lesions are characterized by a consistent number of proliferating cells that may mimic a sarcoma. Mature HO, on the other side, is clearly identified by the specific peripheral ossification pattern. These lesions are well contained in a dense fibrous pseudocapsule (18). Radiological appearance reflects histological stadium. Early non-ossified lesions are barely visible, while mature HO is clearly recognizable by the peripherical pattern of ossification, also known as "eggshell ossification". CT is even more specific in identifying the zonal pattern (19). In contrast, MRI may sometimes be misleading due to the heterogeneous appearance, the presence of peripheral oedema and the possibility of core contrast enhancement that may pose diagnostic questions (20). Clinical signs are often consequence of local inflammation, nerve compression or stiffness. Moreover, only with a clinical examination, it is sometimes difficult to differentiate the early phase of HO from deep venous thrombosis (DVT), cellulitis, osteomyelitis or from bone-forming tumors.

Conservative treatment includes physical therapy, bisphosphonates or NSAIDs. Clinical evidence supporting the use of bisphosphonates is limited. Prophylactic radiation and indomethacin have proven to reduce the incidence of postoperative HO, especially in the setting of hip arthroplasty (1, 21).

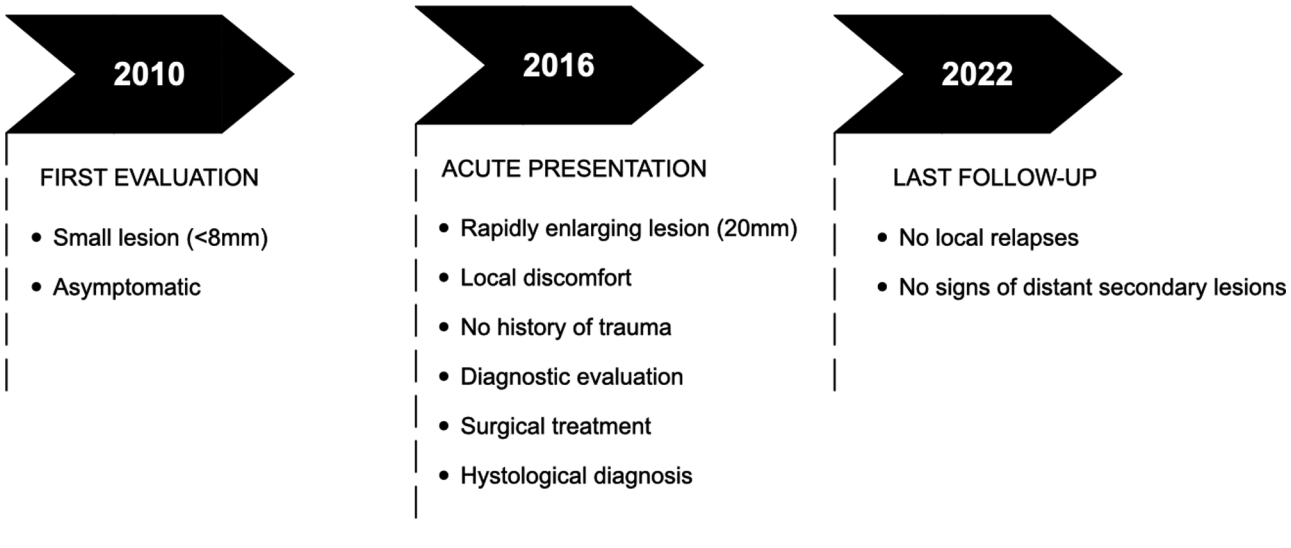

FIGURE 4 | Timetable reporting relevant data from the episode of care.

Surgical excision is often necessary for the treatment of severe HO limiting mobility or causing pain or neurologic symptoms. The optimal timing for surgery is still controversial, but there is a general attitude towards giving importance to the clinical setting regardless the stage of the lesion. Indeed, early excision of HO is not associated with higher rates of recurrence (22).

In this report we presented a case of a lone, non-congenital and non-familiar HO lesion in the medial calcaneal region of a 14-year-old girl. After 6 years without symptoms, the patient experienced sudden onset of pain and rapid growth of the mass. The patient neither had risk factors nor evident triggering causes and was otherwise healthy and without any signs of similar lesions in other districts. She denied local trauma either of major or minor entity, local previous surgery or prolonged immobilization. Family history was completely negative for similar lesions and the patient did not report any signs or symptoms potentially related to secondary lesions. The complete excision of the mass led to complete resolution of the local symptoms. Follow up was performed as routine, and no signs of local relapses or secondary lesions were reported. After 6 years of follow up the patient is completely asymptomatic.

The major limitation of this report is the absence of a genetic evaluation. Nevertheless, this is explained by the fact that the patient presented with a single lesion, without relapses or secondary masses, without clinical suspicion of FOP, POH or Albright hereditary osteodystrophy (AHO) and with a completely negative family history. Genetics in this setting is still largely inconclusive (23, 24).

In conclusion, even though a history of trauma or microtrauma is thought to be present in almost all non-hereditary cases of HO, with this report we underline the importance of considering this diagnosis even when the anamnestic feature of trauma is absent. In fact, this lesion could be identified as idiopathic. In addition, previous silent HO lesion may enter in a sort of proliferative phase even without evidence of trauma or other anamnestic risk factors.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

DF and MB wrote the article and collected bibliography. VC and MM performed the surgery and were primarily involved during the follow up of the patient. APG performed the revision of the article. All authors contributed to the article and approved the submitted version.

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Case report: Reconstruction of distal medial tibial epiphysis using iliac crest apophyseal autograft

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Background: Salter-Harris type VI physeal fracture is a rare injury. This case study aims to present a novel method for treating a rare entity of Salter-Harris type Salter-Harris VI physeal injury of the medial malleolus.

Case presentation: A 6-year-old boy with Salter-Harris type VI physeal injury was successfully treated using the two-stage procedure. In the first stage, the patient was treated with intravenous antibiotics, a series of debridement and lavage followed by a skin graft that left a defect in the medial malleolus. In the second stage, an autogenous iliac crest apophyseal graft was transplanted to reconstruct the medial malleolus, and the ankle joint was stabilized by an external fixator. An additional anticipatory Langenskiold procedure was performed for the physeal bar resection. Although the complete radiological development of medial malleolus compared to the contralateral side was not evident at the last follow-up, the functional and cosmetic outcomes were satisfactory.

Conclusion: The reconstruction of medial malleolus using an autologous iliac crest apophyseal graft and stabilization of the ankle joint with an external fixator is a novel reconstruction technique in treating Salter-Harris type VI physeal injury of the medial malleolus. This technique provides satisfactory functional and cosmetic outcomes in such a fracture pattern; however, a further clinical study using a larger sample size is warranted in order to find the definitive outcome of the technique.

KEYWORDS

physeal transplantation, reconstruction, Salter type VI physeal injury, medial ankle, children

Introduction

Physeal injury of the distal tibia is the second most common among all physeal injuries having a tremendous risk of premature growth arrest resulting in angular deformity and leg length discrepancy (1). Initially, Salter and Harries in 1963 classified physeal injuries into five types (type I–V). Later, Peterson added type VI physeal injury

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to this classification as the loss of osteochondral piece along with the physis because the initial classification system did not classify such injury pattern (2). Type VI injury is usually caused by specific mechanisms, including a lawnmower, motor vehicle, boat propeller, etc., resulting in local injury and avulsion fragment (2). Despite being a rare type of physeal injury, this fracture has the highest rate of complications due to an osteochondral defect in growing children.

A case of a 6-year-old boy with an open Salter-Harris type VI physeal injury and a complete loss of medial malleolus was presented in this case report. The deformity was treated using the two-stage procedure. In the first stage, the patient was treated with intravenous antibiotics, a series of debridement and lavage followed by a skin graft that left a defect in the medial malleolus. In the second stage, an autogenous iliac crest apophyseal graft was transplanted to reconstruct the medial malleolus, and the ankle joint was stabilized by an external fixator. An additional anticipatory Langenskiold procedure was performed for the physeal bar resection. Finally, this patient achieved a satisfactory functional and cosmetic outcome. This case report was approved by the ethical review board of the author's institute, and written informed consent was obtained from the patient's legal guardian.

Case report

A 6-year-old boy was brought to the orthopedic emergency department following a motor vehicle accident (MVA) with an injury to his right ankle. He complained of pain on the right side of his foot and difficulty in walking, with obvious deformity of the injured ankle. The clinical and radiological examination revealed the loss of overlying skin and an osteochondral fragment from the medial malleolus. The condition was diagnosed as the Salter-Harris type VI physeal injury of the medial malleolus of the right ankle.

The patient has been treated with a two-stage procedure. In the first stage in emergency department, the wound was meticulously washed, debrided, and kept in a vacuum sealing drainage for 5 days. Intravenous antibiotics were administered as a part of the management of open fractures. The wound bed was prepared for granulation tissue formation. After the formation of healthy granulation tissue, the split-thickness skin graft was grafted over it with a cast for immobilization by injury surgeons. The boy was discharged from the hospital 7 days after skin grafting and requested follow-up at the outpatient clinic. However, the boy lost the follow-up. At 20 months after the primary surgery, the boy again appeared in the hospital complaining of significant ankle pain, deformity, and abnormal gait. On examination, there was an obvious varus deformity of the ankle joint. Radiographic examination revealed the medial malleolus defect with cavovarus deformity of the right ankle (Figure 1A).

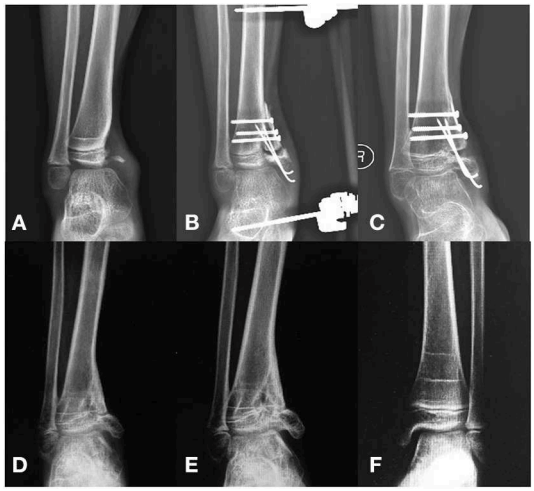

FIGURE 1
Anteroposterior X-ray view of a 7.5 years old boy shows the ankle joint in varus at 20 months after the Salter type VI physeal injury **(A)**. Post-operative X-ray shows a wedge-shaped iliac apophyseal bone autograft **(B)**. Five months post-operative X-ray shows the united iliac crest apophyseal autograft **(C)**. A physeal bar on the distal medial tibia was observed 20 months after reconstructive surgery **(D)**. On 36 months follow up after reconstructive surgery, the reconstructed medial malleolus **(E)** compared with the contralateral side **(F)**.

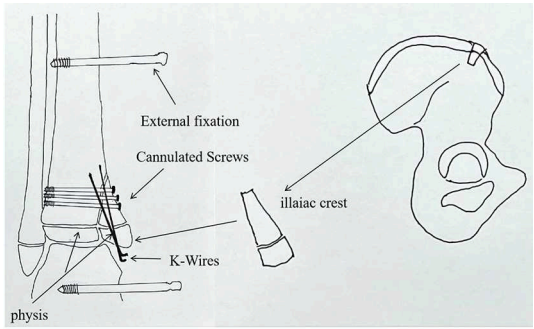

FIGURE 2
An illustration of the surgical plan using an iliac crest apophyseal autograft. The graft is held together by screws and k-wires, and the ankle is held by the external fixator.

In the second stage, the boy was treated with the reconstruction of the medial malleolus using an autogenous iliac crest apophyseal graft (Figure 2) by pediatric orthopedic surgeons. In this procedure, the graft was placed on the medial malleolus in such a way that the physeal line of the iliac crest graft was parallel to the physeal line of the distal tibia (Figure 3). The graft was then held by 4 mm cannulated screws (Asnis III stainless steel screws, Stryker, France) and 1.5 mm Kirschner wires (K-wires) (Figure 1B). The ankle joint was then stabilized with an external fixator (Trauson, ChangZhou, China) without the cast, in order to provide longitudinal traction

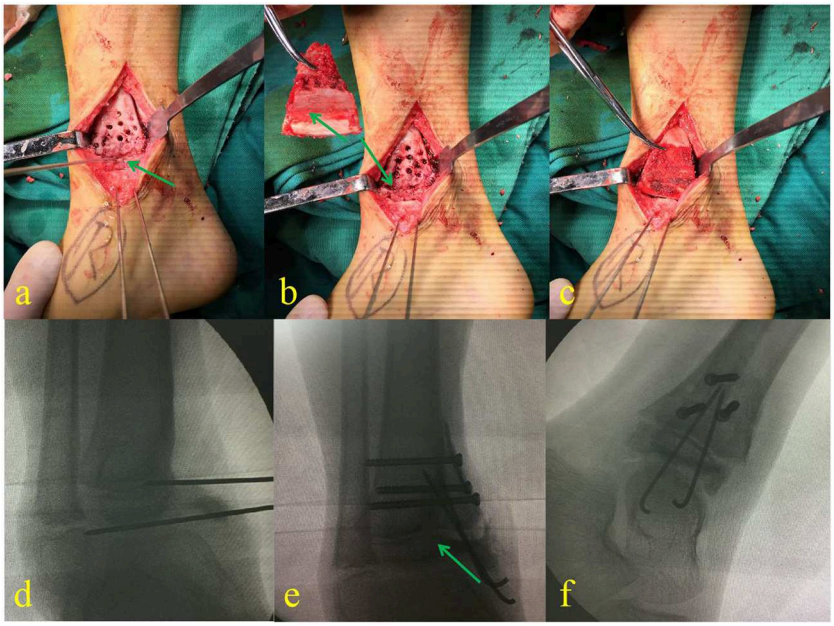

FIGURE 3
Debridement and location of the distal tibial physis with a K-wire **(a)**. Harvested iliac crest apophyseal autograft, ready to insert in an appropriate place **(b)**. The cartilage of the iliac crest autograft was positioned to meet the medial aspect of the talus **(c)**. **(d–f)** Are the fluoroscopic images taken during the surgery.

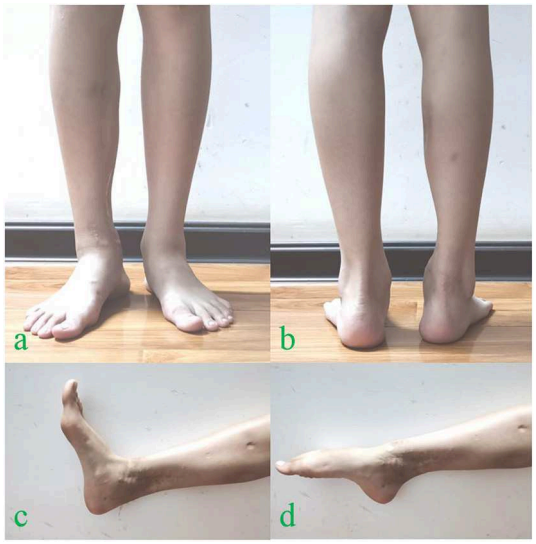

FIGURE 4
At 36 months follow-up after reconstructive surgery, the apparent deformity was not evident **(a,b)**, the functional and cosmetic outcomes of the operated ankle **(c,d)**.

to avoid unnecessary pressure on the graft and correct the cavovarus deformity.

The external fixator was removed after 3 months when the radiological evidence of graft union was present (Figure 1C), and the remaining implants were removed after 12 months following the second surgery. After 20 months following the reconstruction, a physeal bar on the distal medial tibia appeared on the radiograph (Figure 1D), which was excised using the Langenskiold procedure. Despite such an effort, the reconstructed medial malleolus did not develop as expected compared to the contralateral side (Figures 1E,F). There was still a residual varus deformity of the ankle joint; however, no leg length discrepancy was evident 36 months after the second operation. Despite the residual deformity, functional and cosmetic evaluation score was satisfactory, and further supra malleolar osteotomy was not required (Figure 4).

Discussion

Physeal injury is common in children that account for ∼15–18% of all pediatric fractures (3). Anatomic reduction is the mainstay of treatment (4–6). The most widely used classification for physeal injury was suggested by Salter and Harris in 1963. However, it does not describe certain physeal injuries. Salter-Harris type VI injury is rare in which an osteochondral fragment and a portion of physis are lost, bringing significant complications, including angular deformity and growth arrest resulting in leg length discrepancy. Only a few cases have been reported in the literature regarding this fracture pattern until now (7–10).

Peterson and Jacobsen (10) described 4 different treatment options for Salter-Harris type VI physeal injury based on the degree of bone loss and the presence of the bone defect. The authors suggested an application of fat tissue or iliac apophyseal cartilage in acute injury. They suggested using either an iliac crest bone graft or corrective osteotomy, or both in case of delayed injury (10). A prophylactic Langenskiold procedure was recommended by Foster et al. (11), and they reported satisfactory outcomes in both the acute and delayed stages. A correct autologous bone transplant or graft is mandatory for the success of this technique (12). Abbo et al. (9) recommended the utilization of prophylactic physiolysis with the interposition of fat in an acute stage in order to avoid repeated corrective osteotomies in the growing bone.

It is challenging to reconstruct Salter-Harris type VI physeal injuries in one stage because an open injury has a high risk of complications such as infection. To avoid such complications, we used a two-stage technique. In the first stage, only wound care was performed with intravenous administration of antibiotics, wound lavage, and debridement. The wound bed was prepared for the healthy granulation tissue to grow so that the skin graft could be possible later. Another issue is that even if the soft tissue condition is relatively good in the acute stage, it's challenging to perform a free flap and malleolar reconstruction simultaneously. To avoid such complications, reconstruction is usually performed in the second stage after the complete healing of the wound with no evidence of the infection.

The age of the patient and degree of bony loss are crucial factors for developing deformity and growth arrest. For optimum outcomes, the surgeon should always consider these factors before planning the reconstructive surgery. Our patients' age was only 7.5 years at the time of reconstructive surgery, so the risk of post-operative deformity was almost inevitable. The medial malleolus was reconstructed with an iliac apophyseal autograft covering the medial aspect of the talus. The physeal line of the autograft was placed parallel to the physeal line of the distal tibia with the hope that the autograft would heal appropriately and allow for potential growth.

In contrast to Abbo et al. (9), an external fixator was used to avoid the contracture and varus collapse of the ankle joint. The external fixator also reduces the longitudinal pressure on the newly reconstructed medial malleolus. It was removed when there was radiological evidence of graft union at 3 months post-operatively.

At the last follow-up, the age of the patient was 10.5 years. No length discrepancy in our case might be because of the early excision of the bony bar, which was <20% of the distal tibia physeal scope. Although the complete union was evident at the last follow-up, the medial malleolus did not develop as on the contralateral side. However, the external deformity was not apparent, and the patient had satisfactory cosmetic and functional outcomes. Epiphysiodesis is a valuable option to prevent further deformity.

The reconstruction of medial malleolus using an autologous iliac crest apophyseal graft and stabilization of the ankle joint with an external fixator is a novel reconstruction technique in treating Salter-Harris type VI physeal injury of the medial malleolus. Our patient reported satisfactory functional and cosmetic outcomes at the final follow-up; however, a further clinical study using a larger sample size is warranted in order to find the definitive outcome of the technique.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (IORG No: IORG0003571). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

BS were involved in data collection and follow-up assessments. XT, SR, and HZ were responsible for literature search, study design, and finalized the manuscript. CZ drafted the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Epidemiological and clinical characteristics of congenital pseudarthrosis of the tibia in China

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Background: Congenital pseudarthrosis of the tibia (CPT) is a refractory and rare disease. Because of its extremely low incidence, little is known about its clinical features. In this retrospective study, we aim to analyze the clinical characteristics of patients with CPT.

Materials and methods: This is a retrospective study of children with CPT identified by the radiological review. Investigations of CPT included general conditions, the characteristics of CPT, treatment methods, and surgical complications.

Results: We collected 514 CPT cases from March 1999 to March 2020 in our hospital, such as 317 (61.67%) boys, 197 (38.33%) girls; 330 (62.86%) in Crawford IV; 510 (97.14%) in mid and distal 1/3 tibia; 481 (93.58%) in less than 3 years at onset age; 297 (57.78%) in less than 3 years at the first outpatient visit. The most common post-operative complication was ankle valgus (101, 39.60%), followed by limb length discrepancy (91, 35.69%), refracture (38, 14.90%), osteomyelitis (15, 5.88%), and removal of internal fixation (10, 3.93%).

Conclusions: CPT with a higher incidence of Crawford IV frequently occurs in boys and the middle or distal part of the tibia; most patients have the onset age and first outpatient visit before 3 years; the major surgical complications are ankle valgus and limb length discrepancy.

KEYWORDS

clinical characteristics, congenital pseudarthrosis of the tibia, epidemiological features, retrospective study, incidence

Introduction

Background

Congenital pseudarthrosis of the tibia (CPT) is a rare disease of the skeletal system in children, with a prevalence of 1 in 140,000 or 300,000 (1, 2). CPT-related healthcare costs, work or study loss, and psychosocial problems place tremendous burdens on the families of affected children (3). As the most populous country in the world, however, little information regarding CPT epidemiology is available in China.

Due to its low incidence, clinical knowledge of CPT remains scarce and unified understanding is lacking. To this day, only three studies with more than 100 cases, two of which are multi-centered and the other single-centered, were reported (4–6). The incidence of CPT was estimated to be approximately 1 in 140,000, which was reported in a 1972 study with only 13 patients (2). The only large-sample data is a multi-center study (7) organized by The European Pediatric Orthopedic Society (EPOS) in 2000, which collected 340 cases from 20 hospitals in 13 countries. However, the above data are all from European countries, and the different findings were based on small sample sizes. Additionally, to date, there has been no population-based epidemiological study investigating of CPT. Therefore, a retrospective study based on a large sample should be conducted to better explore and enrich the relevant clinical information and knowledge of CPT.

Since the first CPT patient was admitted to our department in 1999, more than 600 patients with CPT have been treated in our unit (8–18). Therefore, based on a large number of cases, we established a Hunan CPT study database. The Hunan CPT study, which is a retrospective study of a general population sample of mainland Chinese, is designed to enhance current knowledge of CPT. The aim of the present paper is to introduce the clinical characteristics of patients with CPT.

Materials and methods

Study design and procedures

We performed a retrospective study on CPT cases between 1999 and 2020 in the Hunan Children's Hospital. Patients who had CPT were identified by the radiological review. All patients visited our hospital. The studies involving human participants were reviewed and approved by the Institutional Review Board of Ethics Committee of Hunan Children's Hospital (protocol code HCHLL-2019-37). All the patients provided written informed consent.

Investigations of CPT included the patient's general condition (affected side, onset age, age at first outpatient visit, age at first operation and whether combined with NF1 fibular cysts, definite injury, and first visit to our hospital), the characteristics of CPT Crawford classification, the location of the pseudarthrosis, the location of the pseudarthrosis, lateral proximal tibial angle (LPTA), lateral distal tibia angle (LDTA), treatment methods, and surgical complications.

Inclusion and exclusion criteria

We included participants aged under 16 years and provided complete data radiological review measurements. The accurate diagnosis was made by patients' medical history, physical examination, and imaging with no trauma or birth deformity of the lower limb (19). We excluded participants aged older than 16 years or other cases caused by osteomyelitis, trauma, and malignant tumor.

Measurements

The location of CPT was recorded as proximal 1/3, mid 1/3, and distal 1/3. Briefly, we divided the tibial length into 3 equal parts and recorded the pseudarthrosis site in each of the proximal, middle, or distal part in X-ray, named the proximal 1/3, mid 1/3, and distal 1/3. The measurement methods: at lateral X-rays, the length of the pseudarthrosis to the proximal tibial epiphyseal growth plate (a) and the length of the pseudarthrosis to the distal tibial epiphyseal growth plate (b), calculates $a/(a + b) = c$ $(0 < c < 1)$. $C < 1/3$, the pseudarthrosis was recorded as proximal 1/3 of the tibia; $1/3 \leq C < 2/3$, the pseudarthrosis was recorded as mid 1/3 of the tibia; $C \geq 2/3$, the pseudarthrosis was recorded as the distal 1/3 of the tibia. The location of the pseudarthrosis of the fibular was measured in the same way. They were recorded as proximal 1/3, mid 1/3, and distal 1/3 of the fibula.

Crawford classification was recorded by anteroposterior or lateral X-rays of the tibia/fibula which were taken at the first visit. We referred to the Springer B et al. method (20) to define LDTA and LPTA. The CPT pathological classification referred to the Crawford method (21) and we defined them into 4 types.

Statistical analysis

The general data of the corresponding children were entered into an EXCEL 2019(Microsoft® Excel® 2019MSO). All data were analyzed using STATA (Version 13.0, StataCorp LP, TX, United States).

Two-sample *t*-tests were used to analyze continuous data, and the chi-square test was used for categorical data.

Results

Summary of demographic characteristics

There were no statistical differences between genders in terms of the affected side, onset age, age at first treatment, age at first operation, NF-1 (Yes\No), and first treatment in our hospital (Yes\No). Between 1999 and 2020, there were 514 children with a recorded diagnosis of CPT: 317 (61.67%) boys, 197 (38.33%) girls; 253 (49.22%) in left, 250 (48.63%) in right, and 11 (2.15%) in bilateral of affected side; 368 (71.60%) birth to <1 year, 113 (21.98%) 1 to 3 years and 33 (6.42%) over 3 years at onset age; 66 (12.84%) birth to <1 year, 231 (44.94%) 1 to 3 years and 217 (42.22%) in over 3 years at first outpatient visit; 51 (11.70%) birth to <1 year, 170 (38.99%) 1 to 3 years and 215 (49.31%) over 3 years at first operation; 349 (67.90%) with NF-1, 165 (32.10%) without NF-1; 456 (88.72%) at first treatment in our hospital, 58 (11.28%) at first treatment not in our hospital; 388 (75.49%) without definite injury, 126 (24.51%) with definite injury, which included 81 (64.29%) walking fall, 9 (7.14%) bruise with weight, 8 (6.35%) sprain, 4 (3.17%) aggravating activities, and 24 (19.05%) falling accidents (Table 1).

TABLE 1 Summary of demographic characteristics.

	Male ($n = 317$)	Female ($n = 197$)	Statistics	*P*-value
Affected side				
Left	146	107	3.5675	0.168
Right	163	87		
Bilateral	8	3		
Onset age				
Birth to < 1 year	235	133	3.0079	0.22
1 to 3 years	65	48		
Over 3 years	17	16		
Age of the first visit of outpatient				
Birth to < 1 year	38	28	1.537	0.464
1 to 3 years	149	82		
Over 3 years	130	87		
Age of first operation				
Birth to < 1 year	31	20	1.21	0.54
1 to 3 years	113	57		
Over 3 years	132	83		
NF-1 (Yes/No)				
Yes	212	137	0.396	0.529
No	105	60		
First visit of outpatient in our hospital (Yes/No)				
Yes	281	175	0.00612	0.9376
No	36	22		
With/without definite injury				
Yes	72	54	1.4493	0.229
No	245	143		
Walking fall	51	30		
Bruise with Weight	7	2		
Sprain	7	1		
Aggravating Activities	3	1		
Falling accidents	4	20		

The radiologic features of congenital pseudarthrosis of the tibia

There were no statistical differences of Crawford classification, cystic changes of the fibula, the location of the pseudarthrosis, LPTA, and LDTA in terms of gender. But there were statistical differences of pseudarthrosis of the fibula in terms of gender ($p = 0.015$). Among the 525 limbs of CPT: Crawford type IV had the most (330), accounting for 62.86% of all types, and the other types were Crawford type I (33, 6.28%), Crawford type II (106, 20.19%), and Crawford type III (56, 10.67%). For the pseudarthrosis and fibular condition, 276 (53.70%) had CPT with pseudarthrosis of the fibula and 238 (46.30%) had CPT without pseudarthrosis of the fibula; 44 (8.56%) had CPT with cystic changes of the fibula and 470 (91.44%) had CPT without cystic changes of the fibula. Among the 525 limbs of CPT, the main locations of the lesion were in the middle and distal tibia: 15 (2.86%) in proximal 1/3 tibia, 191 (36.38%) in mid 1/3 tibia, and 319 (60.76%) in distal 1/3 tibia. Genu valgum and ankle valgus were the main manifestations of CPT (101 cases, 38.11%). Only pseudarthrosis of the fibula was statistically different between boys and girls ($p = 0.015$) (Table 2).

Treatment methods and surgical complications

There were no statistical differences of treatment methods or surgical complications in terms of gender. In our database, 78 (15.18%) cases received conservative treatment and 436 (84.82%) cases received surgical operation. The incidences of surgical complications were as follows: 101 (39.60%) cases occurred in the ankle valgus, 91 (35.69%) cases involved limb length discrepancy, 38 (14.90%) cases involved refracture, 15 (5.88%) cases involved osteomyelitis, and 10 (3.93%) cases involved the displacement of internal fixation (Table 3).

TABLE 2 The characteristics of CPT.

	Male ($n = 317$)	Female ($n = 197$)	Statistics	*P*-value
Crawford classification				
I	20	12 + 1	1.78	0.618
II	54 + 6	45 + 1		
III	33 + 3	18 + 2		
IV	202 + 7	119 + 2		
Pseudarthrosis of the fibula (Yes/No)				
Yes	183	93	5.9228	0.015*
No	134	104		
Cystic changes of the fibula (Yes/No)				
Yes	29	15	0.3653	0.546
No	288	182		
The location of the pseudarthrosis*				
Proximal 1/3	7	7 + 1	3.3066	0.191
Mid 1/3	110 + 2	76 + 3		
Distal 1/3	192 + 14	111 + 2		
LPTA and LDTA				
LPTA	86.91 ± 5.002	86.98 ± 5.456	0.1437	0.8858
LDTA	87.573 ± 10.928	87.079 ± 10.432	−0.5088	0.6111

$n1 + n2$ means $n1$ = unilateral and $n2$ = bilateral. *These data represents the number of affeced limbs.

TABLE 3 Treatment methods and surgical complications.

	Male	Female	chi-square test	*P*-value
Treatment methods#				
Non-operation	41	37		
operation	276	160	3.227	0.072
Surgical complication*				
Ankle valgus	63	38	3.5205	0.475
Limb length discrepancy	56	35		
Refracture	18	20		
Osteomyelitis	8	7		
Removal of Internal fixation	7	3		

This was based on Chi-square tests. #degree of freedom 1, *degree of freedom 4.

The map of regional distribution

The regional distribution of patients was divided by province, autonomous region, and direct jurisdiction city. A total of 514 cases came from 29 provinces or autonomous regions or direct jurisdiction cities, such as 65 cases in Hunan province, 43 cases in Henan province, 33 cases in Shandong province, 29 cases in Guangxi Zhuang Autonomous Region, 28 cases in Jiangsu province, 27 cases in each of Jiangxi province and Hubei province, 25 cases in each of Guangdong province, Hebei province and Zhejiang province, 21 cases in Anhui province, 17 cases in each of Gansu province, Liaoning province and Yunnan province, 15 cases in shaanxi province 14 cases Fujian province, 13 cases in Jilin province, 12 cases in Sichuan province, 11 cases in Guizhou province, 8 cases in each of Shanxi province and Xinjiang Uygur Autonomous Region, 6 cases in each of Heilongjiang province, Inner Mongolia and Chongqing, 5 cases in Beijing, 4 cases in Tianjin, 3 cases in Ningxia Hui Autonomous Region, and 2 cases in each of Hainan province and Shanghai (**Figure 1**).

Discussion

In this study, we present a large CPT sample retrospective study and define cases by clinical features and radiological and clinical characteristics. Thus, we bring a deeper knowledge of CPT in the Chinese context.

We collected 514 cases from 29 provinces or autonomous regions and direct jurisdiction cities. Hunan province had the highest number of cases with 65 (12.65%), in the top 10 provinces with the largest number of cases, only Guangxi Zhuang Autonomous Region 29 (5.64%) and Hubei province 27 (5.25%) were not among the top 10 provinces or autonomous regions and direct jurisdiction cities with the largest population in China. Provinces or autonomous regions and direct jurisdiction cities with larger populations had more cases, but Hunan province was not the top one with the largest population in China, which may be related to the geographical location of our hospital.

Congenital pseudarthrosis of the tibia is a rare pathology occurring in between 1/140,000 and 1/250,000 births (22–24) and is one of the most complex orthopedic situations in pediatrics. Based on the morbidity reported above, in the last 10 years, the number of newborns in China–according to official data reports–was 157.56 million and the number of CPT patients was between 630 and 1125 cases. Of the 514 cases collected in our hospital, 424 cases were collected from 2011 to 2020, and 90 cases were collected from 1999 to 2010. This means that our one center has treated nearly 40% of national CPT cases since 2011. Since the first CPT patient was admitted to our department in 1999, more than 600 patients with CPT have been treated in our unit. We have accumulated rich experience in the treatment of CPT, and have gradually been recognized by peer pediatric orthopedic surgeons over China, as well as by the majority of patients' families. We have also made good self-media publicity so that CPT patients in China are more and more concentrated in our hospital.

We searched CPT-related clinical study from 1944 to 2021 in Web of Science and Pubmed databases, totally, 92 literatures (excluding papers of cases less than or equal to 10) were included, and the number of cases in each paper ranged from

11 to 340. There were only three multi-center studies: F Hefti et al. have 200 cases, Hitesh Shah et al. have 118 cases, and F Vigouroux has 18 cases (4). Sofield HA is the only one with more than 100 cases in the single-center study (6). The epidemiological data compared with other studies show in **Supplementary Table 1**.

Currently, the timing of surgery for CPT is a controversial issue (25). EPOS recommends avoiding surgery for CPT in patients younger than 3 years old, and that operation should be postponed to the age of 5 years, otherwise, patients may have a worse prognosis (7). Harding similarly recommended deferring surgery to the age of 4 years (26). However, Shah H reported that the achievement of the bone union in young children can minimize the abnormal growth and lower limb shortening (27). Joseph reported that bone union of CPT occurred in 12 out of 13 (92%) children treated before the age of 3 years (28). Liu reported on 42 patients with CPT and the frequency of bone union was higher in children with CPT operated on before reaching 3 years of age, and suggested that there is no need to defer surgery for CPT until the child is older than 3 years of age (14). In our study, we reported 514 cases of CPT, surgery was performed in 436 patients which included 221 (50.69%) younger than 3 years old, and the patients had a good prognosis (**Tables 1**, **3**). Considering this controversial issue, in our study, onset age, first outpatient visit and first operation were divided into three groups which were birth to 1 year, 1 to 3 years, and over 3 years. In this study, onset age before 3 years had 481 (93.58%) cases and after 3 years had 33 (6.42%) cases; the age at the first outpatient visit before 3 years had 297 (57.78%) cases and after 3 years had 217 (42.22%) cases; this phenomenon of operations before 3 years being as common as operations after 3 years may be related to the age at the first outpatient visit.

Pseudarthrosis of the fibula (CPF) is frequently associated with CPT, but it becomes uncommon when it is isolated. Isolated CPF is usually considered a less severe condition than CPT. However, its site–most frequently near the ankle–leads to severe valgus and instability of this weight-bearing joint (25–29). In Liu's study (10), patients with fibular pseudarthrosis had a high incidence of refracture and ankle valgus, and he suggested that attention should be paid to the presence of fibular pseudarthrosis when managing CPT. There were 276 (53.70%) cases of CPF of the 514 cases in this study, and 44 (8.56%) cases with cystic changes in his fibula. There were statistical differences in the prevalence of CPF, but no statistical differences in cystic changes of the fibula.

We found that Crawford IV (330, 62.86%) CPT had the most cases, which may be associated with hyperactivity. We treated Crawford IV CPT and developed into Crawford IV CPT by operation. It has been well documented that external fixation in children and adolescents has a significant physical and physiological impact, with studies reporting pain and consequent sleeping problems in approximately half of the patients (30). The operation complications–related primarily to the use of an external or internal device, residual limb-length discrepancy, and valgus deformity–are commonly reported,

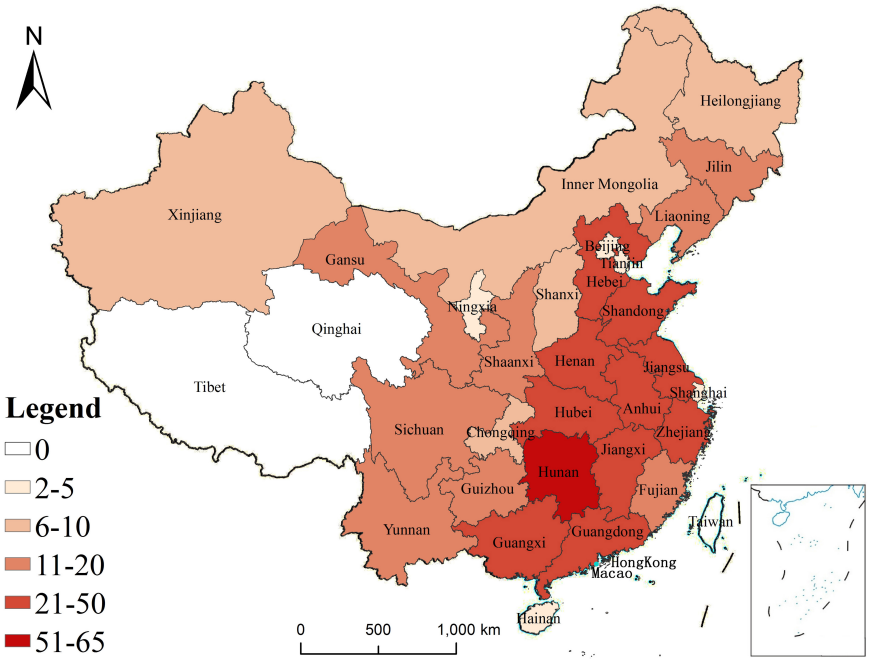

FIGURE 1
Regional distribution of CPT patients included in current analysis.

with an overall complication rate of 30%–100% (31). In our study, the complications also included ankle valgus, limb length discrepancy, refracture, osteomyelitis, and removal of internal fixation. The present study is a retrospective review limited by the heterogeneity of the available data and follow-up. Firstly, this study was a cross-sectional analysis and did not provide prognostic or therapeutic recommendations for cohort studies. Secondly, this study was a single-center analysis. Although our cases came from all over the country, there was still bias. We should combine the China Pediatric Orthopedic Association with expanding multi-center research in future studies; with further detailed documentation, it may be possible to clarify many more issues.

Conclusion

Until now, we have collected 514 cases of CPT, which constitutes the largest single-center study. CPT with a higher incidence of Crawford IV frequently occurs in boys and middle or distal tibia; the major surgical complications are ankle valgus and limb length discrepancy. In subsequent studies, we will further report pathologic mechanism, surgical methods, complications, and prognosis of CPT through prospective studies.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the Institutional Review Board of Ethics Committee of Hunan Children's Hospital (protocol code HCHLL-2019-37). All the patients provided written informed consent.

Author contributions

YZ, GY, and HM: conceptualization and writing – review and editing. YZ, YL, and QT: methodology. KL, GZ, and YL: validation. QT and YZ: formal analysis and investigation. GY and HM: resources, project administration, and funding acquisition. YZ: data curation and writing – original draft preparation. HM and GZ: supervision. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.943917/full#supplementary-material

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Non-traumatic scapholunate dissociation in a 10-year-old female: A case report

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Introduction: Severe or minor repetitive trauma, inflammation, infection, tumors, and congenital ligamentous laxity have been etiologically implicated in scapholunate dissociation (SLD). While a few cases of patients with asymptomatic SLD have been reported in the literature, despite radiographically demonstrated widened scapholunate angles and rotatory subluxation of the scaphoid bone, these patients experienced only mild or no pain and no dorsal intercalated segment instability deformity. Here, we report the case of a monolateral non-traumatic SLD in a young 10-year-old girl that led to an important range of motion impairment with no wrist pain. The case represents a rarity for no previous history of trauma, young age, and no pain.
Main symptoms and important clinical findings: In our patient, an examination revealed a reduced range of motion in the left wrist and no pain during passive or active mobilization. The X-ray showed a 16 mm scapholunate gap in the anteroposterior roentgenogram. In this case, we suggested that congenital or developmental ligamentous laxity may be the cause of SLD. The diagnostic assessment was completed with a wrist MRI and CT.
Therapeutic interventions and outcomes: The patient underwent an open dorsal surgery: we directly reduced the dislocated bones and fixed them with five percutaneous 1 mm k-wires. Finally, the scapholunate ligaments were repaired using bone-absorbable anchor sutures. The wrist was immobilized in a volar cast for 8 weeks. The patient was able to resume her daily life activities (included sport) within 12 months.
Conclusion: Carpus injuries are rare in children, and treatment, especially for young-age patients, is fraught with risks and remains controversial. Our case demonstrates that the patient has had a good clinical outcome. The physio-rehabilitation program for this patient has been of long duration. Most previous studies have shown excellent clinical results after an average of 2.4 years.

KEYWORDS

scapholunate dissociation, child, young age, carpal injuries, non-traumatic

Introduction

Scapholunate dissociation (SLD) is a consequence of a lesion of the ligamentous complex holding two carpal bones, the scaphoid and lunate. The scapholunate ligament is made of three parts: volar, intermediate, and dorsal, which is the strongest component. In particular, when the whole ligament or the dorsal breaks, a radiocarpal

joint instability occurs. SLD occurrence has been consistently attributed to previous trauma that typically occurs with a hyperextended and an ulnar-deviated wrist during a fall. Approximately 5% of SLD is associated with distal radius fractures, in particular fractures of the radial styloid. Even if the main cause of SLD is trauma, other etiologies have been reported in the literature, such as rheumatoid arthritis, spastic paresis, and congenital ligament laxity (1).

SLD has been noted to occur in the setting of severe or minor repetitive trauma, infection, tumors, inflammation, infection, and congenital ligamentous laxity. SD ligament rupture is the first step of a hand lesion series: carpal instability leads to a volar rotation of the scaphoid and dorsal rotation of the lunate, resulting in a misalignment and later arthrosis between the carpal bones and the radius (2).

While a few cases of patients with asymptomatic SLD have been reported, despite a radiographically demonstrated scapholunate gap and a partial rotatory subluxation of the scaphoid, these patients experienced only mild or no pain and no carpal instability or deformity (3).

Here, we report the case of a monolateral non-traumatic SLD in a 10-year-old girl that led to an important range of motion impairment with no wrist pain. This case represents a rarity for no previous history of trauma, young age, and no pain.

Case description

During the Covid lockdown, a 10-year-old female confessed to her parents that she was not able to perform some gym exercises with her sister because of left wrist extension loss. She did not feel any pain and she discounted recent or previous trauma. Her report was fairly reliable because she did not play any sport for a long time and had been spending a lot of time indoors since the beginning of the pandemic. None of her family members noticed her wrist condition before.

A month later, she was seen in our private practice.

Physical examination of patients with SLD usually reveals wrist edema, tenderness point at the dorsal SL interval, and pain during extension and radial deviation wrist movement. A palpable "clunk" can be felt during the performance of the Watson shift test (1), which involves placing an examiner thumb on the distal pole of the scaphoid on the palmar side and moving the wrist from the extended-ulnar deviation to the flexed-radial deviation with constant pressure: this noise indicates scapholunate instability.

In our patient, the range of motion in the wrist was impaired: she had complete flection (85°) but no extension (0°). She had no pain during passive or active mobilization and no edema.

Generally, she was a heathy patient with no underlining chronic disease in her medical history, no drug therapy and no past surgery.

Her recent X-ray revealed a 16 mm scapholunate gap in the anteroposterior roentgenogram (the Terry Thomas sign) and a scapholunate angle of 134° on the lateral view (**Figure 1**).

Diagnostic assessment

According to Cautilli and Wehbe, the normal distance between the scaphoid and the lunate in a posterior-to-anterior radiograph is 3 mm or less in an adult skeleton (4). In a child, this measurement is usually larger due to the presence of a growth nucleus (5), and it becomes necessary to compare the opposite wrist X-ray (**Figure 1**).

In a lateral radiograph, normally the radius and lunate should be perfectly aligned and the scapholunate angle ranges from 30° to 60°. In a scapholunate dissociation, in the lateral view, there is an abnormal dorsal slant of the lunate (DISI deformity) and a rotary subluxation of the scaphoid (6).

The "cortical ring" or "signet ring" sign consists of a radiopaque circle line visible on the posteroanterior hand X-ray in the case of SLD. It represents an overlapping view of the scaphoid tubercle on its axis when the scaphoid is rotated. Sometimes it could be normally present too, so the presence of this sign should be evaluated in light of clinical findings (1).

In our patient, MRI of her left wrist proved useful for definitive diagnosis, demonstrating SLD and a perilunate subluxation pattern. Acute trauma MRI also showed a ligamentous tear with a fluid presence between the lunate and the ligament (bright signal).

In view of the above findings, we also submitted her wrist to a 3D CT.

We did not do a diagnostic arthroscopy for some reasons: as we had already obtained the diagnosis with MRI and CT, we reasoned that the lesion needed an open surgery (direct reduction was necessary in inveterate bone dislocations); we also considered the fact that the radio-carpal space is small in adults and, smaller in children, so the risk of not having a good surgical view was high.

During our first examination of the girl, we noticed a generalized joint laxity in her body, with a Beighton score of 6/9 points. In this setting, like other authors (7), we suggested that congenital or developmental ligamentous laxity may be the SLD cause. Even if hyperlaxity was present and she always denied previous wrist trauma, we could not exclude without any doubt a traumatic cause of the disease: children sometimes do not dare to report an injury.

Therapeutic intervention

SL acute dissociation needs urgent surgical intervention (within 6 weeks) to decrease the risk of carpal deformity, arthrosis, and severe wrist handicap. The recognition of early

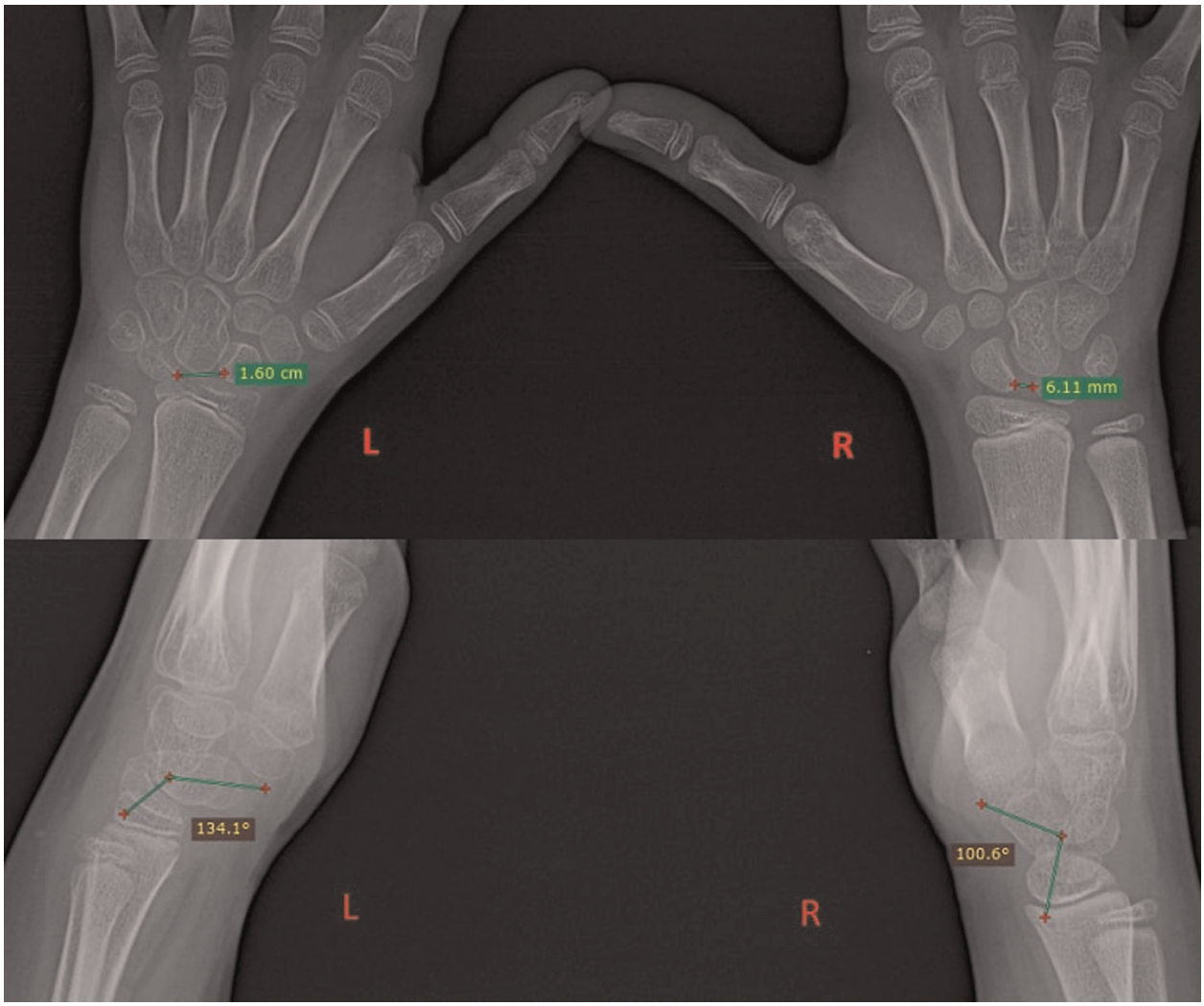

FIGURE 1
Presurgery X-ray: a comparison between an injured wrist (left) and a healthy wrist (right) in PA and lateral views; measuring the scapho-lunate distance and angle.

carpal instabilities is very important, in order to avoid non-diagnosed hand lesions that lead to chronic pain and long-term degenerative changes, including SL-advanced collapse, known as SLAC wrist (1).

Our patient underwent open surgery reconstruction using bone k-wire fixation and anchor suture. She received IV antibiotic therapy before and after her surgery.

A dorsal skin incision on the left wrist was performed, and the radial sensitive nerve was isolated and protected. We partially opened the 4th extensor compartment. Berger-Bishop dorsal capsulotomy was performed to expose the carpal bones. Then, the periscaphoid synovial tissue was removed and the lesions were stabilized: the scapholunate and lunotriquetral ligaments were torn, and the capitate migrated in the scapholunate interspace. Under fluoroscopy, we reduced the dislocated bones and fixed them with percutaneous 1 mm k-wires (two wires to fix the scaphoid and lunate, two wires to fix the scaphoid and capitate, and one wire to fix the lunate and triquetrum). Finally, the scapholunate ligaments were repaired using bone-absorbable anchor sutures (**Figure 2**). After capsular, IV compartment, and skin suturing, the wrist was immobilized in a volar cast.

Follow-up and outcomes

K-wires were removed after 8 weeks. At the first examination, the patient had a 20° active wrist flexion and 40° extension; she did not have any problems with her finger movement and there was good skin closure. She was referred to a hand therapist for passive and active exercises, 2 times a week, so that she could recover her wrist range of motion.

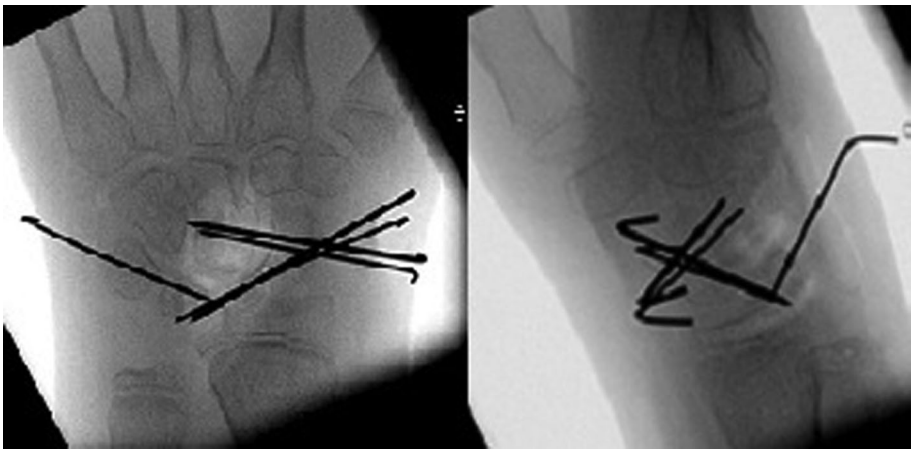

FIGURE 2
Postsurgery X-ray: carpal bones reduced and fixed with k-wires.

The patient resumed her daily life activities (included sport) within 12 months. In her last clinical examination, 10 months after the surgery, she regained almost complete wrist extension (80°) and showed further improvement (50°) in flexion (**Figure 3**) and had no pain during the performance of exercises. X-ray showed a restored carpal alignment (**Figure 4**).

Discussion

Vance et al. reported a case of asymptomatic bilateral SLD in an adult and stated that ligamentous laxity could be a causative factor for this condition (6). We could hypothesize that it was etiopathogenesis in our case.

SLD and perilunate dislocations are rare in adults, but even rarer in children. To the best of our knowledge, only eight cases of perilunate dislocation in the pediatric population have been reported in the literature, and it was only in our case, there was no previous history of trauma.

Moreover, we noticed that in every case that was reported, the age range of patients was between 9 and 12 years, and most of them had an additional injury (different radius fractures).

Multiple surgical techniques have been proposed to treat this problem. For acute SLD, currently, most authors recommended either a closed or open reduction with temporary internal fixation. The treatment of chronic SLD is more controversial than others and is fraught with more

FIGURE 3
Wrist mobility 10 months after the performance of the surgery.

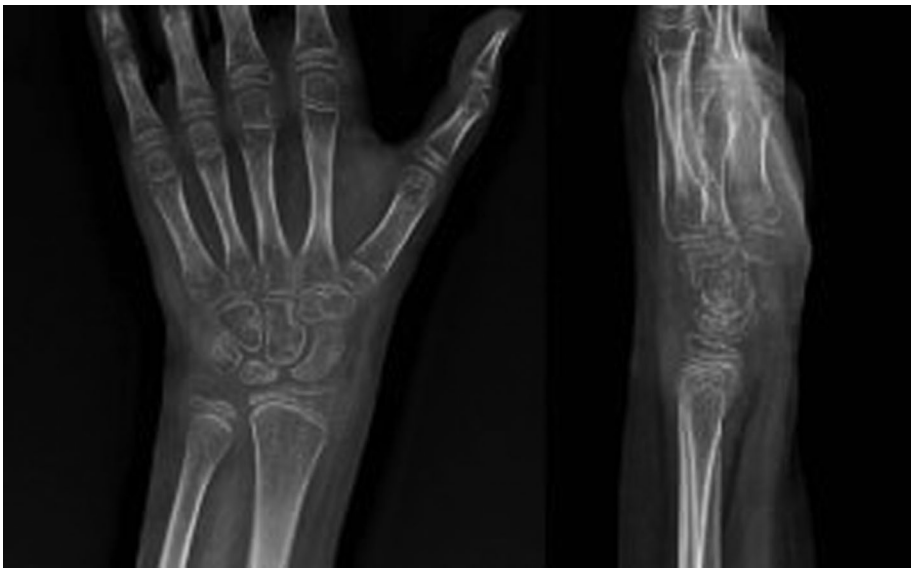

FIGURE 4
An injured wrist X-ray 10 months after the surgery.

risks. Also, it is a much-discussed topic. During the subacute window, between 3 and 8 weeks after injury, the ligaments do not heal spontaneously and the poor quality of tissue does not allow repair by direct suture (8). Tendon grafts have been reported to replace the scapholunate ligament, but this procedure is technically demanding. During one's childhood, an intraosseous reconstruction using the flexor carpi radialis tendon tunneled through the scaphoid should be dismissed for growth plate presence in bones obviously. An extraosseous reconstruction using the dorsal capsule Brunelli flap and dorsal radiocarpal ligament has been described (9).

Non-surgical techniques, such as simply cast immobilization or closed reduction, are unsuitable for people with dislocated bones, with the possibility of such patients developing arthritis being high. Early diagnosis and treatment of acute scapholunate injury has been reported to be the most effective way of preventing degenerative lesions (8).

Management of acute carpal bone dislocations includes early closed reduction and percutaneous wire fixation for 8 weeks. However, in chronic injury, and if closed reduction fails, open reduction techniques have been described with good outcomes (10).

Conclusion

In summary, although carpal lesions are rare in children, we highlight the importance of a meticulous physical examination and radiological analysis for finding carpal instability injuries. If missed, they can cause devastating outcomes in wrist function.

Treatment for such injuries in the young age group is beset with risks and is controversial.

Therefore, we encourage more of our colleagues to flush out these carpal lesions and report about them in order to improve management outcomes in the future.

Patient perspective

Our case demonstrates that the patient has had a good clinical outcome. Her physio-rehabilitation program has been one of long duration. Twelve months postoperatively, the partial range of motion of her injured wrist was evident, but we see more room for improvement. Most studies have shown excellent clinical results after an average of 2.4 years (11). Therefore, we will continue to follow up this case.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation

and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

DB has made substantial contributions to this study in terms of manuscript conception, design, coordination and writing, data acquisition, and interpretation. AP, AGA, EMP, and LB contributed to manuscript writing. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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COL1A1 novel splice variant in osteogenesis imperfecta and splicing variants review: A case report

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Background: Osteogenesis imperfecta (OI) is a rare heterogeneous genetic disorder commonly autosomal dominant with variants in the COL1A1 and COL1A2 genes. It is characterized by bone fragility and deformity, recurrent fractures, blue sclera, dentinogenesis imperfecta, short stature, and progressive deafness.
Case presentation: We present a novel splicing mutation in the COL1A1 gene (c.2398-1G > C) in a 6-year-old Ecuadorian girl with fractures after light pressure and blue sclera. We identified the pathogenic variant, performed a literature review of splice variants, and recognized their location in the COL1A1 functional domains.
Conclusion: We describe the first clinical description of a patient with OI type 1 caused by a splice variant in intron 34 of COL1A1 gene and identify that most of them are localized in the triple-helical region domain. We suggest that the splice variant in signal peptide, von Willebrand factor type C, and nonhelical regions maintain their functionality or that individuals affected with severe cases die early in development and are not reported.

KEYWORDS
osteogenesis imperfecta, splicing, Ecuador, COL1A1, collagen

Introduction

Osteogenesis imperfecta (OI) known as brittle bone disease is a rare heterogeneous genetic disorder of connective tissue with an incidence of 1 in 15,000–20,000 births (1). Clinically it is characterized by bone fragility, deformity, recurrent fractures, blue sclera, dentinogenesis imperfecta, short stature, and progressive deafness (1). Under clinical and radiological parameters, the disease is classified according to the Sillence classification in four types: I (mild) and IV (moderate deforming), frequent but less severe; II (lethal) and III (severe deforming), less frequent but more lethal (2).

OI is mostly autosomal dominant and 95% of cases result from mutations in COL1A1 and COL1A2 that code for type I collagen alpha chains, α1 and α2, respectively (1). Autosomal recessive cases result from mutations in the CRTAP and LEPRE1 genes (3). COL1A1variants include missense, nonsense, frameshift, and splice site (4). RNA splicing is indispensable for protein synthesis. The RNA transcript (pre-mRNA) requires introns being spliced and the exons bound to form mRNA (1). The splicing process is performed by the spliceosome, which consists of five uridine-rich

ribonucleoproteins and more than 200 associated proteins (4). Inappropriate splicing fails to remove introns or removes necessary exons resulting in an abnormal type I collagen chain (5).

Here, we report a patient with fractures after light pressure and blue sclera, identify the pathogenic variant, performed a literature review of splice variants, and recognized their location in the COL1A1 functional domains. Most of articles focus on nonsense and missense variants and splice variant information are not available.

Case report

Patient information and therapeutic interventions

We report a 6-year-old female who came to the genetic outpatient clinic for multiple consecutive fractures. She was born by vaginal delivery from nonconsanguineous parents with no complications and achieved all developmental milestones without delay. These include fine motor, gross motor social-emotional, and behavioral, language, and cognitive milestones (6). At 6 months, she presented hip dysplasia and bilateral valgus cavus that was treated with an orthopedic diaper. In June 2021, she fell from her height and suffered a left femoral shaft close fracture that required surgery and plating nailing placement (**Figure 1** and **Supplementary Figure S1**). Eight months later, the surgeon removed the plating. Fifteen days later, the girl slightly twisted her left leg and fractured her left femur again. The pediatrician ordered additional imaging studies and ruled out malignancy. Her physical examination revealed blue sclera without coloboma and hypermobility in her hands and feet. Her family history information is relevant for blue sclera but no fractures in her mother.

Molecular analysis

We ordered the Osteogenesis Imperfecta and Bone Fragility Panel that analyzes 67 genes and identified a heterozygous G > C c.2398-1 (splice acceptor) pathogenic variant in intron 34 of COL1A1. The variant alters splicing with a frequency of 0 in The Genome Aggregation Database (gnomAD) and in The Exome Aggregation Consortium (ExAC) databases. The splice variant was confirmed by Sanger sequencing.

Review of splicing variants

We reviewed all cases of splicing variants reported in PubMed until June 2022 and filtered the case reports that include the splice variant location and the OI type. We identified 336 splicing variants, most of them were OI type I and located in intron 17. Most of the splice variants were located in introns 28, 33, 35, and 50 and in exon 49 (**Figure 2**, **Supplementary Tables S1, S2**). OI type I was located mostly in intron 17 and 19; type 2 in intron 14, 26, and 47; type 3 in intron 11 and 6; and type 4 in intron 8, 9, 15, 16, and 19. The most intron splice variants were located in introns near exons that become the triple-helical region domain (**Supplementary Table S2**). Splice variant mostly caused OI type 1. Intron 17 includes the most single nucleotide variants (mostly G > C/A) and reported 17 type 1, 3 type 3, and 1 type 4 case. Most of single nucleotide variants

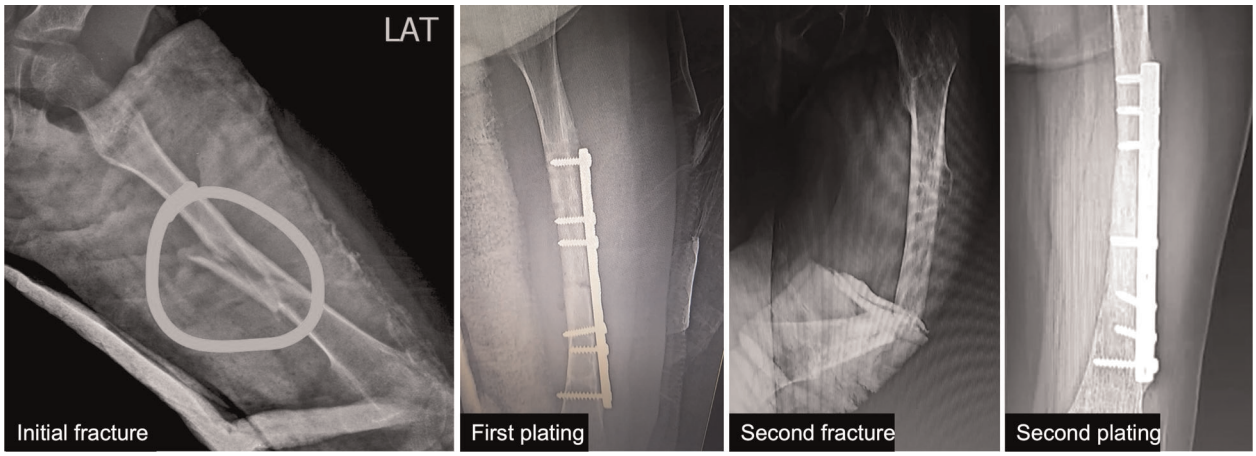

FIGURE 1
Patient's x-rays. First x-ray shows the initial left femoral shaft fracture. Second x-ray shows the first plating fixation. Third x-ray shows the fracture after a slight twist of the leg. Fourth x-ray shows the second plating fixation.

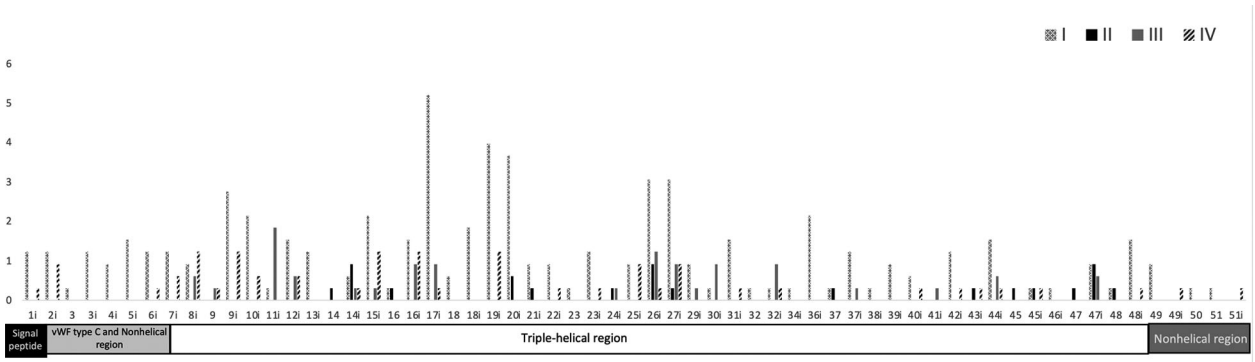

FIGURE 2
Frequency of the location of OI splice variants and COL1A1 domain distribution. Upper region: location of the type of OI splice variants along the COL1A1 introns and exons. OI is classified according to the Sillence classification in four types: I (mild) and IV (moderate deforming), frequent but less severe; II (lethal) and III (severe deforming), less frequent but more lethal. Most splice variants are located in intron 17. Black and white pattern = type I, black = type II, gray = type III, and oblique black = type IV. Lower region: functional domains along COL1A1 introns and exons. Most splice variants are located in the triple-helical region. Black square = signal peptide, light gray rectangle = von Willebrand factor type C and nonhelical region (N-terminal), white rectangle = triple-helical region, and dark gray rectangle = nonhelical region (C-terminal).

in OI type 2 are A > C and type 3 G > C (**Supplementary Table S1**).

Discussion

In this case report, we describe the first clinical description of a patient with a splice variant in intron 34 in the COL1A1 gene with a systemic literature review of splice variants reported in PubMed and used the variant database by Dalgeish et al. We identified that most of the variants localize in the triple-helical region domain.

Our patient presented with two fractures after weak pressure and blue sclera, and neoplasia was excluded. The sequencing panel reported a splice variant in intron 34. A splice variant in exon 34 was reported by Lindahl et al.. and a study in Sweden mentioned that one case had a OI type IA and did not include the clinical description (7). Our case is the first report of a c.2398-1G > C variant, is a OI type I, and the mother of the patient has blue sclera and lacks medical history of fractures.

The differential diagnoses of OI include diseases related to bone fragility (8). Rickets was excluded due to a normal alkaline phosphatase level, normal sclera and audition involvement, or deafness. Osteomalacia is characterized by bone pain and fractures (8). Other disorders to consider include Bruck's syndrome (congenital contractures involving knee or ankle joints), panostotic fibrous dysplasia (cystic lesions in all bones), juvenile Paget's disease (elevated alkaline phosphatase levels), or juvenile idiopathic osteoporosis (9).

The COL1A1 gene is located in chromosome 17, includes 17,554 bp, and produces pro-alpha 1 collagen chains. Type 1 collagen is the most common type of collagen in the body and is part of bones, skin, tendons, and sclera (10). Type 1 collagen contains two pro-alpha 1 chains and one pro-alpha 2 chain. The functional domains include signal peptide (exon 1), von Willebrand factor type C and nonhelical region (exon 2–6), triple-helical region (exon 7–48), and nonhelical region (exon 49–52). The triple helix repeat works as an extracellular structural protein involved in the formation of connective tissue structure. Mutations in COL1A1 alter the production of type 1 collagen resulting in bone fragility, and most published articles focused on missense and nonsense variants. A splice variant is a modification in the DNA sequence in the splice site (the limit between exons and introns), which can cause the inclusion of introns, loss of exons, and alteration of the protein coding sequence, disrupting RNA splicing (11). We found that most of the splice variants are located in the triple-helical region and are mostly OI type I (**Figure 2**, **Supplementary Tables S1, S2**). The triple-helical region includes a series of repeated regions and additional introns, or lesser exons allow for the diverse clinical types. The signal peptide, von Willebrand factor type C and nonhelical region, and nonhelical regions have OI type I (mild) and IV (moderate). We suggest that the splice variant in these regions maintain the functionality or that individuals affected with severe cases die early in development and are not reported.

Examples of different phenotypes by different splice variants

Splice variants in the same gene can cause different phenotypes. Errors during splicing leads to alterations in the reading frame by including introns or excluding exons. For example, the variant c.3718-2477C > T in CFTR that is reported in patients with cystic fibrosis produces a stop

codon, creates a nonfunctional protein, and present a mild phenotype (12). Likewise, most hemophilia B patients with splicing mutations correspond have from to severe moderate to moderate severe phenotypes, consequence of the aberrant splicing that conditions the expression of the functional protein. The c.520 + 13A > G mutation in intron 5 shows moderate mild to mild moderate phenotypes (13). In addition, same substitution at the same location of the DMD gene can cause different clinical manifestations on the patient. Mutation c.3277 + 1G > A occurring in intron 25 completely removes exon 25 resulting in a mild Becker muscular dystrophy, while mutation c.6439 + 1G > A in intron 45 results in the inclusion of a shorter exon 45 leading to a severe form of Duchenne muscular dystrophy (12).

Conclusion

We described the first clinical description of a patient with OI type 1 caused by a splice variant in intron 34 of COL1A1 gene, performed a literature review of splice variants, and identified that most of them localize in the triple-helical region domain.

Data availability statement

The datasets presented in this article are not readily available because of ethical/privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by P2019-102M. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

MD and VDC performed the literature review and wrote the paper. VIR contacted the patient, provided genetic counseling, performed the literature review, analyzed the panel results, and wrote the paper. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.986372/full#supplementary-material.

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Fibrodysplasia ossificans progressiva: A rare disease with spinal deformity and severe hip dysfunction

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Introduction: Progressive fibrous dysplasia ossification (FOP) is a rare genetic disease characterized by congenital bone malformations and soft tissue masses that progress to heterotopic ossification. Congenital great toe deformity and progressive heterotopic ossifications with an anatomical and temporal pattern are the two classical clinical characteristics of FOP. We present a unique case of FOP characterized by mandibular angle fascial contracture and back and iliopsoas muscle ossification managed *via* surgery in a 13 year old girl.

Case presentation: A 13 year old girl with a history of right cervical fascial release surgery and back heterotopic osteotomy presented to our clinic due to recurrence of heterotopic ossification, scoliosis, and progressive joint stiffness. Computed tomography (CT) or magnetic resonance imaging (MRI) examination confirmed heterotopic ossification of the left back and left iliopsoas muscle and spinal scoliosis. Two years after the surgery, the patient presented with recurrence of back heterotopic ossification and rapidly advancing ossification of the left iliopsoas muscle. Six months after surgery, the patient had no disability, pain and clinical recurrence, and the joint function recovered.

Conclusions: In patients with multiple-site heterotopic ossification caused by FOP, oral function and hip stiffness improve with detailed facial release surgery and rehabilitation treatment. However, dorsal fascia ossification and spinal scoliosis can recur shortly after resection.

KEYWORDS

fibrodysplasia ossificans progressive, iliopsoas muscle, heterotopic ossification, fascial release, hip dysfunction

Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare connective tissue genetic disease characterized by congenital big toe deformity and irreversible heterotopic ossification of soft tissue (1, 2). The prevalence of FOP is about 1/2,000,000, and the condition is not affected by ethnicity, geographic predisposition, and sex (3). Heterotopic bone formation leads to joint locking, making movement impossible. FOP progresses with ossification episodes. This extraskeletal bone formation is exacerbated by small soft tissue traumas, myotonia, fatigue, intramuscular injections, and influenza-like infections (4). Thus far, there is no effective preventive or treatment method for FOP. Although surgical treatment is successful in rare cases, new bone formation is observed postoperatively at the surgical site (2). Herein, we present a 13-year-old girl with FOP who presented with heterotopic ossification causing mandibular angle deformity, scoliosis, and severe hip movement limitation.

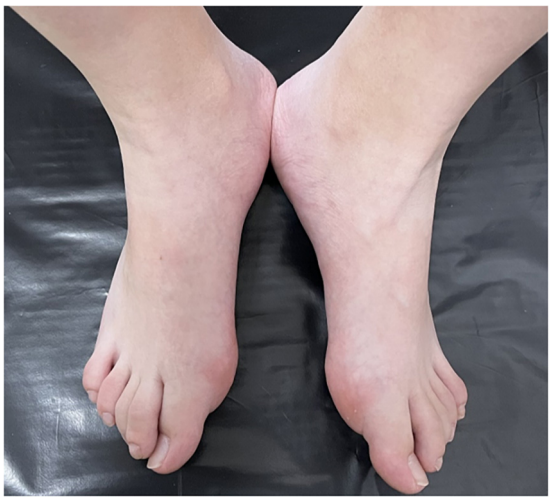

FIGURE 2
Halluces were characterized by hallux valgus deformity with macrodactyly.

Case presentation

A 13-year-old girl who had been experiencing spinal scoliosis and rapidly advancing hip stiffness for 2 years visited our hospital. Two years back, she was admitted due to drooping of the right corner of the mouth and ossification of the back fascia (**Figures 1A,B**, **2**, **3A,B**). Physical examination revealed facial asymmetry, palpable tumors in the left mandibular angle, and limited oral closure. However, pain was not observed. At the age of 8 years, the patient developed soft tissue heterotopic ossification in the back. After several days, the lesion became stiff like a stone. Halluces were characterized by hallux valgus deformity with big toe deformity. The patient did not have a previous history of trauma, surgeries, infections, allergies, other known underlying conditions, and medication use. She is the second child of a healthy non-consanguineous marriage and has a healthy 24-year-old sister. Her mother remembered that her grandmother had microdactyly of the hallux but no extraskeletal bone formation on the body and no signs of limited activity. Anteroposterior and axial radiographic evaluation showed that a large amount of radiopaque formation was mainly located in the back area and scoliosis (**Figures 4A,B**). There was a stiff, osseous lesion originating from the left chest wall and extending to the ilium region (**Figure 3B**). Computed tomography scan revealed spontaneous cervical fusion, heterotopic ossification of the left

Abbreviations: FOP, Fibrodysplasia Ossificans Progressiva; ROM, range of motion.

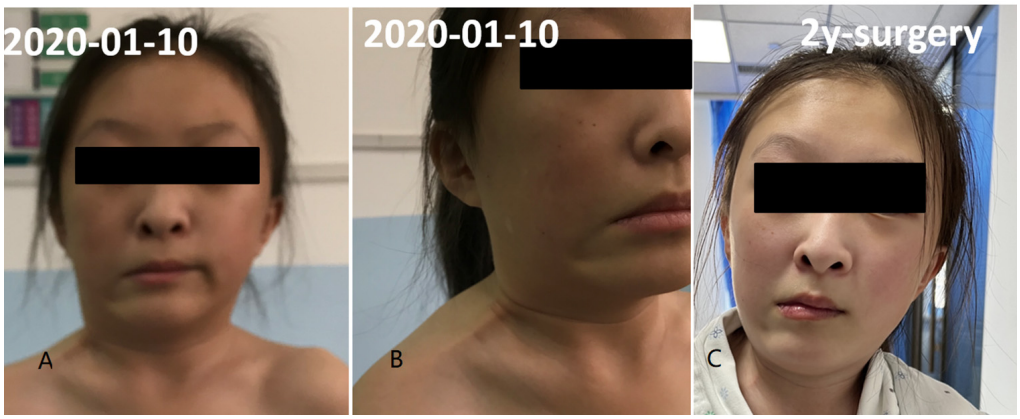

FIGURE 1
Fascial contracture of right neck and mandibular angle. Panels **(A,B)** was preoperative condition and panel **(C)** was 2 years after operation.

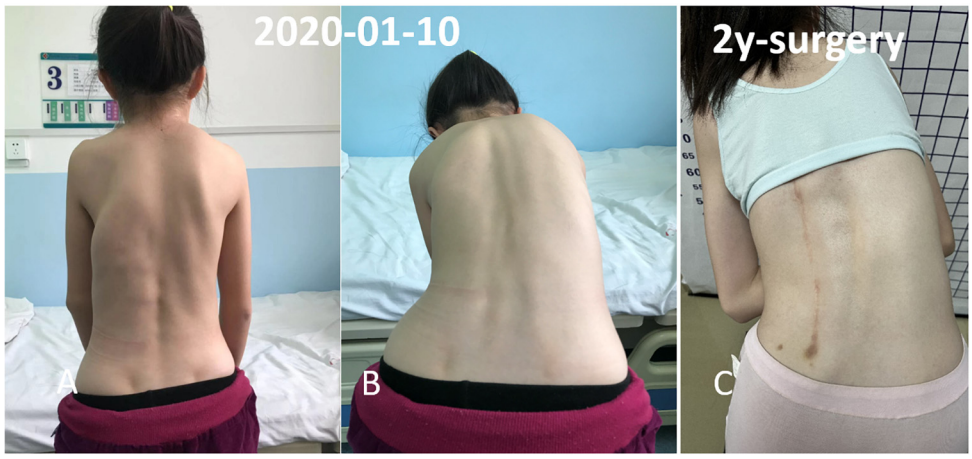

FIGURE 3
Multiple irregular, non-tender, bony hard swellings were found on the back and spinal scoliosis. The osseous lesion beginning from the left chest wall, extending to the ilium region. **(A,B)** Preoperative physical examination. **(C)** Two year follow-up.

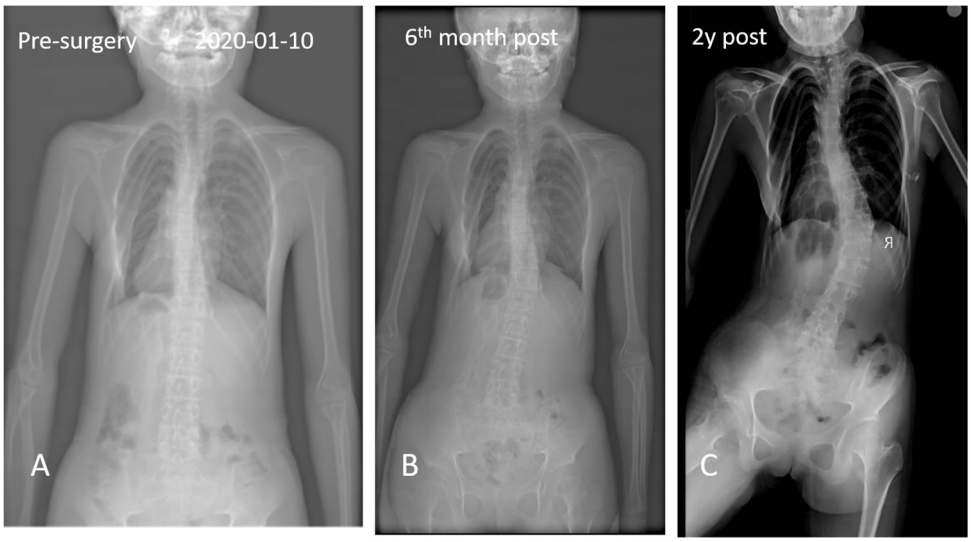

FIGURE 4
Anteroposterior and axial x-ray radiographic evaluation showed a massive radiopaque formation located predominantly in the region of back and spinal scoliosis.

dorsal fascia causing scoliosis, and developmental deformity of the right chest wall (**Figure 5A**). The Risser's sign was grade 0. The patient was then diagnosed with FOP according to the presence of congenital great toe deformity, dorsal fascia heterotopic ossification, and cervical fascia contracture. Therefore, genetic testing was recommended to obtain a definite diagnosis. However, due to financial constraints, the examination was not performed. To prevent the progression of scoliosis caused by tethering during the peak period of spinal growth and oral closure difficulties, back fascia ossification resection and fascial release surgery, which is a minimally invasive procedure, were performed. After 6 months of follow-up, the right cervical fascial contracture, closing movement of the mouth, and facial asymmetry significantly improved. However, the patient developed soft tissue ossification in the back. After several days, the swollen area progressed to ossification. After 2 years of follow-up, the patient came to our hospital for treatment due to continuous right hip pain and rapid progress of hip stiffness, which developed within the last 2 months. Passive left hip range of motions (ROMs) were restricted to 80° flexion, 5° external rotation, and 15° abduction with abnormal gait pattern (**Figure 6**). She had a history of

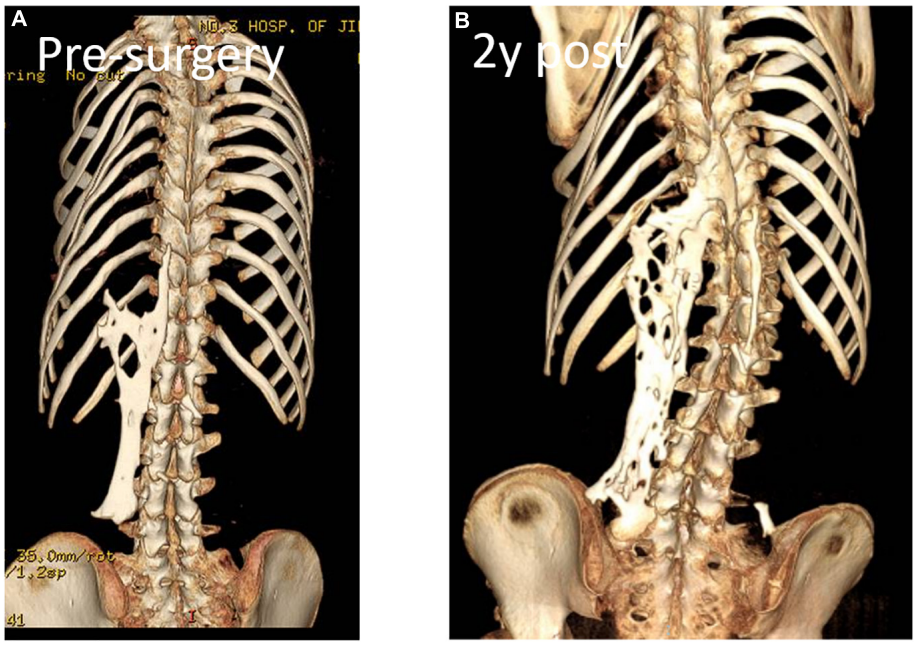

FIGURE 5
Computed tomography revealed spontaneous cervical fusion, heterotopic ossification of the left dorsal fascia causing scoliosis, and developmental deformity of the right chest wall.

snoring for 3 years. Physical examination showed improved facial asymmetry and mandibular angle fascia contracture and a mass in the left iliopsoas muscle with bulging but intact overlying skin (**Figures 1C**, **3C**). The mass originated from the left medial side of the iliac and extended to the lesser trochanter on the left leg region (**Figures 7A**, **9A**). Anteroposterior radiography and computed tomography scan showed recurrent heterotopic ossification of the left back with spinal scoliosis and chest wall malformations (**Figures 4C**, **5B**). The patient was provided with a detailed explanation of her medical condition and treatment options. Based on history taking, clinical examination, and thorough diagnostic investigations, surgical resection of large heterotopic ossification in the left iliopsoas muscle area. However, the heterotopic ossification in the left back was left because the growth in the spine stopped. We performed careful dissection to reach the edge of the heterotopic ossified mass, thereby preventing any damage to the neurovascular supply (**Figure 8**). Resection of the iliopsoas ossification was conducted, and the ossification distal to the lesser trochanter was left to prevent vascular and nerve injury (**Figure 8**). Intraoperative blood loss 50 ml. Apply drainage tube and confirm again that there is no limitation of joint movement before suturing the wound. Immediately after operation, anteroposterior pelvis radiography showed successful resection of heterotopic ossified mass, which was in accordance with the preoperative plan (**Figure 9B**). We administrated indomethacin for 4 weeks and thromboprophylaxis for 3 weeks (5, 6). The patient was discharged 7 days after operation, the pain was tolerable, and the passive left ROM was unobstructed. She walked without crutches and was advised to avoid any intense physical activity (e.g., strenuous hip and stretching exercises) for another 2 months. During the follow-up of 6 months after operation, no signs of disability, hip pain and infection were observed, and there were no radiological indications of ossification recurrence (**Figure 7B**). The passive left hip ROMs were 100° flexion, 35° external rotation, 10° internal rotation, and 30° abduction.

Discussion

Here, we report a special case characterized by fascial contracture of the mandibular horn and back and iliopsoas muscle ossification managed *via* surgery in a 13-year-old girl. The surgical effect was confirmed during follow-up. Two years after the surgery, mandibular angle fascia contracture and joint stiffness caused by iliopsoas muscle ossification significantly improved. However, back fascia ossification recurred after 6 months.

FOP is a rare genetic disease, which is characterized by congenital bone malformation and soft tissue mass progression to heterotopic ossification. In 1740, John freke first described progressive ossifying fibrous dysplasia (MIM 135100). In order to understand the primary connective tissue involvement of tendons, ligaments, fascia and aponeurosis, Bauer and Bode proposed the term "progressive ossifying fibrous dysplasia"

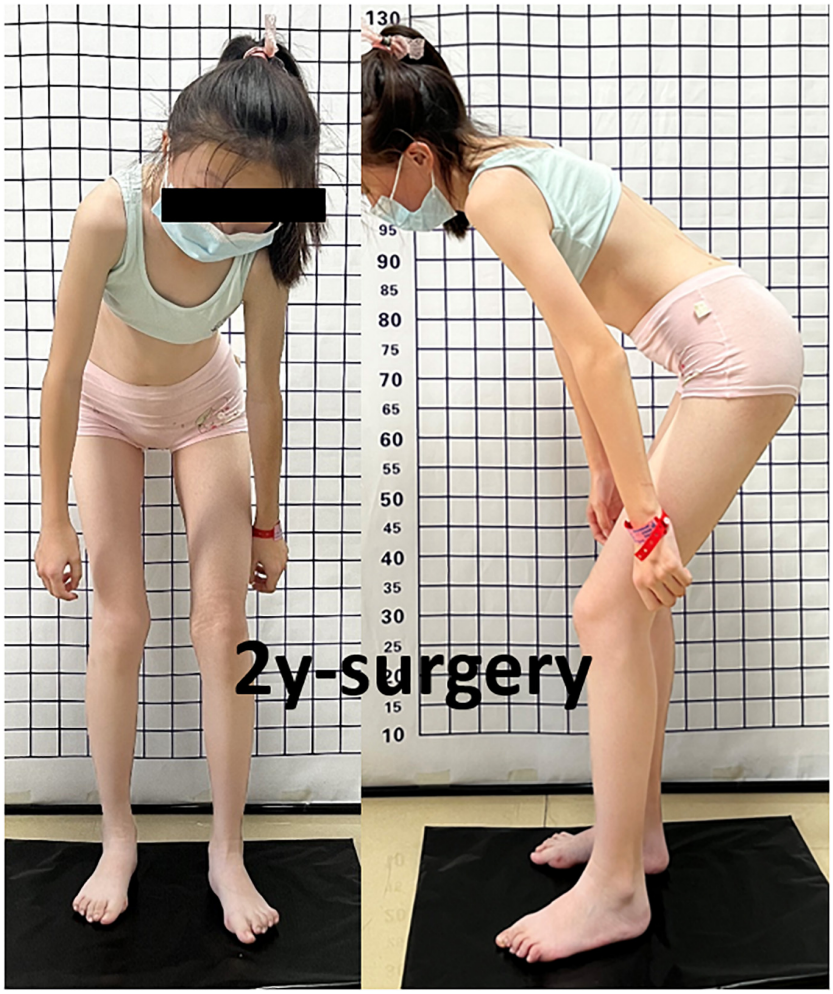

FIGURE 6
Passive left hip ROM was restricted to 80° of flexion, 5° of external rotation, and 15° of abduction with no abnormal gait pattern.

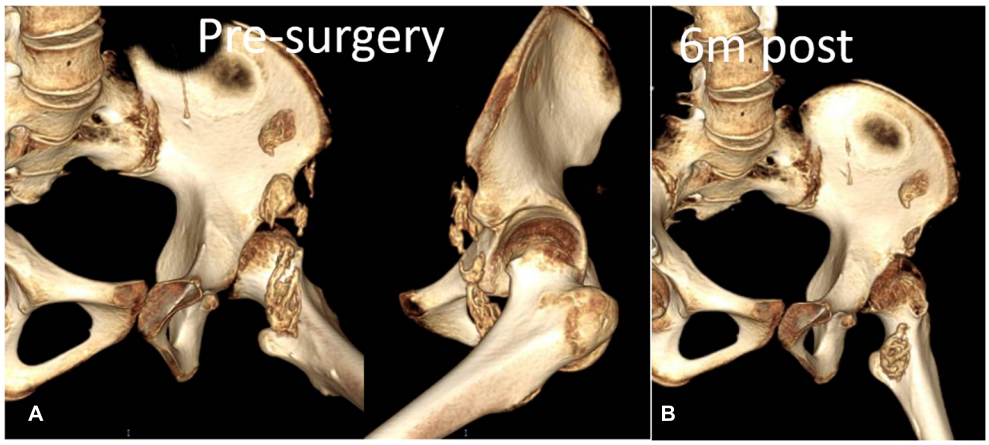

FIGURE 7
Anteroposterior view of the Computed tomography scan of the left hip confirmed aforementioned findings and additionally revealed heterotopic ossification of the iliopsoas muscle. **(A)** Preoperative CT reconstruction. **(B)** 6-month follow-up.

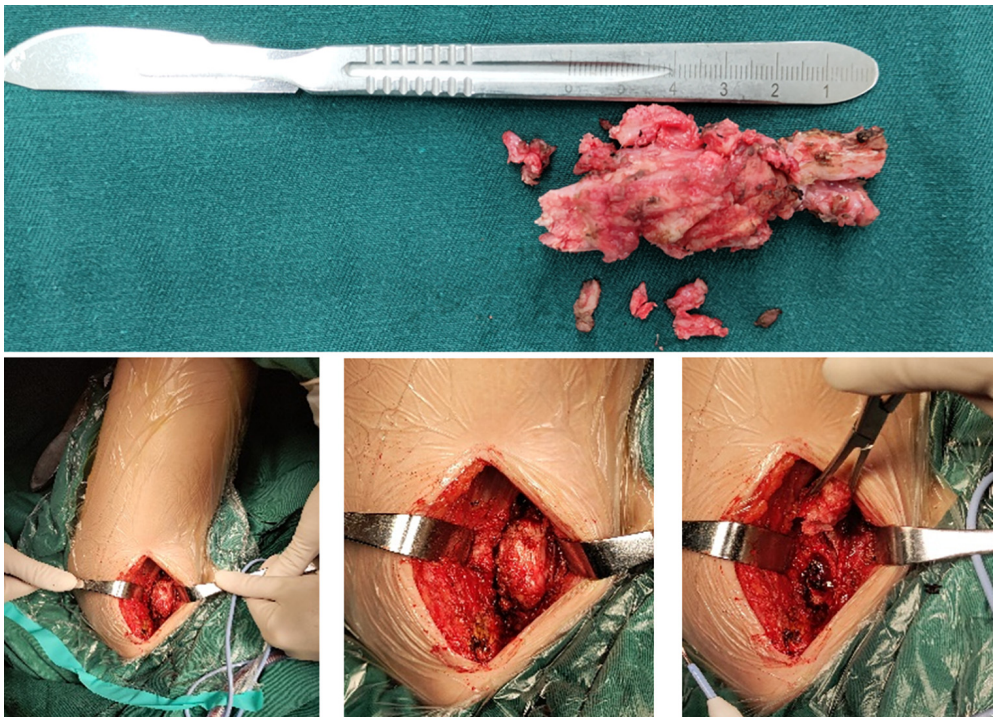

FIGURE 8
Intraoperative removed ossification mass.

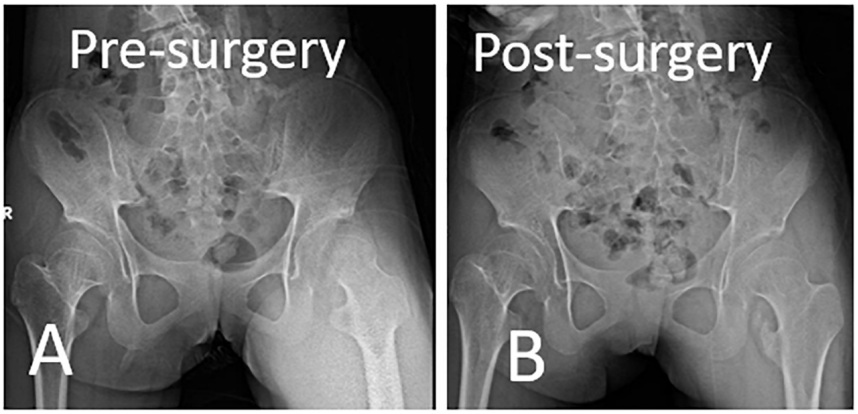

FIGURE 9
Immediate postoperative anteroposterior pelvis x-ray showed tailored removal of ossification mass according to the preoperative plan. **(A)** Preoperative X-ray. **(B)** Immediate postoperative X-ray.

in 1940 and was adopted by Mccussy in 1960 (7). Most patients with FOP have the same ACVR1 gene mutation (c.617g > a; r206h) and classic clinical features. Other mutation sites include L196P, R258S, P197/F198lL, R202I, Q207E, G325A, G328W/G328E/G328R, G356D and R375 (7–15).

Heterotrophic ossification commonly begins in the first decade of the patient's life. FOP is not associated with ethnicity, race, sex, and geographic predisposition (3, 16, 17). FOP patients have normal characteristics at birth, except for big toe deformities such as pseudoepiphysis, abnormal segmentation, first metatarsal fusion, and hallux valgus (18, 19). In the first 10 years of life, they may develop sporadic painful soft tissue swelling (flare-up) and gradual transformation of the skeletal muscle, tendon, fascia, or aponeurosis into heterotopic

ossification These symptoms may occur spontaneously or may be caused by minor trauma, such as muscle stretching, muscular injection, falls, and infections. In a study of 500 patients with FOP, the neck, upper back and shoulder were the first affected areas, with a median age of 8.5–11.5 years. Heterotopic ossification starts from the axis and extends distally to the appendicular area and from the upper limb to the lower limb area, and the latest affected areas are fingers and feet. Chest wall involvement and spinal deformities, including kyphosis, thoracic lordosis and scoliosis, cause thoracic insufficiency syndrome, leading to repeated respiratory tract infections and cardiothoracic failure (20, 21).

In the current case, imaging examination of bilateral short and wide femoral neck and cervical fusion. Moreover, plain radiography revealed high-density tissue ossification on the back and bony bridges of the iliopsoas muscle. High-density muscle calcification and partial fusion with the adjacent bone were observed on computed tomography scans. Kaplan et al. proposed a diagnostic criteria for FOP (22). That is, patients should present with not only clinical and imaging but also definitive genetic characteristics (ACVR1 gene mutation). Therefore, genetic testing was recommended to obtain a definite diagnosis. However, due to financial constraints, the examination was not performed.

Thus far, there is no effective treatment method for FOP. It is necessary to reduce trauma, modify daily activities to an acceptable level, use instruments that can reduce the incidence of falls and injuries, and prevent sports that may cause tissue damage and muscle fatigue. Despite the lack of clinical evidence, brief oral corticosteroid treatment within the first 24 h can inhibit seizures (23). Non-steroidal anti-inflammatory drugs, narcotic analgesics, mast cell and leukotriene inhibitors, and bisphosphate drugs can also be used during or after the attack. However, there is no evidence to support the effect of these drugs on FOP lesions. In the past decade, with the continuous improvement of the understanding of the pathogenesis of FOP, new potential drug targets, such as abnormal regulation of BMP signal, new functions of mutant receptors, the differentiation process of cartilage formation, and the destruction of acvr1/alk-2 expression in transcription and hypoxia regulation around the microenvironment of focal lesions, have been found to be useful in the treatment of FOP (23).

To our knowledge, this is the first case of non-traumatic massive heterotopic iliopsoas ossification described in the literature. Hip joint function and oral closure improved after surgery and rehabilitation treatment. In patients with multiple-site heterotopic ossification caused by FOP, oral function and hip stiffness improve with detailed facial release surgery and rehabilitation treatment. However, dorsal fascia ossification and spinal scoliosis can recur shortly after resection.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Human Ethics Committee of China–Japan Union Hospital of Jilin University. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

Author contributions

DS designed the study, conducted all searches, appraised all potential studies, and wrote and revised the draft manuscript and subsequent manuscripts. PL revised the draft manuscript and subsequent manuscripts. JM and ZW assisted with the presentation of findings and assisted with drafting and revising the manuscript. JC conceived and designed the study, assisted with searches, appraised relevant studies and assisted with drafting and revising the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Reconstruction of metatarsal bone after giant cell tumor resection with no vascularized fibular graft in a pediatric patient: Case report and review of literature

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The Giant Cell tumor (GCT) is a benign, locally aggressive lesion that cause bone destruction and shows a malignant potential. It is a relatively common skeletal tumor that is therefore typically seen in young adults. Few cases are described in literature of GCT in the immature skeleton, and the metatarsal is an unusual location for a primary bone GCT, especially in pediatric age. Therefore, there are very few data reported regarding the management protocol of GCT in metatarsal bones. We report a case about the use of no vascularized fibular graft for an original Y-shaped reconstruction of the metatarsal bone after Giant Cell Tumor resection in a 9 years-old patient, and performed a literature review about metatarsal bone reconstruction in skeletally immature patient.

KEYWORDS
pediatric giant cell tumor, foot tumors, metacarpal replacement, en-bloc resection, non-vascularized fibular graft

Introduction

The Giant Cell tumor (GCT) is a benign, locally aggressive lesion that cause bone destruction and shows a malignant potential with occasional capacity to metastasize. Pulmonary metastases occur in about 2% of patients with GCT (1). It is a relatively common skeletal tumor that usually occurs in young adults, accounting for 4%–9.5% of all primary osseous tumors and 18%–23% of benign bone tumors (2, 3), but it can rarely occur also in skeletally immature patients (4). This tumor develops almost exclusively in the epiphysis of long bones, next to the adjacent joint. The most common location is around the knee region (distal femur, proximal tibia), but distal radius, fibular head, proximal humerus and sacrum can also be frequently involved (5). Its histogenesis is unclear. It presents a typical, but not specific, microscopic structure that justify the different terms used in the past to identify it: myeloid sarcoma, tumor of myeloplexus, osteoblastoclastoma and osteoclastoma. It contains a

prominent and diffuse osteoclast-type giant cell component, uniformly distributed in a population of mononuclear plump epithelioid or spindle cells (6–8). The metatarsal is an unusual location for a primary bone GCT, especially in the immature skeleton. We report a case about the use of fibular graft for the reconstruction of the metatarsal bone after Giant Cell Tumor resection in a pediatric patient and performed a literature review about metatarsal bone reconstruction in skeletally immature patient.

Methods and case description

A review of the literature was performed using common databases (Pubmed, Google Scholar), searching for "metatarsal reconstruction, pediatric giant cell tumor, en-bloc resection, non-vascularized fibular graft". The literature research was focused on cases of GCT of metatarsal bone in pediatric age treated with wide resection and reconstruction with free fibular autograft.

A 9-years-old male, with a history of leukemia, presented to our hospital with a localized pain and a 3 cm area of swelling of the upper part of the right forefoot, first noticed 3 months earlier. There was no history of trauma, fever or any symptoms influencing his general health. Pain also got worse by walking. On examination, there was a fixed swelling area occupying the dorsal and the inner side of IV metatarsus, which was firm to hard consistency. There were no other specific abnormal findings on either of his feet on standard physical examinations.

Diagnostic assessment

The routine hematological examination was within normal limit. The patient was subdued a standard x-ray (**Figure 1A**) of the right foot, that have highlighted the presence of an expansile, osteolytic lesion, which expands and destroys the overlying cortex, without periosteal reaction, involving the base and the middle third of the IV metatarsus and extending into the soft tissue. Distally the growth plate appeared disrupted. Magnetic resonance imaging (**Figure 1B**) was suggestive of GCT and the biopsy confirmed the diagnosis. Chest x-rays ruled out lung metastasis. The patient underwent wide local resection, local adjuvant phenol therapy and a Y-shaped reconstruction with a no vascularized fibular

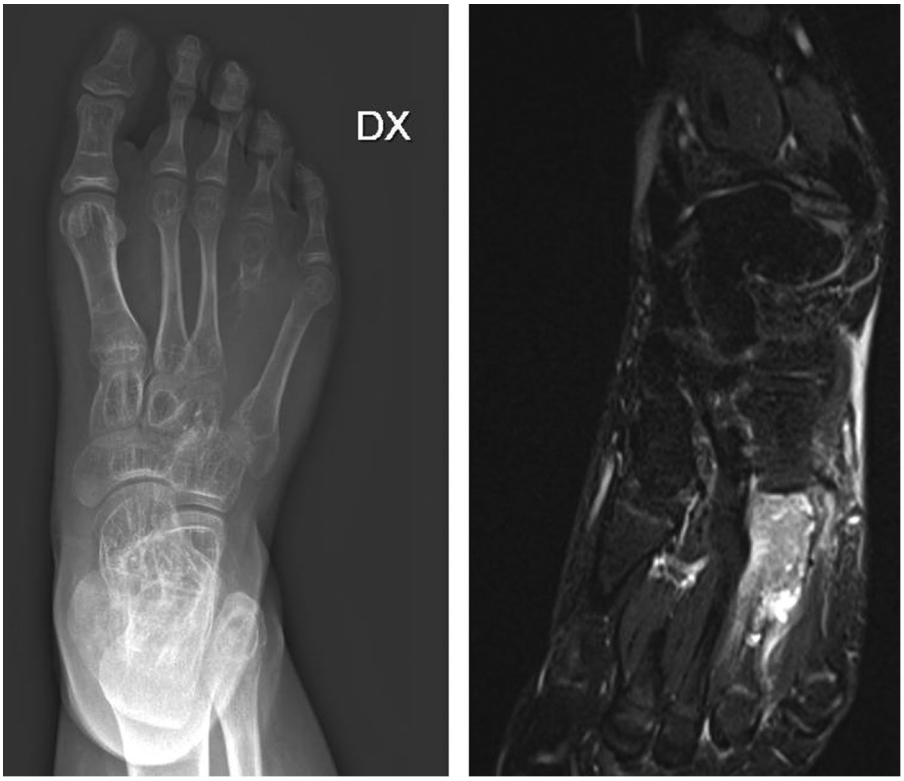

FIGURE 1
Pre-operative x-ray A/P (**A**) and MRI (**B**) view showing an expansile, lytic, encapsulated and iso-intense destructive lesion of the fourth metatarsus with soft tissue involvement.

autograft. The dorsal approach was used for the resection with incision including biopsy track (**Figure 2A**). The length of the required fibular graft was estimated preoperatively, and it was osteotomized out from the distal part of the ipsilateral fibula (**Figure 2B**). Fibula periosteum of the donor site was maintained intact and closed at the end of the harvest. The bone graft was synthesized, using a percutaneous intramedullary Kirschner-wire, from the head of the IV metatarsus to the V metatarsus proximal metaphysis, obtaining an inverted Y shaped construct and maintaining the tarso-metatarsal joint function (**Figures 3A,B**). The V metatarsal proximal medial cortex was scraped to allow an adequate fitting of the graft and to enhance osteointegration. The IV to V metatarsus junction, blocked by the K-wire was also reinforced by a vicryl bone suture. The patient's postoperative course was unremarkable and he was discharged after 5 days from surgery. A cast was applied for 2 months and the Kirschner wire was removed 50 days after surgery, without anesthesia. The patient began to walk, increasing weight-bearing progressively on the affected leg with crutches 70 days after surgery and then progressed to full weight-bearing walk, without pain, 4 months after surgery and after a radiographic control. Clinical and radiographic follow-up was performed at 1, 3, 6, 12 and 24 months (**Figures 4A,B**). Bone union at the proximal and distal junction sites occurred in 6 weeks. There was no evidence of peroneal nerve injury and the patient has achieved a full recovery of functions and normal activities at 12 months from surgery. At two years clinical and radiographic follow-up the patient showed normal walking without pain, no local recurrences or metastases and evidence of new, almost complete, ossification of the fibular bone gap.

Discussion

Our case represents a combination of unusual location and age-group for GCT. Very few cases are described in literature of GCT in the immature skeleton, with an incidence from 1.8% to 10.6% (9, 10). In that case, the tumor is commonly found in bone metaphysis (4). Moreover, Bone GCT is rarely found in the metatarsal bones (11–13), it has more aggressive behavior and tends to grow faster in the foot (or hand) than in other bones, especially in young patients (14). Therefore, there are very few data reported regarding the management protocol of GCT in metatarsal bones. The goals of therapy are eradication of the tumor, to prevent damage to adjacent joint, and to prevent local recurrence. Different surgical procedures are adopted to treat this tumor, from intralesional curettage and bone grafting to wide resection with or without the use of several local adjuvants (phenol, liquid nitrogen, methyl methacrylate, hydrogen peroxide and alcohol) in order to control recurrences (5). The choice of treatment depends on both the site and the type of lesion. In our case, the patient presented a post-operative diagnosis of high grade GCT of bone (Campanacci grade 3 tumor) (15) with a thinned and

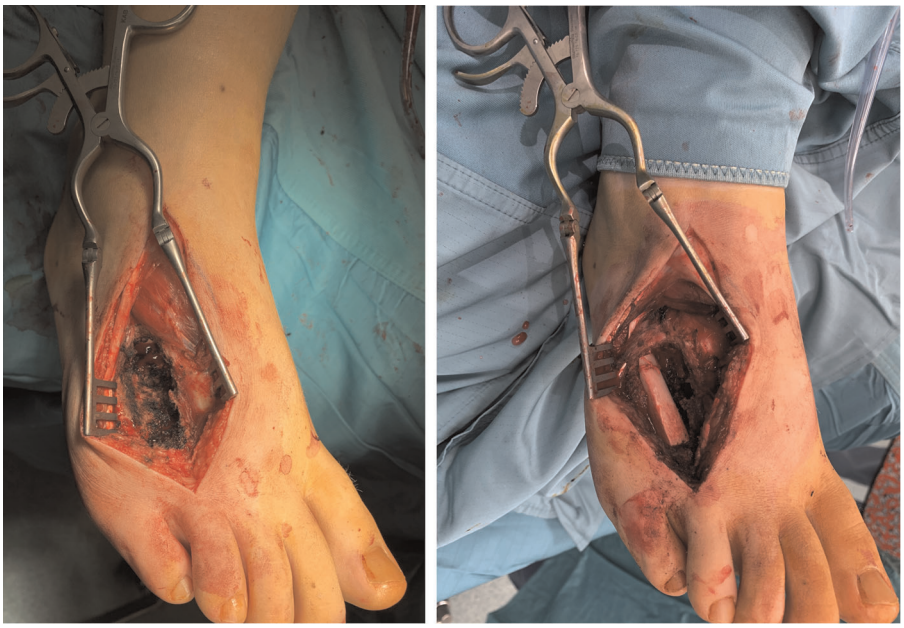

FIGURE 2
Intra-operative picture after en-bloc resection of tumor (A) and fibular grafting (B).

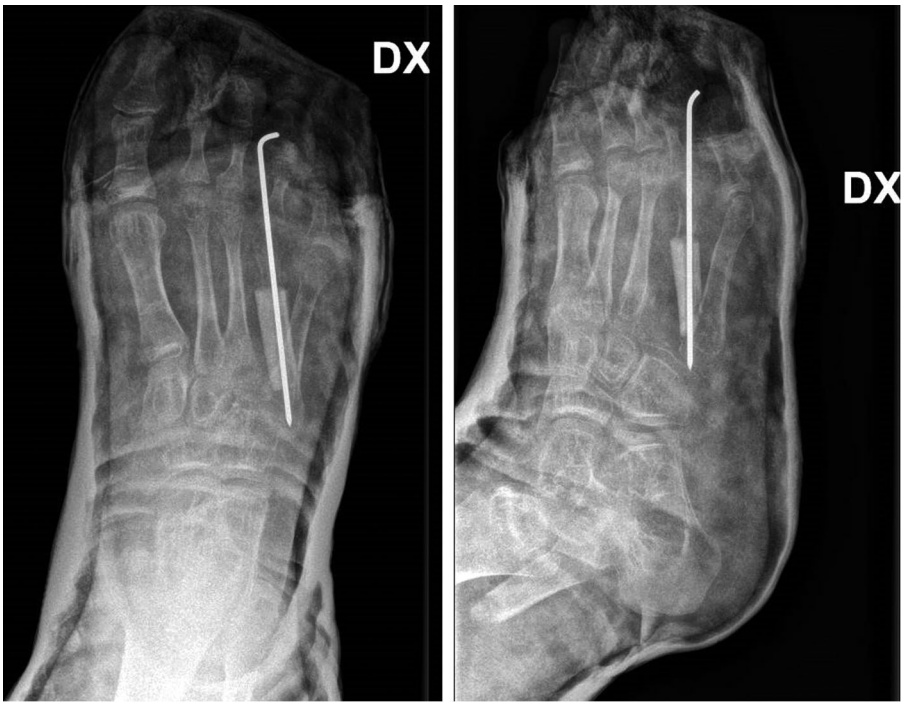

FIGURE 3
Post-operative x-ray A/P (A) and lateral (B) view showing reconstruction of IV metatarsal by fibular graft fixed to the base of V metatarsal (inverted Y shaped construct) using Kirschner's wire and preserving tarso-metatarsal joint.

partially destroyed overlying cortex, therefore it was impossible to carry out an intralesional curettage and wide resection was the treatment of choice.

Wide local resection is associated with a lower recurrence rate (5, 16), but has greater morbidity and higher rates of surgical complications when compared with intralesional curettage. However, metatarsal involvement makes wide resection of the lesion difficult as there is a little space between the rays of the foot. Looking at Enneking staging system and foot compartments (17) a radical resection of an extraosseous metatarsal lesion is difficult to obtain. In that case, the use of local adjuvants associated with surgical en-bloc resection can represent an effective solution in order to avoid amputation and control recurrence rate, as reported in literature (2). There are very few data reported about the reconstruction of metatarsal bones after GCT resection. Treatments described in literature may vary from resection alone to graft reconstruction from iliac crest or fibula. Fixation techniques may include both K-wires and plates.

Sheridan et al. (18), in 2020, in their retrospective review of 10 pediatric cases with non-traumatic primary bone defects, demonstrated that the use of non-vascularized fibular autograft is successful in the reconstruction of large bone defects secondary to malignant or benign pediatric bone tumors, reporting the largest known series of malignant pediatric tumors treated with this technique to date.

Rengsen et al. (19), in 2013, described a case of GCT of the 2nd metatarsal in a 14 years old girl. After resection, the metatarsal was reconstructed with a non-vascularized fibular graft, fixed with a dynamic compression plate. The outcome was good.

Compared to Rengsen procedure, our technique allows to remove the k-wire without further surgery and anesthesia and with less risks of hardware infection. Moreover, the use of a K wire through the growth plate did not caused damages of the cartilage. As already demonstrated by Guzzanti et al. in 1994 (20) the passage of a small, smooth hardware across the physis, then removed, do not stimulate physeal growth disorders. The tarso-metatarsal joint was maintained intact, avoiding walking impairment. In order to obtain that, an inverted Y shaped construct was chosen. Despite it was not an anatomical construct, pediatric orthopedic surgeons are used to Y-shaped metatarsal as a variant of post-axial polydactyly. The original construct was so carefully planned to avoid walking impairment, tarso-metatarsal joint disfunction and, at the same time, further surgeries to remove hardwares. Furthermore, one of the advantages of this technique is the remodeling capacity of the fibula and its relative ease of harvest. The periosteum

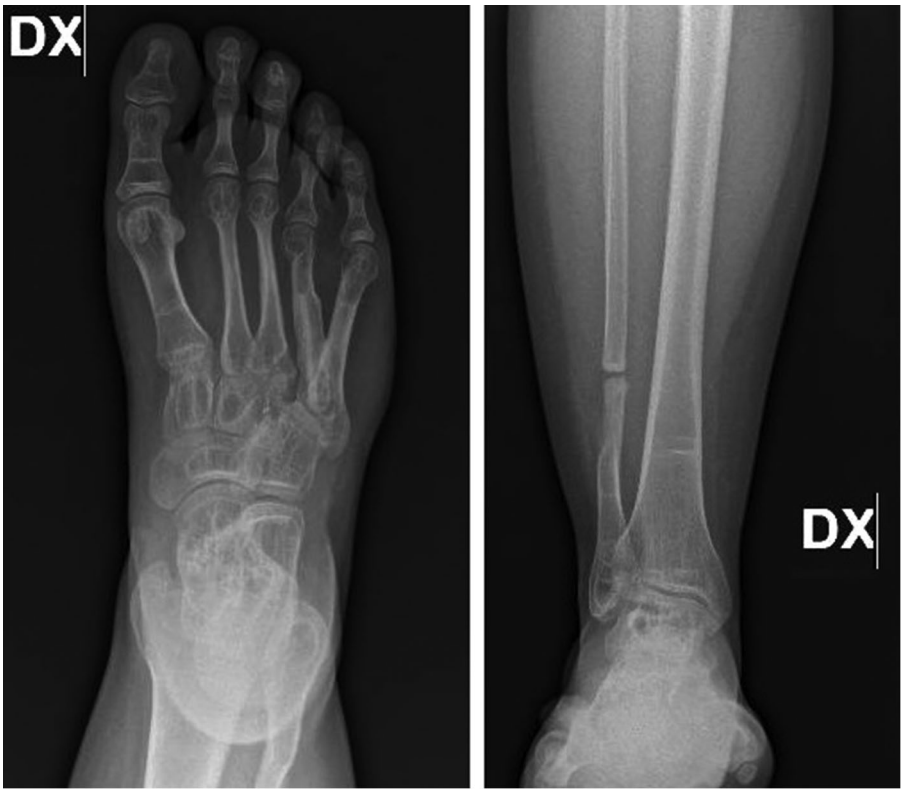

FIGURE 4
Follow-up x-ray of the foot and leg respectively taken at 12 months (A) and 24 months (B) showing incorporation of graft with no evidence of recurrences or other lesions and the donor site with an almost full recovery of the bone fibular gap.

preservation and closure has allowed a recovery of the bone gap. The closed membrane creates a biological chamber that permits revascularization and produces growth factors. The membrane also gathers growth factors with osteogenic potential. Looking at similarities with Masquelet technique, it's important to underline that there isn't bone union in cases with induced membrane, like periosteum, removal (21).

Conclusion

The proximal meta-epiphysis of the metatarsus is an unusual place for primary bone GCT and it is important to know atypical locations in order to perform a proper diagnosis and treatment, especially in young patients. GCT should be conceded in the differential diagnosis of destroying lesions in the immature skeleton. This case study assessed the good outcomes with no recurrences of metatarsal GCT treated with resection and original reconstructive technique that shows to be a valid surgical option in the treatment of this particular and difficult condition.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

MG conceived the idea and edited the manuscript. MF performed the majority of the writing. SC made the literature

review and contributed to manuscript drafting. FF, AGA, CZ and RMT made the revision of the manuscript for intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The reviewer [FL] declared a past co-authorship with the author(s) [MF] to the handling editor.

Publisher's note

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Case Report: Giant cell-rich osteosarcoma of the cervical spine in the pediatric age. A rare entity to consider

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Background: Although osteosarcoma is the most common primary malignant bone tumor in children, its location in the axial skeleton is rare, particularly at the cervical spine. Early diagnosis, together with multidisciplinary management, improves survival rates. Safe resection and stable reconstruction are complicated by the particular anatomy of the cervical spine, which raises the risks.
Case Presentation: A 12-year-old male patient presented with cervical pain for several months and a recent weight loss of 3 kg. The complementary workup revealed a large destructive bone lesion in C7 with vertebral body collapse, subluxation, partial involvement of C6 and T1, large associated anteroposterior soft tissue components, and spinal canal narrowing. A biopsy suggested giant cell-rich osteosarcoma (GCRO). After 10 cycles of neoadjuvant chemotherapy, surgical resection was performed through a double approach: anterior, for tumoral mass resection from C6-7 vertebral bodies and reconstruction placing a mesh cage filled with iliac crest allograft plus anterior plate fixation; and posterior, for C7 complete and C6 partial posterior arch resection, thus completing a total piecemeal spondylectomy preserving the dura intact, added to a C5-T3 posterior fusion with screws and transitional rods. Postoperative chemo and radiotherapy were administered. Clinical and radiological follow-up showed disease-free survival and no neurological involvement at 3 years.
Conclusion: An extensive review of the literature did not find any published cases of GCRO of the cervical spine in pediatric patients. This can be explained by the combination of three peculiar conditions: its location at the cervical spine region, the young age, and the GCRO variant.

KEYWORDS
osteosarcoma - pathology, spine, cervical cancer, surgical oncology, reconstructive surgical procedure

Introduction

Primary tumors of the spine are rare, representing between 2% and 8% of skeletal tumors, but should always be considered in the differential diagnosis of back symptoms in children. Within this age group, benign bone lesions such as osteoid

osteoma and osteoblastoma prevail (1). Osteosarcoma is the most common primary malignant bone tumor in young patients, frequently arising in the limbs but only rarely in the axial skeleton (3%–5%) (2, 3). In this location, it is more prevalent in the lumbar spine and sacrum and quite infrequent in the cervical spine.

It is common for osteosarcomas of the spine to be initially misinterpreted as benign osteoblastomas since their clinical, radiological, and histopathological characteristics are difficult to differentiate (3, 4), thus, biopsy is essential to conduct a proper approach. Giant cell-rich osteosarcoma (GCRO) is considered an uncommon variant of osteosarcoma (5), representing only about 3% of them (6). This atypical variant is characterized by an abundance of osteoclastic giant cells and a paucity of osteoid tumor (7), leading it to be confused with giant cell tumors (8, 9). Infiltration of adjacent bony trabeculae, focal osteoid deposits, and a Ki67 proliferative index of 20%–30% have been reported to be useful for differentiation from giant cell tumors (8).

This study aims to present a young patient diagnosed with this rare variant of osteosarcoma of the cervical spine, the diagnostic sequence, and multidisciplinary treatment, with a focus on the surgical strategy for oncologic resection and cervical spine reconstruction. In addition, the literature on cervical spine osteosarcoma is reviewed along with a summary workup of the published cases of GCRO.

Case presentation

A 12-year-old male patient presented with cervical pain with onset several months before and no reported history of trauma or overuse. After a detailed anamnesis, the pain appeared to be both mechanical and inflammatory in nature, causing the interruption of sleep and achieving only slight relief with basic analgesia. The patient also reported a recent weight loss of 3 kg. On examination, his neck appeared tilted to the left side and the pain was localized posteriorly on his lower cervical spine, irradiating to the left arm. Spurling test was negative, with limited motion of the neck and tenderness of the paravertebral muscles bilaterally. Strength and sensitivity were preserved in both upper and lower limbs.

Simple anteroposterior and lateral radiographs of the cervical spine were taken on the initial visit (**Figure 1**). Further examination by Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) revealed a significant destructive bone lesion in C7, with vertebral body collapse, subluxation, partial destruction of the left lamina and spinous process and large associated anterior and posterior soft tissue components. The spinal canal was markedly narrowed at C6–C7, partly due to altered alignment and partly due to invasion by the tumor, obliterating the left posterolateral subarachnoid space (**Figure 2**). There was also partial involvement of the left pedicle, lamina, and spinous process of C6 and, to a lesser extent, the T1 left pedicle. The left vertebral artery was not visible, suggesting tumoral invasion and blockage which was later confirmed by CT angiography.

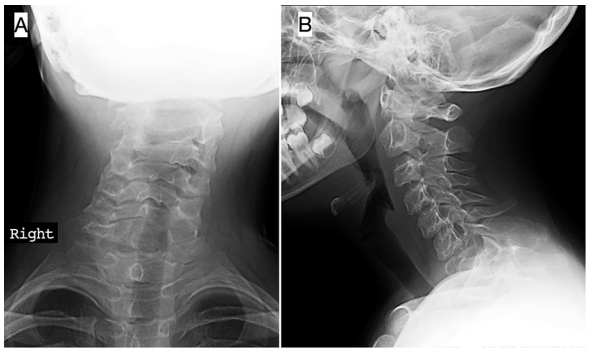

FIGURE 1
Anteroposterior and lateral radiographs of the cervical spine: (A) Osteolytic expansive lesion on C7 vertebral body, with ill-defined borders, expansion and interruption of the upper and lower endplate of the left half of the vertebral body and absent spinous process and left pedicle; also, abnormal cervical alignment in the frontal plane with a slight left-sided tilt of the neck is noted. (B) Enlargement of the posterior elements and upper endplate of C7 vertebral body, thinning of the cortical bone, without apparent interruption, periosteal reaction, or soft tissue mass.

A CT-guided percutaneous core needle biopsy was suggestive of GCRO. Extension studies ruled out distant disease, being staged as: stage IIB of the Enneking (10) and American Joint Committee on Cancer (AJCC) systems (11); Tomita type 6, this being an extra-compartmental tumor with adjacent vertebral extension (12) and 1–10/A–D of the Weinstein-Boriani-Biagini (WBB) tumor classification system (13). The Spinal Instability Neoplastic Score (SINS) was 16 points indicating instability.

According to the national protocol for localized osteosarcoma in children (SEHOP-SO-2010) (14), the patient underwent ten cycles of neoadjuvant chemotherapy, two of them being omitted due to nephrotoxicity and hepatotoxicity. He remained immobilized during this time with a plain cervical collar. Once neoadjuvant ChT was over, new imaging examinations were done, showing minimal bone tumor size reduction, but delimitation and a slight decrease of the soft tissue component. Also, spinal canal compromise (**Figure 3**) was evidenced on MR myelography that manifested clinically with increased left radiculopathy.

Consecutively, surgical resection of the tumoral mass and reconstruction (**Figure 4**) was performed at week 15. Firstly, with the patient in a supine position, a standard left sternocleidomastoid anterior cervical approach was used to expose the anterior longitudinal ligament and C6–C7 vertebral bodies. With a gentle and thorough dissection, laterally to the vertebral bodies, the tumor was found to have

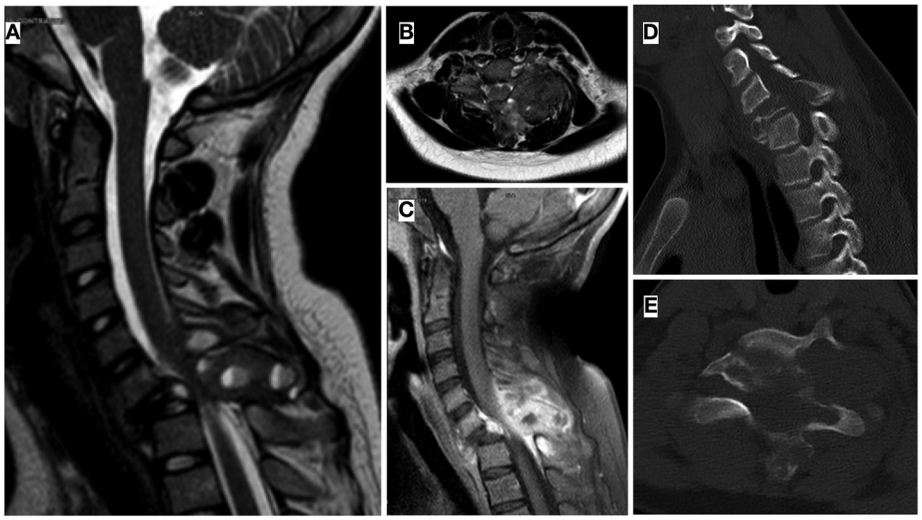

FIGURE 2
(**A**–**C**) Sagittal and axial MRI cuts of the cervical spine showing a multiloculated bone lesion in C7 that conditioned vertebral body collapse and subluxation, associated large soft tissue component, with intradural and paravertebral extension, without myelopathy signs. Partial destruction of left posterior elements of C6 and T1 is also visible. (**D**,**E**) Cervical spine CT revealing a destructive collapsing lesion in C7 vertebra, affecting the posterior part of the vertebral body and the posterior elements, and causing subluxation and angular kyphosis of the cervical spine. There was also partial involvement of the left pedicle, lamina, and spinous process of C6 and, to a lesser extent, the T1 left pedicle.

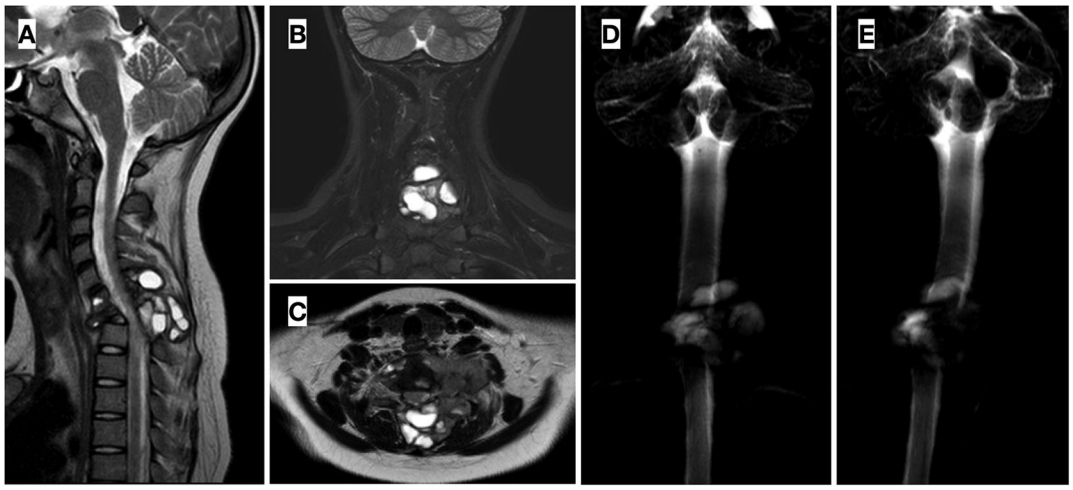

FIGURE 3
(**A**,**B**,**C**) post neoadjuvant chemotherapy MRI showing delimitation and minor shrink of the soft tumor mass. (**D**,**E**). MR myelography demonstrating significant compromise of the spinal canal, especially at C7 level.

invaded the left pedicle and the posterior part of the C7 vertebral body and the inferior part of C6, as seen in the preoperative images. Resection of the tumoral mass in C6 and C7 vertebral bodies was performed followed by an anterior reconstruction, placing a titanium mesh (DePuy Synthes®) filled with iliac crest allograft and completing the first stage fixation with an anterior plate and screws secured to C5 and T1 vertebral bodies (SkylineTM Anterior Cervical Plate, DePuy Synthes®). Subsequently, with the patient in a prone position and through a longitudinal posterior approach, ligaments and muscles were dissected to expose the tumoral mass and C7 posterior elements. A solid cystic tumoral mass was identified in the left paravertebral region, and infiltration of the left posterior arch was also perceived. Wide resection of

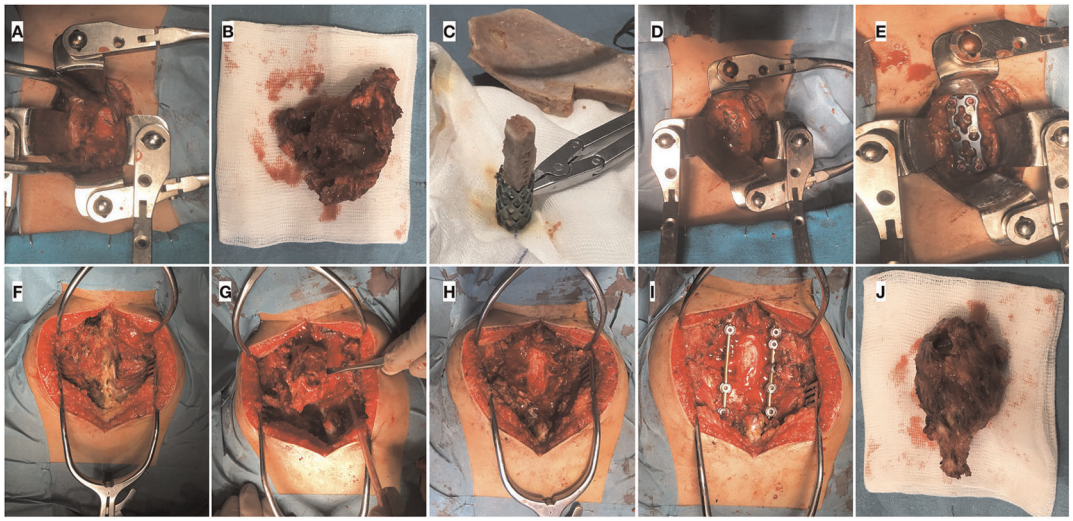

FIGURE 4
Intraoperative images: (A–E). Anterior approach: (A) Exposure of anterior part of C6-C7 vertebral bodies; (B) Tumoral mass within vertebral bodies; (C) Preparation of Moss mesh with iliac crest allograft; (D) Placement of mesh with allograft in the cervical spine defect; (E) Anterior plate fixation. (F–J). Posterior approach: (F) Exposure of posterior vertebral elements; (G) Posterior vertebral arch resection for total piecemeal spondylectomy; (H) Spinal cord and roots decompressed; (I) Posterior instrumentation fusion C5-T3 with bilateral screws and rods; (J) Posterior part of the tumoral piece.

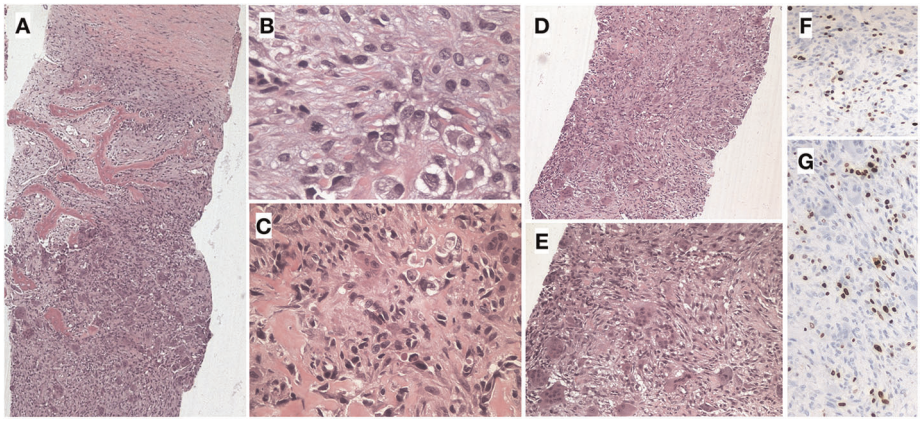

FIGURE 5
Resected tumor histology of the patient. (A) Plexiform and fibrous bone tissue infiltrated by solid neoplastic proliferation (HE, 40x). (B) Tumor cells with fusiform and epithelioid morphology with marked cellular atypia and numerous mitotic figures (HE, 400x). (B,C) Malignant cells are surrounded by fibrovascular stroma and subtle osteoid deposits (HE, 400x, 200x). (D,E) Numerous osteoclastic multinucleated giant cells are identified (HE, 100x, 200x). (F,G). Expression of the Ki-67 proliferation marker.

the posterior arch of C7 and left part of C6 was completed, performing a total spondylectomy of C7 and partial of C6, thereby releasing the spinal cord, preserving the dura intact and verifying bilateral decompression of C6-T1 roots. T1 left pedicle was also resected due to apparent tumoral invasion. To provide spinal stability, adequate alignment, and balance, a C5-T3 fusion was performed, with bilateral screws to the lateral masses of C5 and right C6, as well as pedicle screws to T1 right and bilaterally to T2 and T3 pedicles plus transitional rods (Synapse System, DePuy Synthes®). Drainage was applied and the wound was closed in layers. Neurophysiological monitoring showed no alterations during the procedure, and fluoroscopic control was satisfactory.

The histopathological results mentioned that the surgical resection piece consisted of a bony tissue measuring $7 \times 3.5 \times 2.5$ cm covered by muscular tissue (Figure 5). Osteoforming neoplastic proliferations infiltrating into adjacent reticular bone trabeculae were identified. They were arranged in a

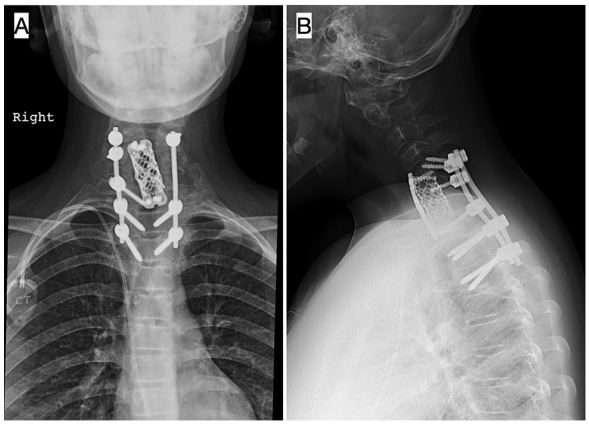

FIGURE 6
Anteroposterior (A) and lateral (B) x-rays of the cervical spine at 3 years postoperatively: interbody moss mesh, anterior plate fixation, and bilateral posterior instrumentation fusion with screws and rods from C5 to T3. Adequate alignment and balance, without signs of implant loosening or lack of consolidation.

fibrovascular stroma in which numerous osteoclastic multinucleated giant cells could be observed. Ki-67 proliferative index was 26%. A larger piece showed various cystic areas, accompanied by areas of postchemotherapy necrosis that accounted for 30% of the total area of the neoplasm.

During the immediate postoperative period, the patient evolved positively, and the surgical wound showed no signs of infection. The patient initiated sitting and ambulation with a rigid cervical collar for two weeks and no neurological symptoms or other complications appeared. Two weeks after surgery, adjuvant chemotherapy was started and subsequently radiotherapy was added as indicated in the proposed protocol. The cervical and upper dorsal spine C4-D1 was irradiated with Volumetric Intensity Modulated Arcotherapy technique with daily Cone Beam CT, 6 MV photons, using isocentric technique, planned with CT at a dose of 50.4 Gy with fractions of 1.8 Gy/fraction. Periodical clinical and radiological visits were set for 1, 3, 6, 12, 24, and 36 months after surgery at the spine clinic, as well as closer visits by the oncologists, with the patient being disease-free to date. In the last evaluation, he was healthy, did not require technical aids for walking or cervical immobilization, and had neither pain nor neurological symptoms. The last radiological examination can be seen in Figure 6.

Discussion

The case of a rare variant of osteosarcoma located in the cervical spine of a pediatric patient is presented here. A complete initial investigation revealed an aggressive bone lytic lesion located at C7 with soft tissue involvement and compromised spine stability. Distant disease was discarded, and a biopsy confirmed the GCRO diagnosis. Treatment followed the national protocol that combined neoadjuvant ChT, surgical resection and reconstruction, adjuvant ChT, and RT.

After a thorough review of the literature, we were only able to find 42 published cases of GCRO (Table 1), none of which located in the spine, aside from ours. In the current case, infiltration of bone tissue by a solid neoplastic proliferation, subtle osteoid deposits, and a Ki67 proliferative index of 26% help to differentiate it from a giant cell tumor. GCRO is found mostly in children, adolescents, and young adults, with half of the cases analyzed occurring in patients under 20 years old. However, there are reported cases in patients up to 67 years old (23). Most of the reported GRCO occurred in the knee region, 13/42 in the proximal tibia, and 10/42 in the distal femur. Regarding the treatment strategy, 12 out of 42 patients received neoadjuvant chemotherapy, whereas 21 patients were treated with postoperative chemotherapy and only 5 patients received postoperative radiotherapy. Regarding the first surgical treatment, the resection performed was radical in 11 cases, wide in 14 cases, and intralesional in 13 cases. On follow-up, local recurrence was reported in 12 cases and metastasis in 13, with a median follow-up of 36 months.

The appearance of osteosarcomas in the cervical region has rarely been reported in the literature. There are only 5 published cases of cervical spine osteosarcoma in pediatric patients and the number would increase by 8 more if our research were to include adult patients (Table 2), for a total of 13 cases. Regarding the treatment strategy, 8 cases received neoadjuvant chemotherapy, while 12 patients were treated with postoperative chemotherapy and 10 patients received postoperative radiotherapy. Even though radiotherapy has not proven remarkably effective at influencing the long-term prognosis of osteosarcomas, the difficulty of achieving free tumoral resection margins at this anatomical location justifies the necessity of adding radiotherapy as a supplemental therapeutic tool. The histological type of osteosarcoma was telangiectasic in 3 cases, osteoblastic in 2 cases, and chondroblastic, giant cell osteosarcoma, and osteoblastoma type in one case each, with 6 other cases in which the type of osteosarcoma was not registered. As previously mentioned, to date there have been no published cases of GCRO located at the cervical spine. At a median follow-up of 44 months in the published cases, there were 4 local recurrences and 4 metastases.

Concerning local tumor management, the definitive treatment for any malignant tumor should be a wide en-bloc resection including surrounding intact tissue, without violating the tumor capsule to avoid the risk of satellite tumor cells being left behind and thus limiting the possibility of recurrence. Total en-bloc resections of tumors at the cervical

TABLE 1 Outline of the cases of giant cell-rich osteosarcoma published in the literature.

Study	N	Age	Sex	Location	NA ChT	Resection	Reconstruction	ChT	RT	Local recurrence	Metastases	Follow-up (months)
Barhust 1986 (7)	9	41	F	Femur diaphysis	-	1° Intralesional; 2° Radical	1° Curettage; 2° Disarticulation	-	-	+	+	36
		13	F	Tibia diaphysis	-	1° Intralesional; 2° Radical	1° Curettage; 2° Amputation	-	+	-	-	192
		21	M	Femur diaphysis	-	1° Intralesional; 2° Radical	1° Curettage; 2° Disarticulation	-	+	+	-	108
		12	M	Femur diaphysis	-	Radical	Disarticulation	-		-	+	36
		6	F	Proximal tibia	-	1° Intralesional; 2° Radical	1° Curettage; 2° Amputation	+	-	-	-	84
		16	F	Femur diaphysis	-	1° Wide; 2° Radical	1°Arthroplasty; 2° Disarticulation	+	-	+	+	24
		12	M	Proximal tibia	-	1° Intralesional; 2° Radical	1° Curettage; 2° Amputation	-	-	+	+	24
		20	M	Distal femur	-	1° Intralesional; 2° Radical	1° Curettage; 2° Amputation	+	-	-	-	24
		8	M	Femur diaphysis	-	Radical	Amputation	+		-	-	12
Sciot 1995 (15)	1	26	M	Distal femur	NR	NR	NR	NR	NR	NR	NR	NR
Sato 1996 (16)	1	19	M	Distal femur	+	Wide	Reconstruction + Autograft	+	-	-	-	72
Shuhaibar 1998 (17)	1	32	F	Distal femur	-	1° Wide; 2° Radical	1° Resection; 2° Amputation	+		+	+	NR
Bertoni 2003 (18)	1	19	M	Femur diaphysis	-	Wide	Arthroplasty + Autograft	NR	NR	+	+	240
Shinozaki 2004 (19)	1	17	M	Distal radius	-	Intralesional	1° Curettage; 2° Autograft	NR	+	+	+	41
Hong 2005 (20)	1	29	F	Proximal tibia	+	Wide	Arthroplasty	+	-	-	-	11
Nagata 2006 (21)	1	32	M	Distal femur	-	Intralesional	Curettage + cement	-	-	-	-	20
Kinoshita 2006 (22)	1	16	M	Rib	+	Wide	Soft tissue flap	+	-	-	-	60
Fu 2011 (23)	1	67	F	Mandible	-	Wide	Soft tissue flap	+	+	-	-	12
Verma 2011 (24)	1	56	F	Maxilla	-	Wide	Soft tissue flap	+	+	-	-	NR
Gambaroti 2011 (25)	1	29	M	Distal femur	-	Intralesional	1° Curettage; 2° Resection	+	-	+	-	36
Imran 2012 (26)	1	16	F	Proximal tibia	NR	NR	NR	NR	NR	NR	NR	NR
Kinra 2012 (27)	1	21	M	Femur diaphysis	+	NR	NR	NR	NR	NR	NR	NR
Wang 2013 (6)	9	51	M	Proximal femur	+	Intralesional	Arthroplasty	-	-	+	+	18
		18	M	Proximal tibia	-	Radical	Amputation	+	-	-	-	92
		36	F	Proximal tibia	-	Intralesional	Curettage + cement	-	-	+	-	90
		13	M	Proximal tibia	-	Intralesional	Curettage + cement	-	-	+	+	13

(*continued*)

TABLE 1 Continued

Study	N	Age	Sex	Location	NA ChT	Resection	Reconstruction	ChT	RT	Local recurrence	Metastases	Follow-up (months)
		19	F	Distal femur	-	Radical	Amputation	+	-	-	-	74
		33	F	Proximal tibia	-	Radical	Amputation	+	-	-	-	111
		16	M	Proximal tibia	-	Radical	Amputation	+	-	-	+	20
		15	F	Proximal tibia	-	Radical	Amputation	+		-	-	114
		32	M	Proximal tibia	+	NR	NR	NR	NR	NR	NR	5
Vijayan 2015 (28)	1	19	F	Cuneiform		Intralesional	Curettage + cement filling	+	-	-	-	36
Chow 2016 (29)	8	16	M	Proximal tibia	-	Radical	Amputation	+	-	-	-	110
		26	F	Distal femur	-	Radical	Amputation	+	-	NR	+	14
		12	M	Proximal fibula	-	Radical	Disarticulation	+	-	+	+	21
		33	F	Distal femur	+	Wide	NR	-	-	-	-	48
		15	F	Proximal tibia	+	Wide	NR	-	-	-	-	38
		31	F	Metatarsal	+	Radical	Ray amputation	+	-	-	+	30
		11	M	Metatarsal	+	Wide	NR	-	-	-	-	21
		15	M	Distal femur	+	Wide	NR	-	-	-	-	12
Chobpenthai 2019 (30)	1	11	F	Patella	+	Wide	Rotational flap	-	-	-	-	13
Cahayadi 2019 (31)	1	46	M	Proximal ulna	NR	Wide	Arthroplasty	NR	NR	NR	NR	NR
Current report 2022	1	12	M	Cervical spine	+	Intralesional	Reconstruction + allograft	+	+	-	-	36

F, Female; M, Male; NA ChT, Neoadjuvant Chemotherapy; ChT, Chemotherapy; RT, Radiotherapy; OS, Osteosarcoma; GCRO, Giant Cell-Rich Osteosarcoma; NR, Not registered.

spine with vertebral artery control or sacrifice of one of them have been described previously (39, 40). However, in some cases, the proximity of the spinal cord and roots and vascular structures can prevent a wide resection, which forces the surgeon to obtain limited margins. Hence, this being a rare location for osteosarcoma, management poses a special challenge. Total en-bloc spondylectomy refers to a resection where the tumor mass together with the vertebral body and posterior elements are removed as a single unit. Although, it is not a synonym for a wide resection since it is usually a marginal type of resection alongside the tumor capsule. On the other hand, a total piecemeal spondylectomy is an intralesional resection where most of the tumor is excised, but some macroscopic tumor cells might be left, usually due to their proximity to noble structures or, as in the case of our patient, due to the need to remove the tumor from two different approaches and in two separate pieces. In all the cervical spine osteosarcoma cases reviewed, an intralesional resection was performed, except for one en-bloc marginal resection (38). Three of them were done by an anterior approach, and seven with a combined anteroposterior approach as in our case.

Following tumor resection, the challenge is to restore the stability, biomechanics, and global alignment of the cervical spine. Most of the cases evaluated were reconstructed with a circumferential fusion. The cases involving the upper cervical spine were handled with an occipitocervical fusion. A special concern in our case was that the tumor was located in the cervicothoracic area, which is a high-stress junctional zone that is exposed to high mobility and does not tolerate bone loss easily. Hence, a stable reconstruction was performed using a combination of anterior and posterior spinal fusion with the addition of a tricortical iliac crest allograft, a titanium Moss mesh, and an anterior plate. Transitional rods

TABLE 2 Summary of the cases of cervical spine osteosarcoma reported in the literature.

Study	N	Age (y)	Sex	Cervical spine location	NA ChT	Resection	Approach	Reconstruction	Pathology	ChT	RT	Local recurrence	Metastases	Follow-up (months)
Gandolfi 1984 (32)	1	39	F	C6	NR	Intralesional	Anterior	Interbody fusion with autograft	Chondroblastic OS	+	+	NR	NR	NR
Ozaki 2001 (33)	1	5	F	C4	+	Intralesional	Anterior	Anterior fusion + bone graft	Telangiectasic OS	+	+	-	-	26
Ponnampalam 2012 (34)	1	62	F	C2-C4	+	Intralesional	NOT	NOT	Osteoblastic OS	NR	+	NR	NR	NR
Turel 2012 (35)	1	15	M	C5	-	Intralesional	Combined	Posterior fusion + auto/allograft	Telangiectasic OS	+	+	NR	-	12
Feng 2013 (36)	6	22	F	C1	+	Intralesional	Combined	Occipitocervical fusion with bone graft + internal fixation	NR	+	-	+	+	44
		41	M	C2-C3	+	Intralesional	Combined		NR	+	-	+	+	75
		58	M	C3	+	Intralesional	Combined	Titanium mesh filled with bone cement ± posterior internal fixation with pedicle screws.	NR	+	+	-	+	39
		50	M	C6	-	Intralesional	Anterior		NR	+	+	+	+	50
		27	M	C7	+	Intralesional	Combined		NR	+	+	-	-	53
		40	F	C7	+	Intralesional	Combined		NR	+	+	-	-	36
Zils 2013 (37)	2	5	F	C4	`-	Intralesional	NR	NR	Telangiectasic OS	+	+	-	-	168
		11	M	C7-T2	-	Intralesional	NR	NR	Osteoblastic OS	+	+	-	-	86,2
Clarke 2016 (38)	1	8	F	C1	+	Marginal	Combined	Occipitocervical fusion+ graft	Giant cell OS	+	-	-	-	16
Current report 2022	1	12	M	C7	+	Intralesional	Combined	Anterior fusion with titanium mesh, bone graft & anterior plate + Posterior fixation	GRCO	+	+	-	-	36

F, Female; M, Male; y, years; OS, Osteosarcoma; NA ChT, Neoadjuvant Chemotherapy; ChT, Chemotherapy; RT, Radiotherapy; GCRO, Giant Cell Rich Osteosarcoma; NOT, Non-operative Treatment; NR, Not registered.

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and screws were applied in the transition from the cervical to the thoracic spine, and the screw diameter employed was different for the cervical vertebrae (4.5 mm) than the thoracic ones (5.5 mm).

Osteosarcoma of the cervical spine is exceptional (5 cases in children and 8 in adults), as is the GCRO variant in any location (42 cases). To the best of our knowledge, this is the first published case of GCRO in the cervical spine in a pediatric patient, which can be explained by the combination of three peculiar conditions: its location in the cervical spine region, the young age of the patient, and the GCRO variant. Henceforward, despite its unlikeness, this diagnosis should be considered when dealing with a tumor in the spine. In the cervical spine in particular, oncological resection is almost always intralesional due to the proximity of the neuraxis, which is why radiotherapy is often administered. Following oncological resection, the reconstruction phase pursues local stability, regional alignment, and global spine balance, bearing in mind the growing condition of pediatric patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

RME-G, MG-O, AG-M and RG-D contributed to the conception and acquisition of data, drafting the manuscript and revising the manuscript critically for important intellectual content, provided final approval of the version of the manuscript to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Bone wax in the treatment of partial epiphysiodesis of distal femoral growth plate: Case report at 10-year follow-up

Luca Basiglini[1]*, Angelo Gabriele Aulisa[1,2], Diletta Bandinelli[1], Renato Maria Toniolo[1] and Francesco Falciglia[1]

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The growth plate is the weakest structure in the skeleton of a child and a frequent site of injury or fracture; physeal injuries represent 15%–30% of all fractures in children. Of all growth plate fractures, the incidence of growth arrest and disorders is around 15%. Here, we discuss a female patient who, at the age of 5 years, was treated for a polytrauma that involved a complex lesion of the growth plates of the knee. Four days after trauma, she underwent closed reduction surgery and internal fixation with cannulated screws for femoral and tibial fractures of the growth plate. A 20° valgus deviation of the left knee was found at 3-month postoperative clinical check-up likely as a result of a growth disorder of the femur. She was diagnosed with valgus knee secondary to epiphysiodesis of the lateral portion of the femoral physis and she was readmitted to the hospital. In the operating theater, an open femoral de-epiphysiodesis was performed with a burr; the drilled hole was then filled with bone wax. At 20-month post-trauma follow-up, the left knee was still valgus about 20° relative to the other side. During follow-up, a slow but progressive improvement in the axis of the lower limbs was noted. Clinical and radiographic control 10 years after the trauma showed a complete recovery of the axis of the lower limbs. In the initial stages, the presence of bone wax in the area of de-epiphysiodesis allowed for stabilization of the deformity on the 20° of preoperative valgus. The interpretation of the growth cartilage activity occurred in an asymmetrical way such as to realign the femoral load axis, it can be based on the different mechanical stimulus on the two knee areas due to the preexisting deformity. There is no unanimous evidence in the literature in terms of management of growth disorders resulting from this type of injury. Bone wax resulted in effectively filling the hole of de-epiphysiodesis in the distal femoral growth plate and allowed us to obtain the response of the growth plate and to improve the recovery time in young children.

KEYWORDS

epiphysiodesis, growth plate, bone wax, long follow-up, case reports, physeal injury, polytrauma, growth arrest

Introduction

The growth plate is a cartilage region located at the end of the long bones of children and adolescents, which serves as the primary center for longitudinal growth and characterizes the immature skeleton; physeal lesion may result from musculoskeletal injuries including fracture, infection, malignant tumor, or iatrogenic damage (1). The growth plate is the weakest structure in the skeleton of a child and a frequent site of an injury or fracture; physeal injuries represent 15%–30% of all fractures in children (1, 2). Several factors must be considered when evaluating a child with a physis fracture such as the patient's age, location of the physis, type of fracture, and growth potential of the involved physis (2, 3). Of all growth plate fractures, the incidence of growth arrest and disorders is around 15% (4). In case of injury to a large undulating physis, as in the fracture of the distal growth plate of the femur, the plane of the fracture would cross different areas of the physis (2). Similarly, intra-articular physis fractures, such as Salter–Harris (SH) types III and IV, would traverse several or all areas of the physis. Such injuries have a worse prognosis possibility of bone formation through the physis (1). When the formation of bone bars occurs in patients with potential growth disorder, the current gold standard therapy is the resection of the bone bar with subsequent interposition of material such as free fat graft, polymethylmethacrylate (PMMA), silastic, cartilage, bone wax, and dura (2).

Here, we discuss about a 5-year-old patient treated for a polytrauma that involved a complex lesion of the growth plates of the knee and we review the treatment for subsequent deformities.

Case report

In this paper, we discuss about a 5-year-old patient overwhelmed by masonry elements following a collapse of the chimney at the patient's home in May 2012. The child was transferred from another university polyclinic to our emergency room with a diagnosis of crushing polytrauma. She had a fracture of the right ischiopubic branch, a lesion of the distal femoral and proximal tibia physis of the left knee, both type IV according to the Salter–Harris classification; a bifocal fracture of the left fibula; and diffuse torn wounds (**Figure 1**). The patient came in spontaneous breathing, hypotension, and tachycardia; a plasma expander was, therefore, infused and the child was then hospitalized in the Intensive Care Unit. Once stabilized, she was transferred to the Traumatology Department and underwent closed reduction surgery and internal fixation with cannulated screws for femoral and tibial fractures of the growth plate (**Figure 2**). After 10 days of hospitalization and treatment, the patient was discharged in good clinical condition. A weightless cast on the left lower limb was prescribed for 40 days; following a clinical-

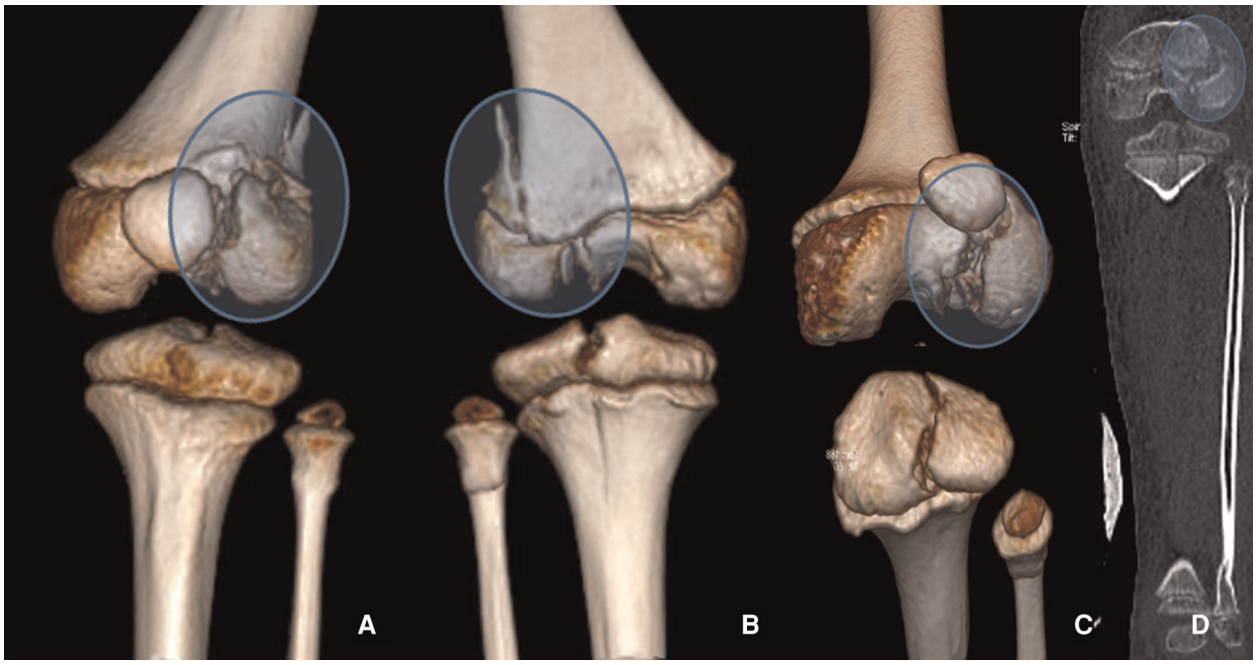

FIGURE 1
3D CT reconstruction of physis injuries of the left knee in anterior view (A), in posterior view (B), inlet view (C), and 2D CT coronal view (D).

radiographic examination, the cast was then removed and kinesitherapy aimed at the gradual and complete recovery of knee movement was started. A valgus deviation of the left knee was found at 3-month postoperative clinical follow-up likely as a result of a growth disorder of the femur. Therefore, an x-ray examination of the lower limbs' weight-bearing was performed at 4 months after operation, which showed a valgus (20°) of the left lower limb, and she presented 5 mm of limb length discrepancy. For this reason and with the diagnostic suspicion of femoral bony bar formation or growth arrest, the patient underwent a CT scan that confirmed the presence of femoral bone bridge (Figure 3). She was diagnosed with valgus knee due to partial epiphysiodesis of the femur and she was readmitted to the hospital. In the operating theater, both screws were removed percutaneously. Through a lateral surgical approach to the distal third of the left thigh, a femoral cortical bone dowel was placed near the bone bridge; then an open femoral de-epiphysiodesis with a burr from proximal to distal carefully avoiding damage to the joint surface from the inside was performed; the drilled hole was then filled with bone wax. About a month after the second surgery, the patient underwent an MRI scan that highlighted the results of the recent de-epiphysiodesis operation with placement of bone wax and minimal residual bone bridge of limited entity (2 mm × 4 mm) compared to the previous CT control (Figure 4). The patient underwent further II level investigation 18 months after trauma such as a bone scintigraphy that noticed an area of growth plate hypercaptation around the surgically performed bone hole sign of metabolic overactivity of the growth cartilage around the bone wax area (Figure 5). The young patient was then followed up over time with clinical/instrumental investigations approximately every 6 months. At 20-month post-trauma follow-up, the left knee was valgus about 20° relative to the other side with an acquired length discrepancy of 14 mm and compensatory pelvic obliquity (Figure 6). From that clinical follow-up, a slow but progressive improvement in the axis of

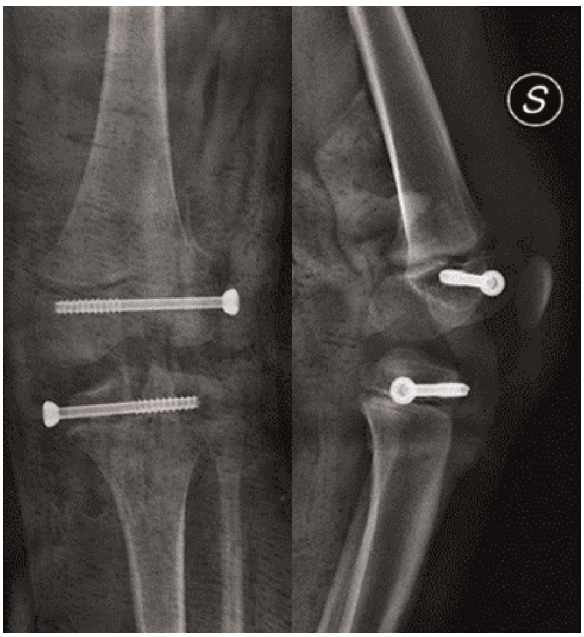

FIGURE 2
Postoperative x-ray control after reduction and synthesis of left knee growth plate fractures.

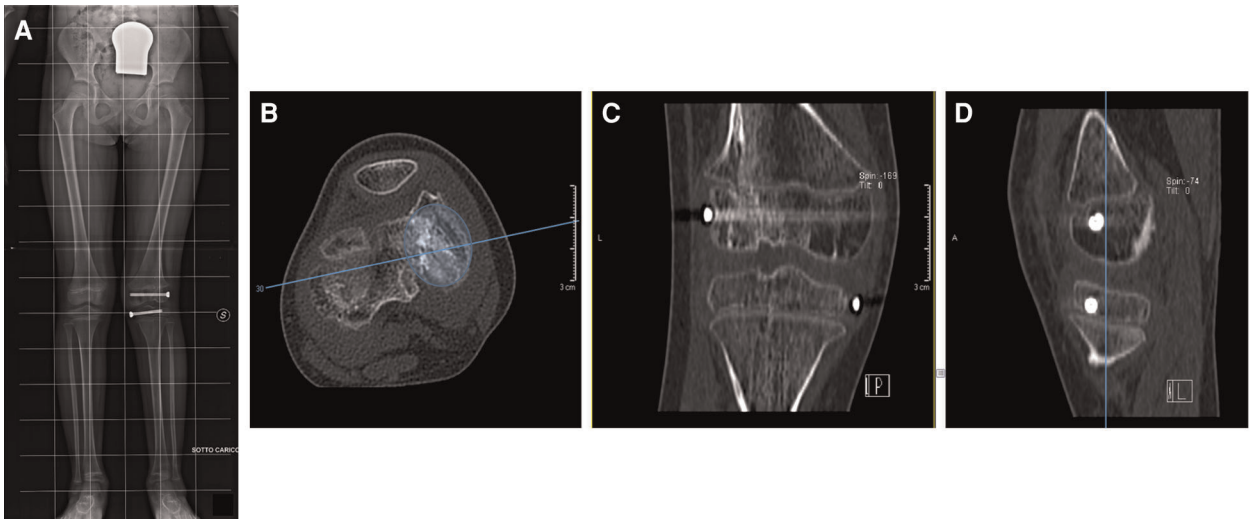

FIGURE 3
Four months postoperative x-ray showing a valgus (20°) of the left lower limb and the absence of dysmetria (A). CT scans confirm the presence of femoral bone bridge in three different projections (B–D). (B) shows that the bony bar is 30% of the entire area of the growth plate.

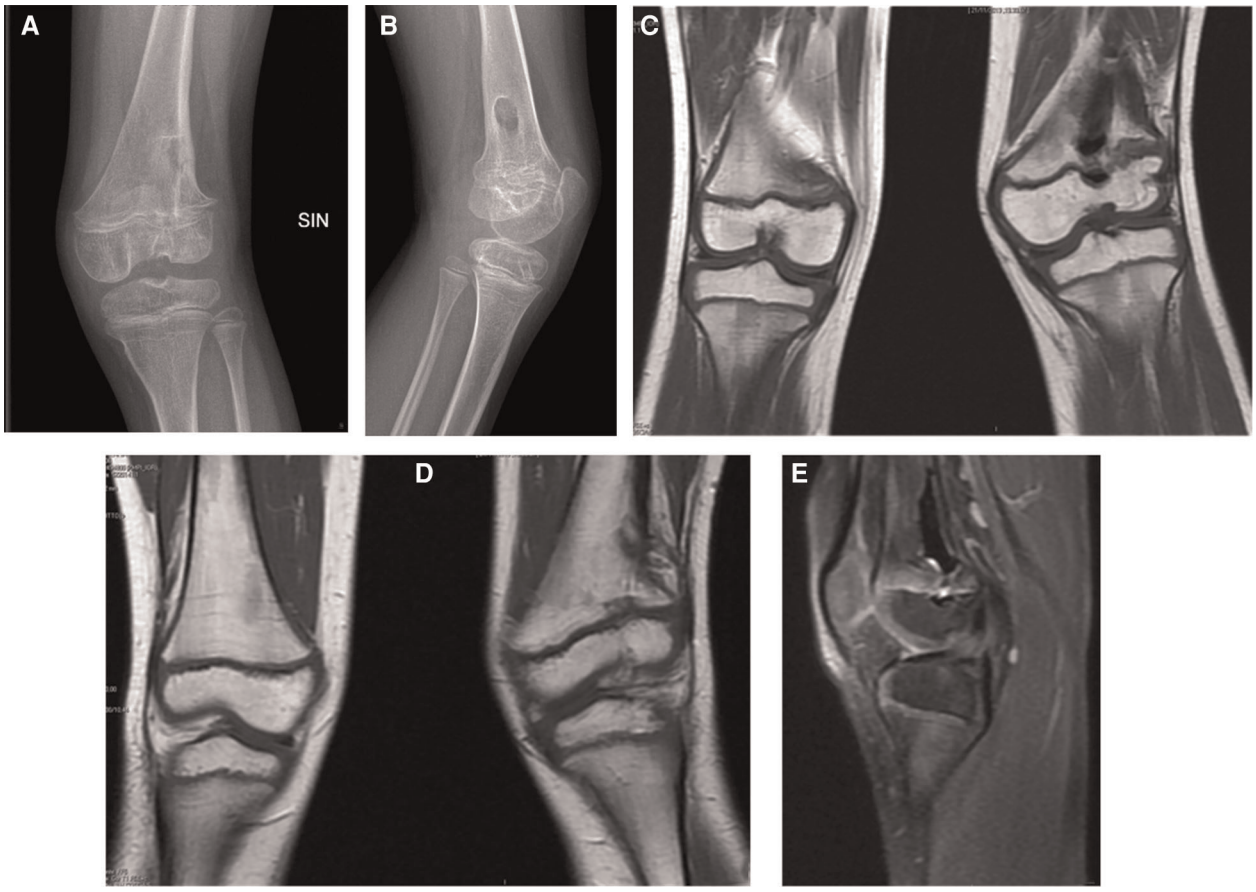

FIGURE 4
X-ray (A,B) and MRI (C–E) highlighted the results of the recent de-epiphysiodesis operation with placement of bone wax and minimal residual bone bridge.

the lower limbs was noted; the patient was then monitored over the years with clinical and radiographic follow-ups, which showed constant improvement up to complete recovery. Clinical and radiographic control 10 years after the trauma showed a complete recovery of the axis of the lower limbs associated with the absence of limitations on the left knee; in addition, the x-rays confirmed the known lowering of the left hemipelvis of about 20 mm and the known morpho-structural alteration localized at the level of the distal third shaft of the left femur as a result of the bone wax placement surgery (**Figure 7**).

Discussion

Physeal injuries represent 15%–30% of all fractures in children. Fortunately, although growth plate injuries are common, growth disturbance related to physis lesions is rare, accounting for around 1%–15% of all physis injuries. There are factors that contribute to the increased likelihood of growth disturbances, such as comminuted fractures, high-energy injuries, and physeal injuries that cross the germinal layers (Salter–Harris type III and IV injuries) (5). Such injuries have a worse prognosis possibility of bone formation through the physis producing consequences like growth arrest, angular rotational deformities, and subsequent altered joint mechanics (1). As reported by Garrett et al. (6), also in this case, there was a correlation between the high-energy traumatic mechanism and the formation of the bone bridge. The type of fracture, Salter–Harris type IV, was also mostly associated with complicated risk of growth disturbance (7).

Distal femur fractures often involve the growth plate, which contributes up to 70% of the length of the femur. These kinds of fractures are known to be associated with a high incidence of complications (8). Distal femur growth disorder is the most common complication (7); growth arrest is a frequent occurrence of fractures in this region, resulting in axial and length-related deformities. Long-term surveillance is recommended to identify evolutionary deformity and provide an opportunity of early intervention (9). Adams et al. found

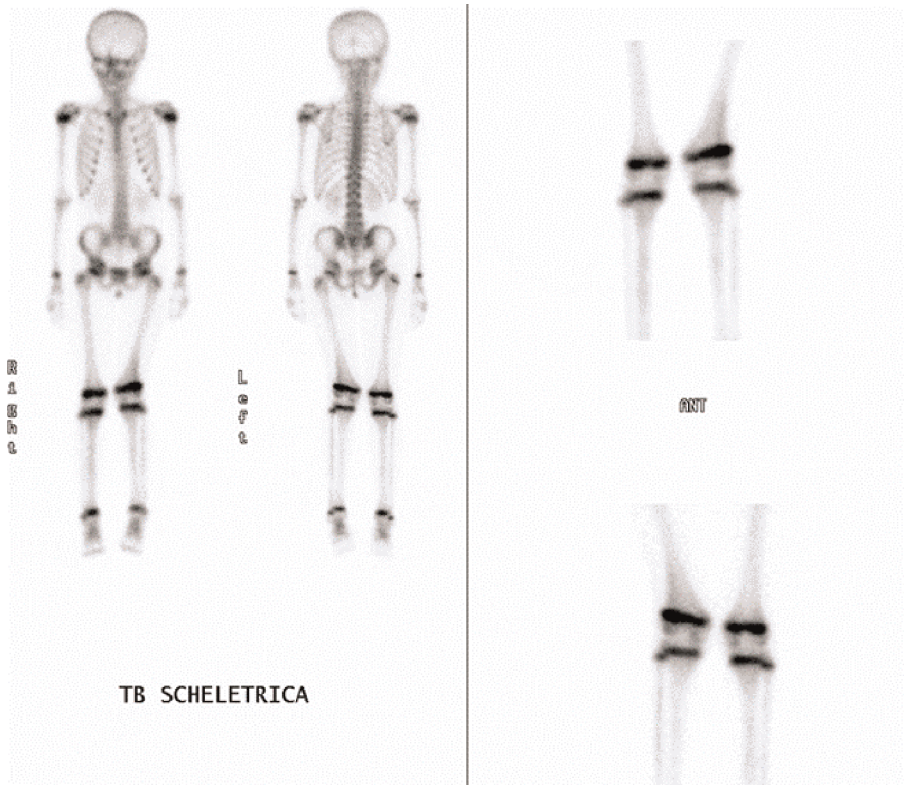

FIGURE 5
Bone scintigraphy highlighted an hypercaptation of the lateral portion of the left femoral physis.

that physeal arrest is the most common consequence following this type of injury, and when it is associated with growth disturbances such as axial and length-related deformity, it should require surgical intervention in up to 60% of cases (8).

Although it has been reported that a 50% bone bridge of the physis area can be successfully removed, 30% appears to be a threshold based on recent reports in the literature (2). Similarly, the general indications for performing hemiepiphysiodesis and osteotomy are >5° and >10° of axial deformity, respectively. This can vary according to the type of physiology, the residual growth, and the decision shared with the patient (2). Surgical resection of the bone bridge is important because the bar should be completely removed ensuring the least possible trauma to the surrounding tissues; at the same time, the bone bridge must be clearly visible and identifiable to obtain an acceptable resection (10). The techniques for removing the bar depend on its location: the peripheral bone bridges can be approached directly while the central bone bridges can be approached either through a metaphyseal window, or through a metaphyseal osteotomy and curettage of the cancellous bone up to the bone bridge. A high-speed burr is usually used for complete removal of the bone bridge (10).

The spatiotemporal growth factor control model of bone elongation has been held to be majorly responsible for the growth plate stimulus in the past two decades (11). However, advances in articular cartilage biology have turned the attention to the potential regulation of growth by mechanical forces. Indeed, several recent papers have presented evidence supporting a primary role of mechanical forces in promoting normal growth plate cartilage function. It would seem in fact that additional compressive stress avoided bone growth, whereas reducing compressive stress enhances bone growth, with differences between static and dynamic mechanical forces (11). The initial goal of our treatment was to stabilize the deformity during the further phases of growth and then to indicate a possible corrective osteotomy. The interest of our case lies in the fact that the removal of the bone bridge was more than 30% of the entire growth plate area. In the initial stages, the presence of bone wax in the area of de-epiphysiodesis allowed the stabilization of the deformity on the 20° of preoperative valgus. The interpretation of the growth cartilage activity occurred, during the adolescent spurt of growth, in an asymmetrical way such as to realign the femoral load axis, it can be based on the different mechanical stimulus on the two knee areas (medial and lateral) due to the preexisting deformity. The chondrocytes of the lateral

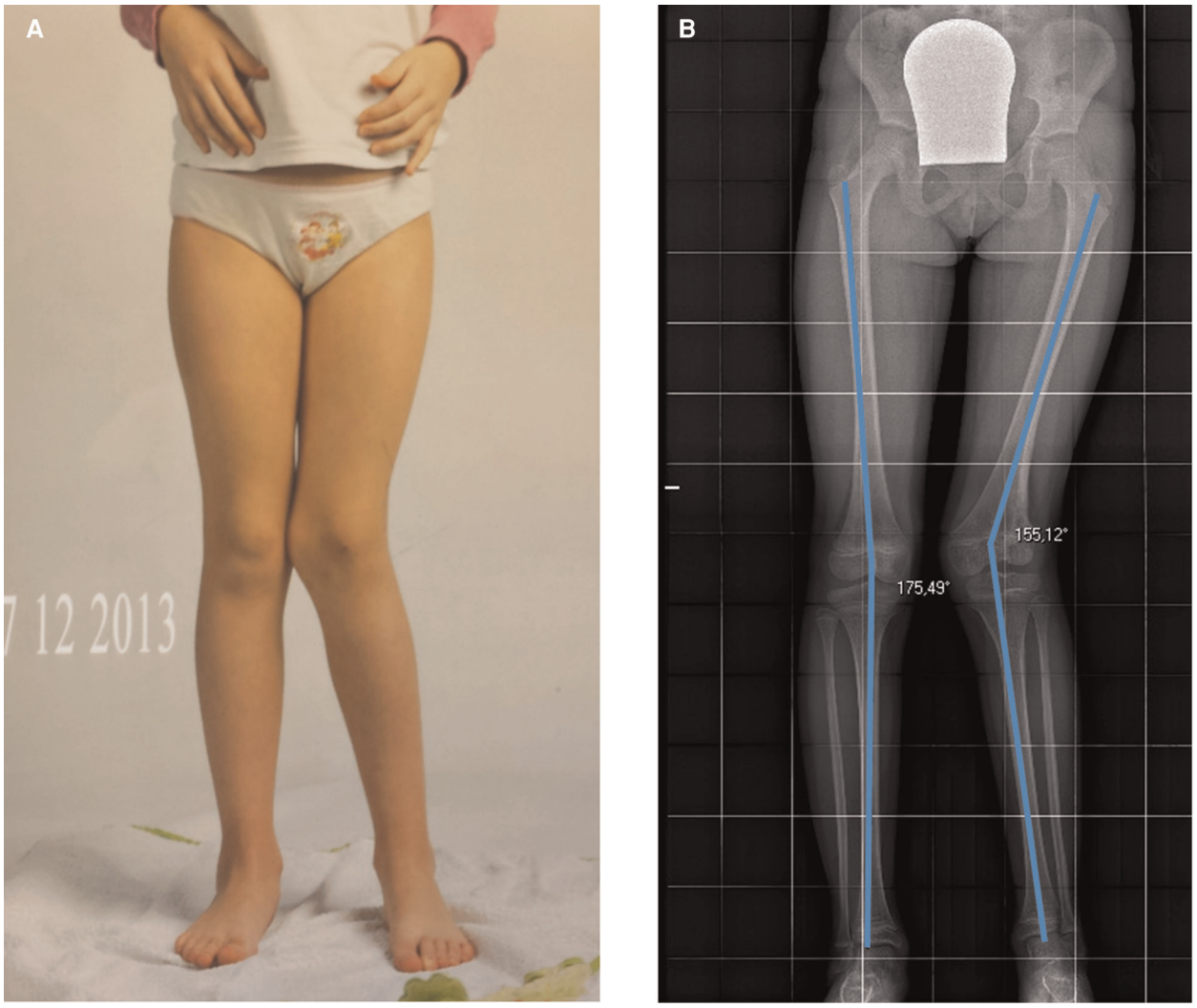

FIGURE 6
Twenty-month post-trauma follow-up showing 20° valgus deviation of the left knee with respect to the contralateral side. (A) showing clinical results, (B) showing radiological results.

zone, receiving a different mechanical stimulus, responded with a hyperactivity up to the recovery of the joint plane and, therefore, of a similar mechanical stimulus in the two areas. Ultimately, the outcome of the treatment was a 20 mm discrepancy, which could lead in the long term, if not compensated, to recurrent low back pain due to overload. Furthermore, if we had not obtained the 20° valgus correction, the patient would have risked an overload of the lateral compartment with an increased risk of long-term osteoarthritis.

There is no unanimous evidence in the literature in terms of the management of growth disorders resulting from this type of injury. With fractures at high risk of complications, such as type IV SH or distal femur fractures, an acute Langenskiöld procedure could prevent bone bar formation (12). When the formation of bone bars occurs in patients with potential growth disorders, the current gold standard therapy is the resection of the bone bar with subsequent interposition of materials such as free fat graft, PMMA, silastic, cartilage, bone wax, and dura (2). Bone wax resulted in effectively filling the hole of de-epiphysiodesis in distal femoral growth plate and allowed us to obtain the response of the growth plate and to improve the recovery time in a young child. Future treatment alternatives include treatments ranging from physeal transplantation to regenerative and tissue-engineering approaches (13).

Conclusion

To the best of our knowledge, this is the first case described in the literature of long-term follow-up of complex injuries of

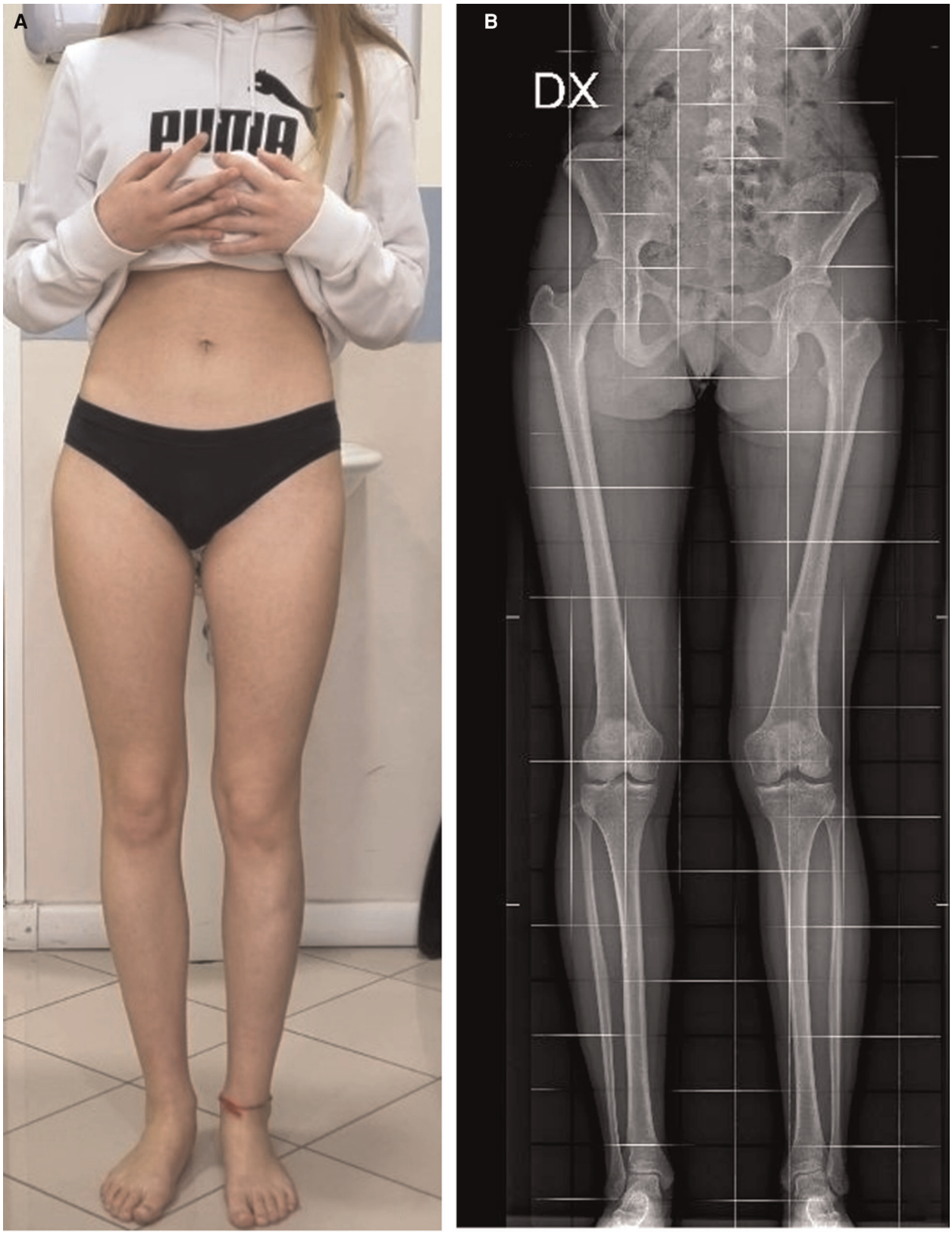

FIGURE 7
Ten-year post-trauma follow-up showing complete clinical (A) and radiological (B) recovery.

physis of the knee in 5-year-old patient involved in crushing polytrauma. Early diagnosis and physeal-sparing techniques are important but not sufficient to prevent future physeal growth arrest and resultant growth disturbances.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

LB participated in the conception, design and coordination, acquisition of the data, and drafted the original manuscript. AGA participated in the drafting of the manuscript. DB, FF, and RMT helped in drafting and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Case report: Kaposi hemangioendothelioma of the right upper limb with the Kasabach–Merritt phenomenon: A potentially lethal diagnostic challenge

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Kaposi hemangioendothelioma (KHE) is a rare vascular neoplasm that presents usually within the first year of life. Because of its rarity and complexity, there is often a delay in diagnosis. KHE could be associated with a life-threatening consumptive coagulopathy named the Kasabach–Merritt phenomenon (KMP). Here, we present the case of a 2-month-old girl who presented with progressive redness and swelling of her right upper limb over 6 weeks. Multiple health practitioners misdiagnosed her condition as an insect bite, cellulitis, and necrotizing fasciitis and gave treatment accordingly, which proved futile. A full blood count revealed bicytopenia of anemia and thrombocytopenia, a normal coagulation cascade, low fibrinogen, and raised D-Dimer levels. The imaging was suggestive of a high-flow vascular tumor likely to be a KHE. Subsequently, she was started on single-agent oral sirolimus with a dose increment to achieve satisfactory therapeutic levels and was treated for 1 year. She successfully completed the treatment regimen and had only transient hypertriglyceridemia, which resolved upon the completion of treatment. Currently, she is in remission 3 years after treatment. Keeping her case as an example, we would like to highlight the potentially lethal misdiagnosis of KHE with KMP, the importance of an early diagnosis of this condition, and the successful treatment outcome with single-agent sirolimus.

KEYWORDS

kaposi hemangioendothelioma, Kasabach–Merritt, upper limb, sirolimus, treatment outcome

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Introduction

Kaposi hemangioendothelioma (KHE) is a rare vascular neoplasm diagnosed during infancy or early childhood with a prevalence and incidence of 0.91 and 0.071 per 100,000 children, respectively (1). Men have a slight predominance over women, as reported in two large retrospective studies (2, 3). KHE is mostly evident (90%) within the first year of life (4). The etiology of this disease remains unknown, and in most cases, KHE occurs insidiously (5). The Kasabach–Merritt phenomenon (KMP) is a life-threatening coagulopathy occurring in 70% of KHE cases (1). In view of the rarity of KHE with KMP, delay in diagnosis may lead to morbidity and mortality of up to 30% mostly due to life-threatening hemorrhage, cardiac failure, and local invasion of the neoplasm (6).

Case presentation

A 2-month-old girl presented with a 6-week history of progressive swelling over the right forearm. She was delivered at term *via* emergency lower-section cesarean section with a birth weight of 2.92 kg. Antenatally, the mother had gestational diabetes mellitus and had a history of threatened preterm labor. The intrapartum and postpartum periods were uneventful. At 2 weeks old, a small erythema was noted at the lateral right forearm that progressed to involve the entire right forearm, with progressive swelling in the next 3 weeks. There was no history of trauma or fall. There was no family history of malignancy. The child remained active, was feeding well, was not fretful, and was afebrile. There was no limitation to her range of motion, nor did she cry upon handling.

At 1 week of illness, her mother brought her to a general practitioner, and she was treated symptomatically for urticaria, presumably caused by an insect bite. However, as the redness in her upper limb persisted and the swelling enlarged, she was brought to another medical practitioner and was then admitted to a hospital a week later and treated for cellulitis of the right upper limb with intravenous antibiotics. However, a radiograph of the affected upper limb findings was found to be unremarkable. Clinically, the girl remained afebrile, active, and thriving, and did not have any limitation of her right upper limb range of motion. Despite treatment with two courses of antibiotics, no signs of improvement were observed. Then, ultrasound imaging and magnetic resonant imaging (MRI) of the right upper limb were performed, and subsequently, the private orthopedic surgeon referred the girl to our center for further management. Following multiple investigations by a multidisciplinary team, a definitive diagnosis was arrived at.

She was initially referred for soft tissue infection of the right upper limb with a differential of necrotizing fasciitis. The resident orthopedic team assessed the child at the age of 2 months. A clinical examination revealed a huge discrete swelling of the right upper limb extending from her right wrist up to the mid-arm and was associated with red-bluish discoloration, which was dry, cool, and non-tender (**Figure 1A**). The range of motion of her elbow was 0–120° and her neurovascular status of the limb was intact and normal. She was active and afebrile.

Initial blood tests revealed that the child had bicytopenia. Her hemoglobin level was 6.2 g/dl with a platelet count of 8×10^9/L. Further investigations were suggestive of consumptive coagulopathy with a fibrinogen level of 1 g/L and a D-Dimer level of 11.5 µg/ml. Her coagulation profile was normal with a PT of 13.8 s, APTT of 43.6 s, and INR of 1.08. The blood investigation results were not suggestive of bacterial infection. Subsequently, she was referred to the pediatric hematology team and a clinical diagnosis of Kaposi hemangioendothelioma with the Kasabach–Merritt phenomenon (KMP) was made. The MRI of the right forearm demonstrated a diffuse infiltrative lesion that crossed multiple planes in the forearm without a clear margin (**Figures 2A,B**), and the ultrasound doppler confirmed the lesion to be a high-flow vascular tumor (**Figure 1B**).

The infant received packed red blood cells, platelet, and fresh frozen plasma transfusions during admission as she bled from the intravenous line insertion site. Single-agent oral sirolimus was commenced with an initial dosage of 0.2 mg BD (0.8 mg/m^2/dose). According to the institutional policy, sirolimus can be used only for children aged 2 years and above; however, ethical approval was obtained for the drug to be used in this infant. After 14 days of sirolimus treatment, a reduction in redness and swelling of the right upper limb was observed and the platelet normalized to 123×10^9/L. The patient was discharged home after 1 week of admission, and oral sirolimus of the same dose was continued for 4 months before the dose was increased to 0.4 mg BD, 0.6 mg BD, and then 0.8 mg BD up to a total duration of 1 year. There was an issue related to compliance with sirolimus during months 3 and 4 of the treatment. During treatment, the serum sirolimus levels were closely monitored to achieve a trough level of between 10 and 15 ng/ml. The serum levels were checked weekly during the first month of treatment, then biweekly for the subsequent month, and then monthly. After a stable dose was achieved, therapeutic drug monitoring was performed every 3 months. A prophylaxis for pneumocystis pneumonia, trimethoprim/sulfamethoxazole, was started concomitantly until the treatment was completed. An ultrasound-guided biopsy was performed under sedation 2 months after treatment started with a normal coagulation profile, and the histopathological examination showed a proliferation of multiple scattered, small, round, and some

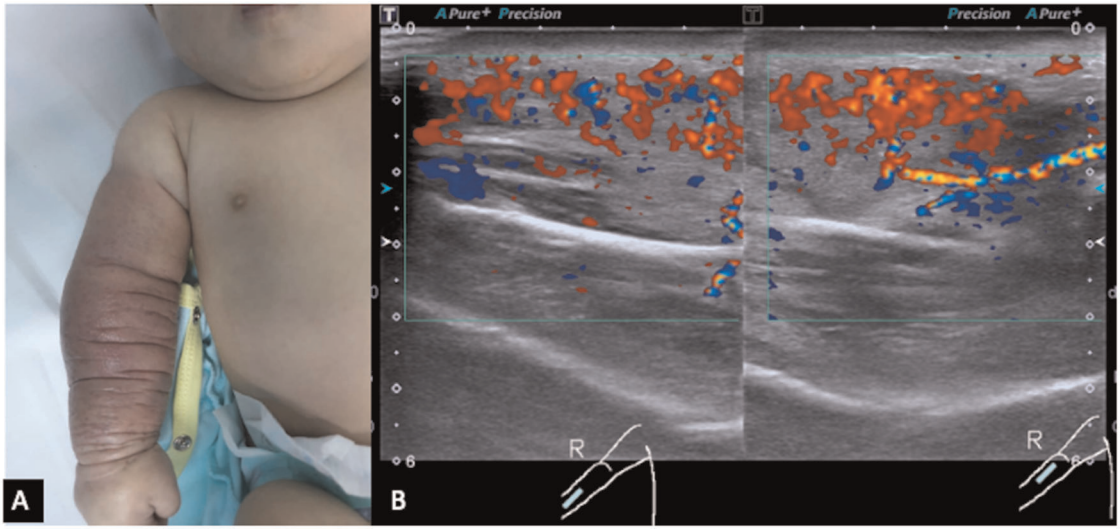

FIGURE 1
(A) Red discoloration and swelling of the right forearm up to the mid-arm. Redness and swelling are circumferential throughout the forearm and mid-arm. (B) Ultrasound color Doppler of the right forearm in longitudinal view shows marked hypervascularity in the swollen subcutaneous layer and muscles. Both arterial and venous spectral waveforms are detected. There is no margin seen bordering the lesion. These findings are suggestive of a high-flow vascular tumor.

slit-like vascular channels within the deep dermis and subcutaneous fat that are lined by bland endothelial cells. Some of the cells appeared to form a glomeruloid structure. The endothelial cells were positive for CD31 and CD34, which were suggestive of a vascular lesion favoring KHE.

She was also followed up regularly following the treatment protocol to monitor the full blood count, renal profile, liver function, and fasting serum lipids. She had transient hypertriglyceridemia, which resolved after the treatment was completed. A repeat MRI after 6 months of treatment revealed a complete resolution of the lesion (**Figures 2C,D**); however, clinically, there was some residual skin discoloration. After the completion of the dosage of 1 year of oral sirolimus, the right upper limb swelling and discoloration resolved completely (**Figure 3A**). Currently, at the age of 3 years, she remains in remission (**Figure 3B**). Her parents are highly satisfied with the treatment outcome and are compliant with the follow-up regime.

Discussion

A right upper limb redness and swelling in infants is often diagnosed as cellulitis, necrotizing fasciitis, hematoma, or a vascular tumor. The baby girl who was referred to our center initially presented herself to multiple health practitioners, who misdiagnosed her condition and delayed the definitive diagnosis of KHE with KMP, which could potentially be fatal. The delay in diagnosis could be explained by the rarity of the disease condition, a lack of experience in clinical diagnosis, the deep location of the tumor (mediastinum or retroperitoneum), and coagulopathy, making biopsy challenging (7).

The clinical diagnosis of KHE requires a thorough history and examination, blood investigations, imaging, and biopsy. KHE presentation could be heterogenous and variable, thus providing a diagnostic challenge. The spectrum of presentation could vary from cutaneous lesions with variable appearances to deep masses without any cutaneous signs. Patients with KMP and without KMP could also be distinguished through examination (5). KHE presents commonly with a single soft tissue mass with cutaneous findings, which range from an erythematous papule or nodule to a firm purplish tumor (5). These lesions are usually painful, hot to the touch, swollen, and purpuric in patients with KMP (5). In this case, the initial presentation to the orthopedic team did not lead to the diagnosis of KHE just through clinical history and examination. Differential diagnoses of such lesions include infantile hemangioma, congenital hemangiomas that include rapidly involuting congenital hemangioma (RICH), and kaposiform lymphangiomatosis (5, 8, 9).

Hematological investigations reveal thrombocytopenia and consumptive coagulopathy in cases suggestive of KMP. KMP is a rare, life-threatening condition that occurs in 70% of patients diagnosed with KHE (10). Thrombocytopenia in KMP is usually severe, with a median platelet count of 21×10^9/L (11). In this case, the infant presented with

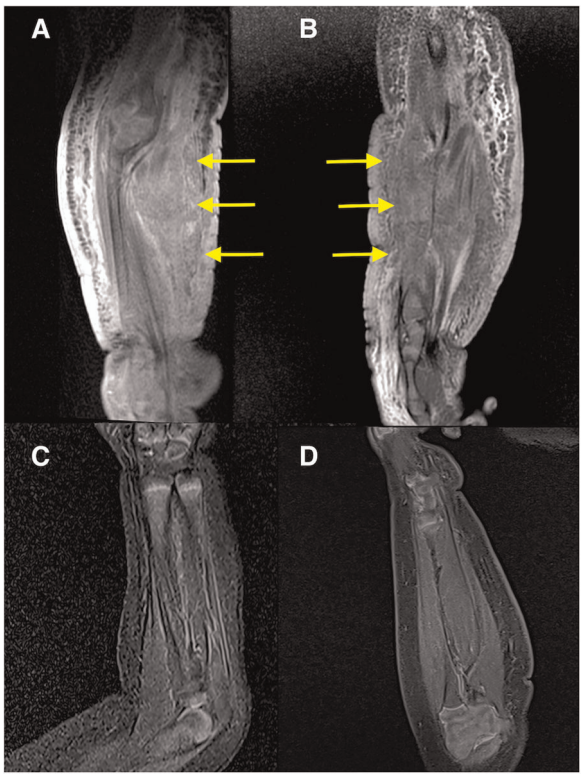

FIGURE 2
MRI of the right forearm: (A,B) at diagnosis; (A) coronal T1 fat-saturated post-contrast; (B) sagittal PD fat-saturated. Both images show a diffuse infiltrative abnormal signal and thickening of the skin, subcutaneous layer, and muscles of the forearm without a clear margin (arrows). The subcutaneous oedema extends into the arm. Moderate enhancement is seen in the post-contrast sequence (A). MRI of the right forearm: (C,D) at 6 months after treatment started; (C) Coronal STIR; (D) Sagittal T1 fat-saturated post-contrast. Both images show a resolution of the abnormal changes.

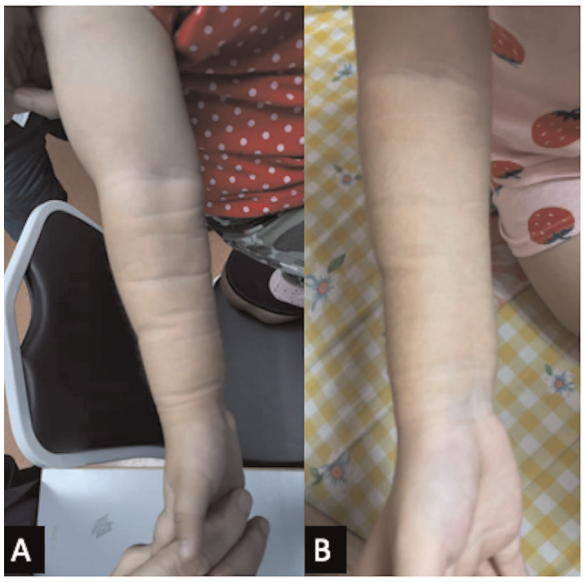

FIGURE 3
(A) The right upper limb shows a resolution of discoloration and swelling after 1 year of oral sirolimus. (B) The girl's current photograph of her right upper limb at 3 years of age.

thrombocytopenia of 8×10^9/L, which could likely cause severe bleeding within the compartment of her right upper limb, leading to anemia and consumptive coagulopathy. The postulation behind the thrombocytopenia has been attributed to platelet trapping within the lesion due to extracellular damage or alteration in KHE, leading to activation and aggregation of platelets, which results in subsequent consumptive coagulopathy (5). In KHE, the thrombi in the microvasculature cause vessel occlusion and prevent normal blood flow. This could lead to increased shear stress and induce increased platelet activation. This process, in turn, causes further platelet trapping and activation during the active phase of KHE (5). Given the life-threatening nature of thrombocytopenia and consumptive coagulopathy, we treated the patient with a regime of blood products to stabilize her condition upon admission as she bled from the peripheral line insertion site. The utilization of blood product support is crucial during active bleeding despite a potential worsening of KMP, with platelet transfusion aggravating platelet aggregation. In cases of active bleeding, severe coagulopathy, and/or thrombocytopenia, fresh frozen plasma and/or cryoprecipitate can be used in the treatment of KMP (12).

Imaging modalities such as ultrasound and MRI are helpful to aid the diagnosis of KHE. Ultrasound is recommended in superficial and small lesions, while MRI is helpful to diagnose deep infiltrating KHE, which may not be apparent on physical examination (13). The features suggestive of KHE on ultrasound and MRI were discussed above. A biopsy of the lesion remains the gold standard in the diagnosis of KHE and it should be performed when the patient's condition allows it and when it is considered safe (5). The infant underwent a percutaneous ultrasound doppler–guided biopsy, which was a closed biopsy under sedation performed by an experienced pediatric radiologist. A confirmatory diagnosis was crucial to differentiate KHE from other vascular abnormalities and could predict the long-term outcome and benefits of the subject therapy. The hallmark features of KHE are the infiltrating, defined, rounded, and confluent nodules that are composed of spindle endothelial cells. These cells form a malformed lymphatic channel and slit-like vascular lumen. The lumen contents include erythrocytes, platelet thrombi, eosinophilic hyaline bodies, and hemosiderin deposits (5). Immunohistochemical staining of KHE includes positivity for CD31 and CD34, which are the vascular endothelial markers that were present in this case (14).

The heterogeneity and the presence of disease-related comorbidities make the management of KHE challenging. The

optimum treatment for KHE with KMP has not been established, and to date, there are no medications approved by the FDA for this condition. Ideal therapies for KHE with KMP would target cellular pathways important in abnormal vascular proliferation and growth (2). A treatment used previously includes systemic pharmacotherapy such as vincristine, corticosteroids, sirolimus, topical sirolimus or tacrolimus, ticlopidine, and aspirin (5). Multiple treatment regimens have been used for KHE with KMP with varying success, and the most recent randomized clinical trials reported encouraging results of using combination therapy with sirolimus plus prednisolone (5, 12, 15). Sirolimus, an inhibitor of the mammalian target of rapamycin (mTor), has been demonstrated to show satisfactory efficacy as oral administration in the treatment of KHE (16–19). There are a number of published reports on the use of sirolimus monotherapy in KHE with KMP, and it appears to be effective and safe in patients with life-threatening vascular anomalies (18, 20). The pathophysiology of KHE involves dysregulation of both angiogenesis and lymphangiogenesis. The classic spindle cell morphology found in KHE is thought to have a significant lymphatic component since these lesions stain with lymphatic endothelial markers D2-40 (podoplanin) and Prox-1 (21, 22). Sirolimus is effective on the lymphangiogenesis pathway, in which ligand-binding-induced signaling through VEGFR-3 on the surface of the lymphatic endothelium results in the activation of the PI3K/Akt/mTOR pathway (23, 24). The duration of treatment with sirolimus for KHE has been reported to be variable, and in a case series, it was reported that 12 months of treatment with sirolimus was associated with no disease recurrence. However, more studies are needed to investigate the most feasible duration of therapy required. Our experience suggests that sirolimus monotherapy of 12 months is a reasonable treatment for an infant with KHE with KMP, as it showed a good resolution of the lesion over the right upper limb and coagulopathy. We also monitored the patient for possible adverse effects of sirolimus including bone marrow suppression, metabolic derangements of hypercholesterolemia and hypertriglyceridemia, gastrointestinal side effects, as well as the rare side effect of pneumonia (14, 25). The patient tolerated the oral sirolimus well with only transient hypertriglyceridemia. The patient has been on a multidisciplinary team follow-up for 3 years now and has remained in continuous remission.

Conclusion

Kaposi hemangioendothelioma with KMP is a rare vascular neoplasm that can pose a diagnostic challenge to many treating physicians. A delay in diagnosis may lead to a potentially devastating outcome for the patient. Early diagnosis and initiation of treatment promise a good outcome.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Ethics statement

Ethical review and approval were not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the patient's next of kin for the publication of any potentially identifiable images or data included in this article.

Author contributions

LB, JS, SA, C-KL, and HA were responsible for the clinical management of the patient. EYH was responsible for the imaging of the patient. LB acquired the clinical data and drafted the initial manuscript. HA reviewed the intellectual contents of the manuscript and made substantial modifications during revision. All authors contributed to the article and approved the submitted version.

Conflict of interest

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Case Report: Bilateral symmetrical primary kaposiform hemangioendothelioma of the femur

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Kaposiform hemangioendothelioma (KHE) is a rare borderline vascular tumor that usually presents as a mass of skin or deep soft tissue. We report a unique case of an 8-year-old KHE patient with bilateral symmetrical sites involving both femurs. The laboratory, radiographic, and pathological findings of the patient were minutely described. During the 6-month follow-up, the symptoms of pain and dysfunction of this patient were relieved. This study aimed to arouse clinicians' concern about the symmetrical sites of KHE patients.

KEYWORDS
kaposiform hemangioendothelioma, bone, case report, Kasabach–Merritt phenomenon, pediatric

Introduction

Kaposiform hemangioendothelioma (KHE) is a rare borderline tumor with locally invasive features, which are mostly seen in children and adolescents, with an incidence of 0.71/100,000 (1). Clinical manifestations are more involved in the skin of the purplish red hard mass, and the surrounding tissue clearance is not clear. Only 10% of KHE patients showed deep lesions without skin involvement, while primary bone lesions were rarer, and most of the lesions were single lesions (2, 3). We report a unique case of KHE symmetrically involving both femurs, accompanied by pain and claudication, who was misdiagnosed as synovitis at an early stage. We aimed to alert clinicians to the early identification of KHE patients at specific sites, which is important for the management and prognosis of KHE patients.

Case description

An 8-year-old female child was referred to our tertiary medical institution for pain and discomfort in both knees accompanied by claudication. Before admission to our hospital, she was treated for "joint synovitis" with anti-inflammatory treatment in a local hospital. The pain symptoms were relieved once, but the pain accompanied by

claudication symptoms worsened 1 week after drug withdrawal. The patient showed local tenderness and percussion pain on both knees, but with no redness or palpable mass. Additionally, she showed no abnormal vital signs, such as fever and weight loss.

Laboratory tests, including white blood cell count of 12.56×10^9/L (reference value was 4.3×10^9/L–11.3×10^9/L), D-dimer of 0.90 mg/L FEU (reference value was lower than 0.55 mg/L FEU), and C-reactive protein of 8.24 mg/L (reference value was lower than 5.00 mg/L), were mildly abnormal. Other tests, such as blood count, coagulation function, biochemical electrolyte, various metabolic indicators (including thyroid hormone- and bone metabolism-related indicators), erythrocyte sedimentation rate, antigen indicators of parasites, and various immune antibody indicators, were negative.

Imaging examinations included bilateral knee x-rays, computed tomography (CT) scans, magnetic resonance imaging (MRI), and whole-body bone imaging (**Figures 1–3**). Plain radiography and CT of both knee joints indicated uneven bone density in the bilateral femoral diaphysis, epiphysis, and proximal tibia, with multiple low-density sites and calcification. However, the joint space showed no obvious narrowing. MRI indicated that lump-shaped shadows with long T1 and T2 signals were observed in the bottom of the femurs and in the upper end of the tibias on both sides, and no abnormalities were observed in the shape and signal of the medial and lateral meniscus. No abnormalities were observed in the anterior and posterior cruciate ligaments or the tibial and fibular collateral ligaments. There was no fluid accumulation in the joint cavity and no swelling in the soft tissue around the joint. Whole-body bone imaging showed increased radiation in the bone metabolism of bilateral lower femurs after intravenous 10 mCi of 99 mTc-MDP.

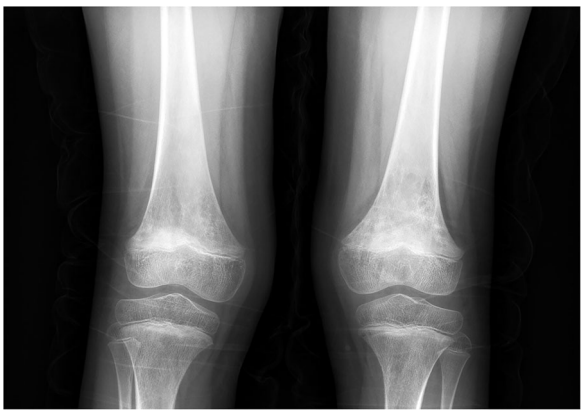

FIGURE 1
X-ray of both knee joints indicated uneven bone density in bilateral femoral diaphysis, epiphysis, and proximal tibia, with multiple low-density sites and calcification.

To further clarify the patient's diagnosis, a biopsy operation opening the window of the left femur distal lesions and plaster external fixation were conducted after improving the preoperative examination. During the operation, we could see that the left side of the distal femoral bone cortex was changing slightly, and the surrounding tissue was not swollen. There was no obvious mass or edema around the periosteum, and yellow fat-like tissue could be seen in cancellous bone after opening the bone cortex window. Postoperative pathology results showed positivity for CD31, SMA, Ki-67, CD34, FA-8, ERG, and D2-40, and negativity for NSE (**Figure 4**). The above immunohistochemical and histological morphology results all supported the diagnosis of KHE.

After surgery, the patient was given oral sirolimus (0.8 mg/m^2) monotherapy daily, and the blood concentration of sirolimus was maintained in the range of 3–8 ng/ml during the follow-up. Fortunately, the symptoms of claudication disappeared, and the hematological results completely returned to normal after a period of 6 months.

Discussion

KHE can be divided into superficial, mixed, and deep types, and the most common one is the mixed type (4, 5). Nearly 70% of KHE cases can be accompanied by the Kasabach–Merritt phenomenon (KMP) of severe thrombocytopenia and coagulopathy (1). Although 62.8% of KHE patients were reported to have musculoskeletal diseases, most of the KHE lesions were deep soft tissue that invaded bones. Lesions primarily originating from bone and limited inside bone are very rare (6). Among a series of 31 KHE patients, Kuo et al. reported that there were six primary bone KHE cases involving the unilateral limb bones, spine, sacrum, scapula, and sternum (3). To the best of our knowledge, the KHE case involving bilateral femur symmetry reported in this study is the first to be reported in the literature world.

Among the 107 KHE patients reported by Croteau et al., only 3 cases were confined to bone without KMP (1). Additionally, in our case report, blood coagulation function was approximately normal, and KMP did not appear. This might be because the lesions are confined to the bone, and the soft tissue around the lower femurs on both sides was not involved. There was no periosteal reaction, and the lesions may be physically limited by the cortical bone, which could not be further invaded. The risk of KMP was smaller than that of skin and muscle lesions.

The most common lesions of KHE occur in limbs (7). However, in current studies on KHE, there were no cases with symmetric limbs involved and confined to the bone. Bilateral intraosseous lesions can be easily misattributed to osteomyelitis, fibrous dysplasia, and so on, which are caused

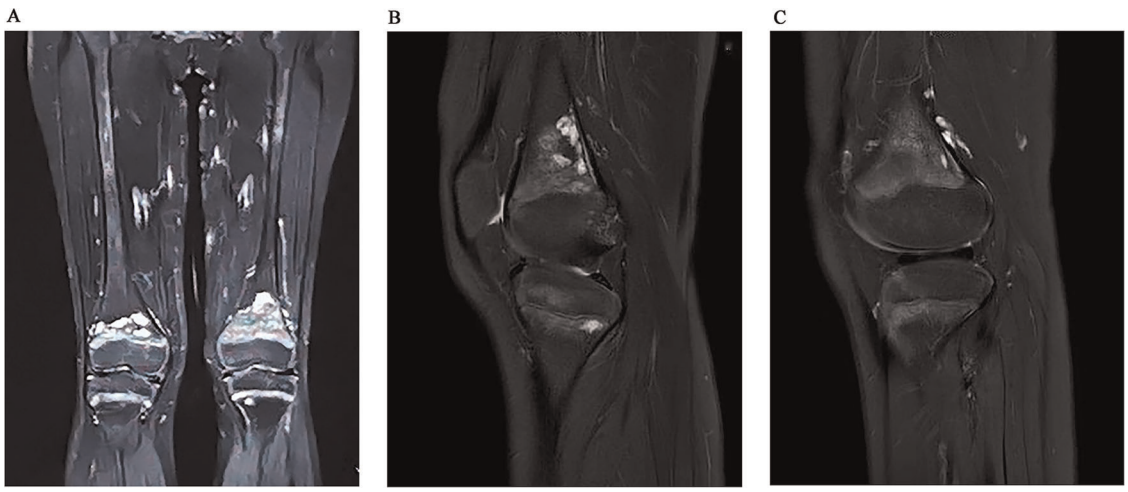

FIGURE 2
Coronal (**A**) and sagittal (**B**) MRI images indicated that lump-shaped shadow with long T1 and T2 signal was observed in the bottom of the femurs and in the upper end of tibias on both sides, no abnormality was observed in the shape and signal of the medial and lateral meniscus. After 6 months follow-up, we could see that the lesion was smaller than before (**C**).

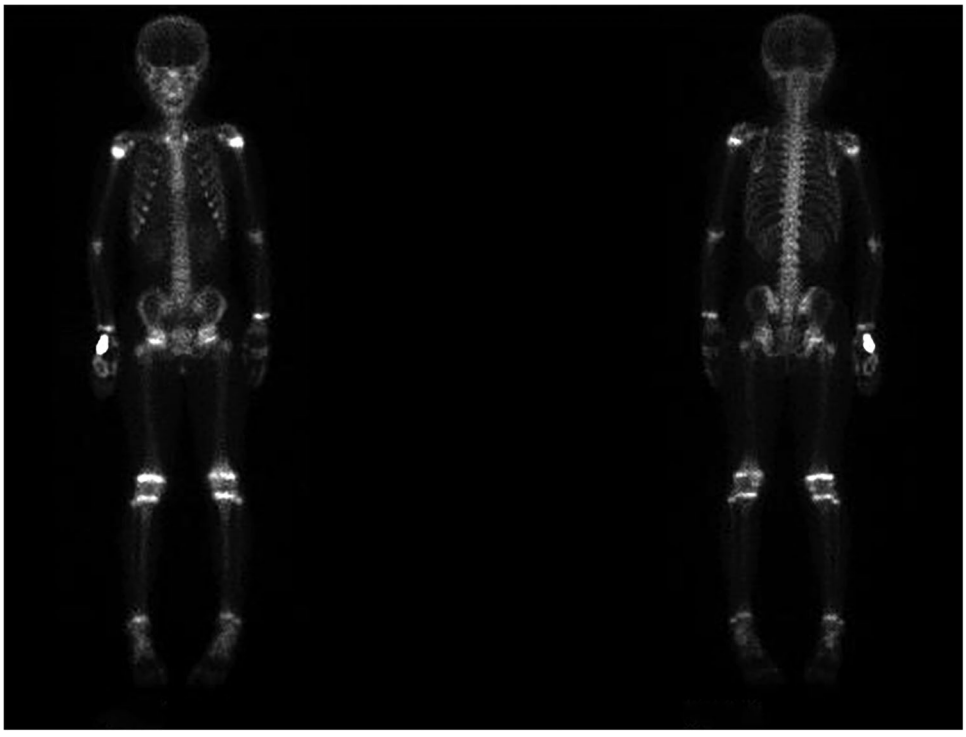

FIGURE 3
Whole-body bone imaging showed increased radiation in bone metabolism of bilateral lower femurs after intravenous 10 mCi of 99 mTc-MDP.

by trauma, infection, or abnormal growth in clinical practice. The diagnosis of KHE depended on the comprehensive evaluation of clinical manifestations, hematology, imaging, and pathological results. The diagnosis of KHE can often be ignored and delayed for such rare symmetrical lesions, resulting in significant disability and mortality rates.

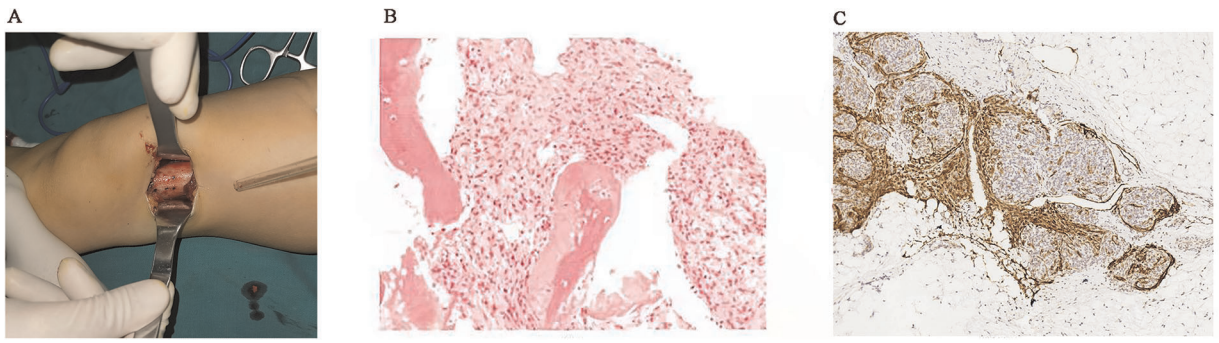

FIGURE 4
The left side of the distal femoral bone cortex was changing slightly rough in the operation (**A**), and the postoperative pathology results were showed (**B**: HE, ×200; **C**: positive D2-40, ×100).

Therefore, definite diagnosis through biopsy is particularly important for treatment direction, which can reduce the long-term complications of KHE.

Extensive resection of the lesion was not recommended for the KHE patient we reported to have bilateral femur lesions, which might lead to long-term complications and disability. Sirolimus is currently the first-line treatment for KHE (8–10). In our previous study, it was found that patients receiving sirolimus plus prednisolone therapy had fewer blood transfusions and a lower overall incidence of disease sequelae than those receiving sirolimus monotherapy. Sirolimus plus prednisolone is considered to be an effective treatment for KHE with KMP (2). We usually used sirolimus plus prednisolone to treat KHE patients with KMP, but for bone KHE patients without KMP, monotherapy with the mTOR inhibitor sirolimus acting on the PI3K/AKT/mTOR signaling pathway through inhibition of angiogenesis and lymphangiogenesis can effectively control and reduce mass and complications (11, 12).

Conclusion

In conclusion, we should also be alert to the possibility of KHE of symmetry osteopathy in the clinic. Biopsy is the gold standard for clear diagnosis of this challenging disease. Early and timely diagnosis is crucial for the prognosis of complications such as pain and dysfunction and the quality of life of children.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee on Medical Research of West China Hospital, Sichuan University. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

TQ, YL, and YJ contributed to the conception and design. All authors contributed to the collection and assembly of data. TQ and YL contributed to the manuscript preparation. SC and TQ contributed to the manuscript editing. YJ contributed to the manuscript revision/review. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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The conservative treatment of congenital scoliosis with hemivertebra: Report of three cases

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Introduction: Scoliosis is the most common type of congenital vertebral disease. This spinal disorder may be due to a failure of formation, segmentation, or a combination thereof. Complete failure of formation causes hemivertebra which can lead to unbalanced growth and deformation. Statistically, 25% of congenital curves do not evolve, 25% progress slightly, while the remaining 50% develop quickly and require treatment. Hemivertebrae can be divided into three types: non-segmented, semi-segmented, and fully-segmented. The fully-segmented types are most likely to progress. Hemivertebra in the thoracolumbar region shows higher rates of progression compared with those in the lumbar area. The treatment may be either conservative or surgical. In general, bracing is not recommended in short and rigid curves, although it may help process secondary curves.

Objective: To assess the effectiveness of bracing in congenital scoliosis due to hemivertebra.

Cases presentation: Searching in our database, we found three cases of patients with congenital scoliosis due to fully-segmented hemivertebra. The first of them was 6 years old at the time of diagnosis with a fully-segmented hemivertebra in L5, determining an L1-L5 (S1) lumbar curve. The second one was 10 years old at the time of diagnosis with a fully-segmented hemivertebra in L2 and a T11-L4 (L5 sacralized) thoracolumbar curve. The last one was 3 years old at the time of diagnosis with a fully-segmented hemivertebra in L3 (in six lumbar bodies), determining a thoracolumbar curve T12-L4.

Results: We utilized a Milwaukee brace for the first patient, a Boston brace for the second patient, and a Progressive Action Short Brace (PASB) for the third patient. At the beginning of the treatment, the Cobb angles measured 23°, 53°, and 25°, respectively. During treatment, the Cobb angles measured 22°, 35°, and 15°, respectively. At the end of treatment, the Cobb angles measured 18°, 45°, and 12°, respectively. At long-term follow-up, the curves measured 20°, 45°, and 12° Cobb angles, respectively.

Conclusions: Comparing our cases with those found in the literature we can confirm the ability of conservative treatment to change the natural history of congenital lumbar scoliosis due to failure of formation. From our experience,

in all cases of CS with hemivertebra, before considering a surgical approach, conservative treatment should be implemented as early as possible without waiting for the progressive deformation of the adjacent normal vertebrae.

KEYWORDS

hemivertebra, congenital scoliosis (CS), conservative treatment (CT), failure of formation, bracing

Introduction

Congenital scoliosis (CS) is a congenital spinal lateral curve caused due to developmental defects of the vertebrae that induce unbalance in the longitudinal spinal growth (1).

It is the most common congenital spinal disorder (1 in 1000 births) (2) and is considered to be associated with any fetal injury during intra-uterine spinal development. This occurs very early, from the fifth to the eighth week of gestation, and it is frequently associated with other pathological conditions, like congenital kidney disorders, congenital heart disease, and spinal cord dysraphism (3). There are three main causes of CS: failures of formation, failures of segmentation, and mixed failures. Failure of formation is the most widespread type of congenital disorder where the normal shape of the vertebra is disrupted. Complete formation failures lead to hemivertebrae with the lack of one pedicle and a part of the vertebral body, while incomplete formation failures result in a wedged vertebra. Both defects can be lateral, determining scoliosis; posterolateral, determining lordoscoliosis; dorsal, determining lordosis; anterolateral, determining kyphoscoliosis; or ventral, determining kyphosis (4, 5). Failure of segmentation results in abnormal synostosis between vertebrae. This can lead to spinal anomalies such as blocked vertebrae and unilateral bars. Mixed failures represent an undefinable mosaic of formation and segmentation defects with no defined classification (6).

In 1910, Putti was the first to distinguish three types of hemivertebra: fully segmented (a disc from either side), semi-segmented (a disc from one side, but the other side welded to the contiguous vertebra), and non-segmented (welded on both sides to the contiguous vertebrae). Putti felt that the fully segmented type was most likely to progress (7). In 1968, Winter proposed a new classification adding unsegmented bars (8), and Nasca, in 1975, analyzed 60 cases of scoliosis or kyphoscoliosis due exclusively to a hemivertebra, hemivertebrae, or a unilateral bar concomitantly with hemivertebrae and classified these into six categories. He also reported that the position of the hemivertebra or hemivertebrae and the presence of unilateral bars are the main determining factors of deformity (9).

The natural progression of congenital scoliosis is not easily predictable because it depends on a large number of factors. In a 1986 study of 104 patients, McMaster reported that four principal factors determine the degree of scoliosis: the variety of hemivertebra, their location, the number of hemivertebrae and their relations, and the age of the patient (10). He also reported that semi-segmented and non-segmented hemivertebrae generally do not demand treatment, while fully segmented hemivertebrae may need prophylactic treatment to avoid severe deformity. It is difficult to determine which congenital curves will evolve quickly. Statistically, 25% of curves do not evolve, 25% evolve slowly, and 50% show fast evolution and require treatment (11). In general, hemivertebra in the thoracolumbar region show higher rates of progression compared with those in the lumbar area (12). The treatment can be surgical or conservative, but it is tilted toward surgery as shown by the literature (2, 13). Certainly, cases with formation failures such as fully-segmented, semi-segmented, or non-segmented hemivertebrae receive a range of treatments from observation to conservative treatment with brace or early spinal surgery, while patients with specific types of segmentation defects, like unilateral unsegmented bars, will not be improved with brace treatment (14).

Most of the congenital scoliotic curves are rigid and consequently resistant to corrective actions with braces. Therefore, the main purpose of brace treatment is to prevent the evolution of secondary curves which grow up above and below the congenital main curve, causing imbalance (2).

Since the secondary curves, contrary to the main congenital curve, are normally flexible, brace treatment may have a beneficial effect on these curves, and although the primary curve can be resistant to brace treatment the stabilizing potential exists.

The purpose of the study is to assess the effectiveness of conservative treatment in congenital scoliosis due to formation failures.

Cases presentation

Searching in our database, we found three cases of patients with congenital scoliosis due to fully-segmented hemivertebra.

The first case is a 6-year-old girl with a fully-segmented hemivertebra in L5 and a curve L1-L5 (S1), with associated urinary malformation. In the initial years after diagnosis, the Milwaukee brace was used and then graduated to the PASB.

At the beginning of the treatment at 6 years of age, the curve was 23° Cobb, and at the weaning at 19 years of age, the curve was 18°; after 12 years of follow-up, the curve was not evolving. In particular, we noted that the vertebrae adjacent to the hemivertebra were hypertrophied (Figure 1).

The second case is a 10-year-old girl with a fully-segmented hemivertebra in L2 and a T11-L4 (L5 sacralized) curve, who refused surgical treatment. In the first year after diagnosis, a Boston brace was used, and then the PASB. At the beginning of the treatment, the curve was 53° Cobb. During treatment, the x-ray in-brace showed an improvement until 35° Cobb. At the weaning, the curve was 45° Cobb and at 19 years of follow-up, the curve was not evolving further (Figure 2).

The third case is a 3-year-old boy with a fully-segmented hemivertebra in L3 (in a 6 lumbar body) and a T12-L4 curve. The PASB was used, and the compliance was very good. At the beginning of treatment at age three, the curve was 25° Cobb and at the weaning, the curve was 12° Cobb degrees. After 5 years of further follow-up, the curve was not evolving and the vertebrae adjacent to the hemivertebra, similar to the first case, were hypertrophied (Figure 3).

The treatment protocol for all patients consisted of full-time brace treatment, with part-time free periods based on residual growth. All three cases did not show deviations in the sagittal plane, and for this reason, we did not take into account in our study the lumbopelvic parameters and their evolution over time.

Discussion

Treatment of spinal deformity in early childhood is difficult to manage. Literature shows that in severe cases with failures

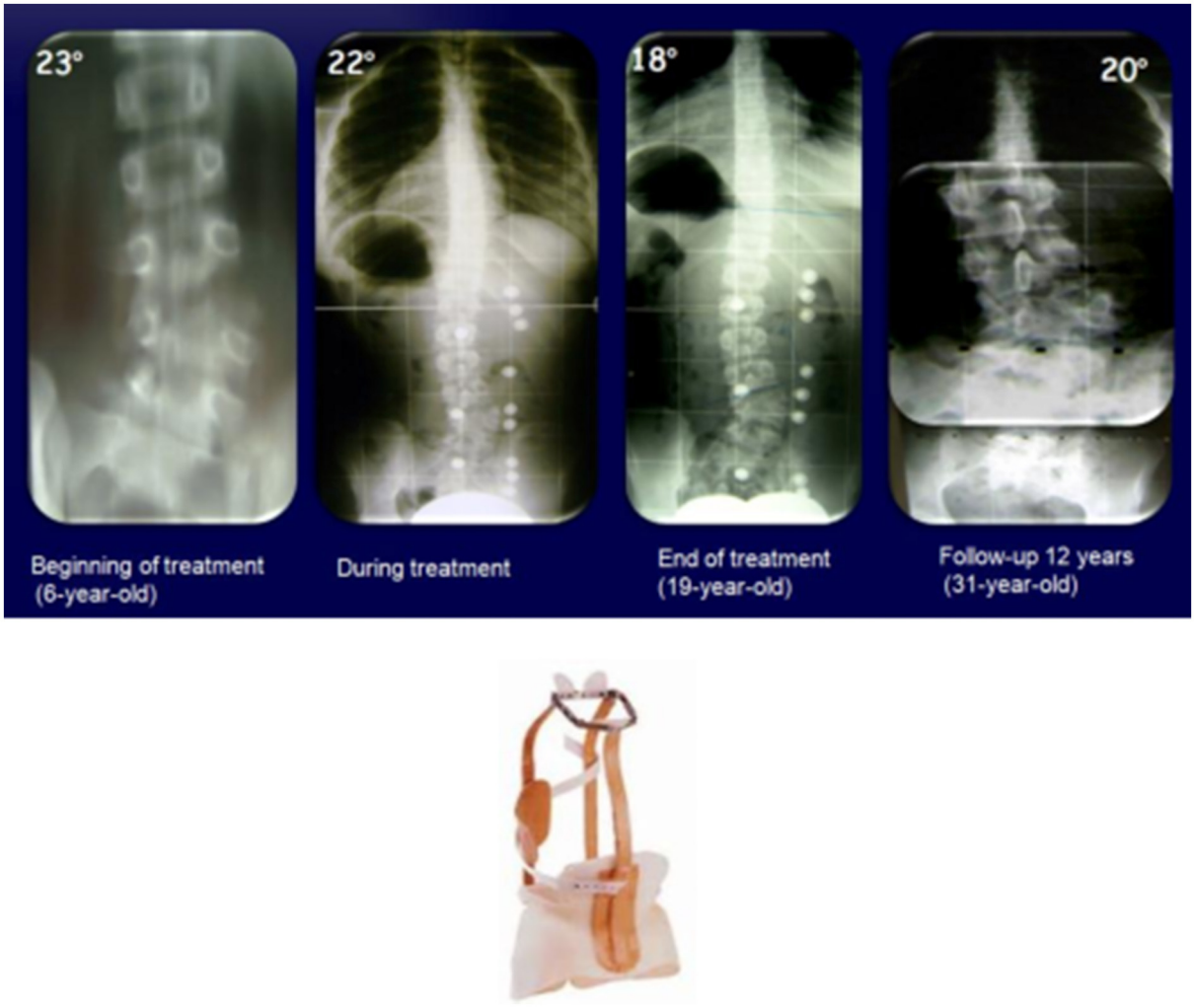

FIGURE 1
A 6-years-old girl with a hemivertebra in L5 and a curve L1-L5 (S1), with urinary malformation associated, treated with the Milwaukee brace in the first years and then the PASB.

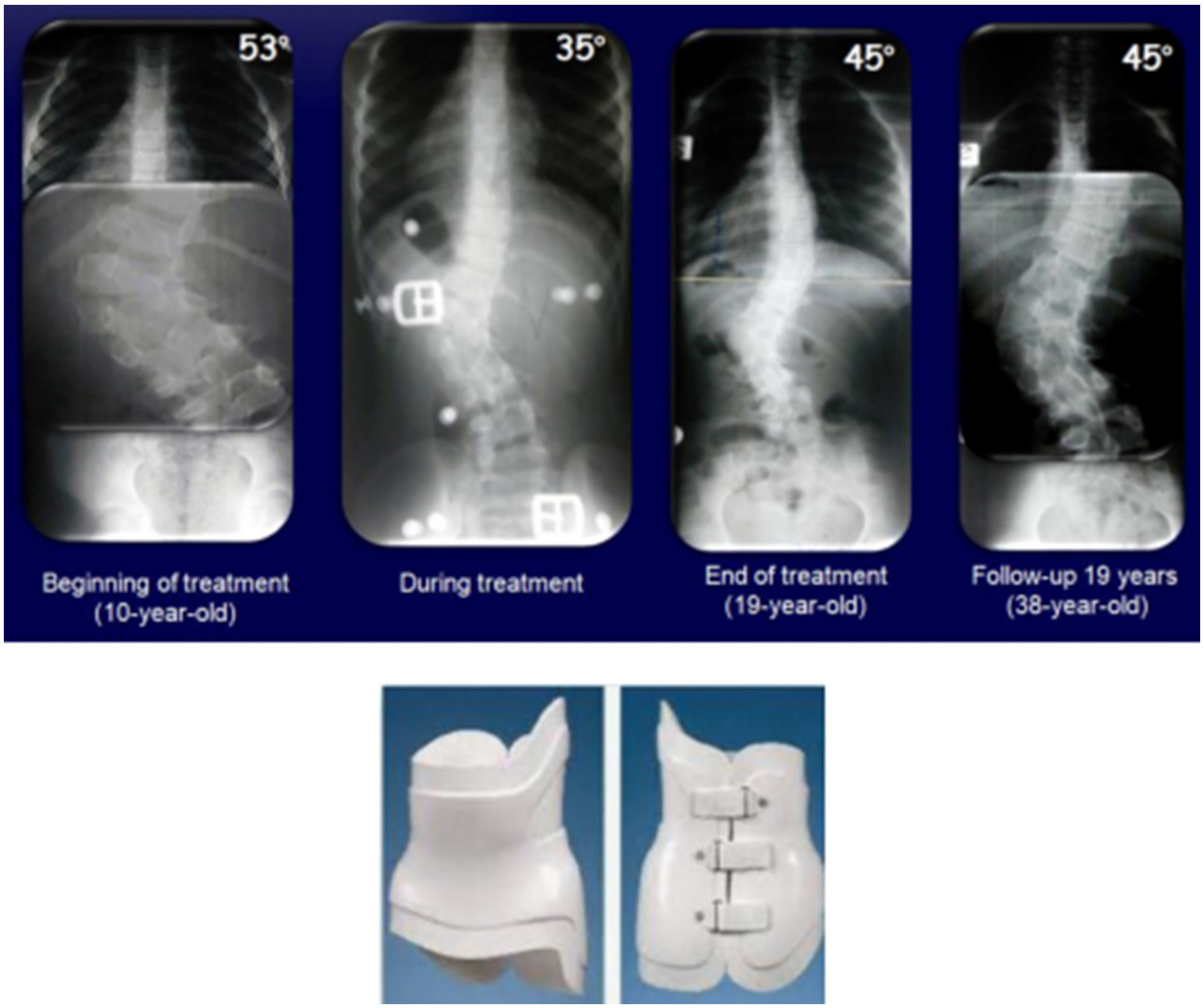

FIGURE 2
A 10-years-old female with a hemivertebra in L2 and a T11-L4 (L5 sacralized) curve treated with the Boston brace for first year and then the PASB.

of segmentation, surgery is performed as early as possible in an attempt to control the relentless progression of the curve. Instead, in cases of failure of formation, as the ones reported, the indication of surgical or conservative treatment is not so mandatory.

These cases we have just presented show that bracing can be considered as a valid and effective treatment of CS due to hemivertebra, also considering that the fully-segmented hemivertebrae are the most likely to progress.

The age of discovery of scoliosis is an important factor (10). The three patients we have presented were treated after 2 years of age and thus were beyond the major risk of progression. However, the risk of progression in congenital curves is throughout the growth period, and starting a conservative treatment before the age of two is very difficult.

The conservative treatment is to be extended over time compared with a surgical approach. For this reason, the compliance of patients is often difficult and many prefer to undergo surgery to reduce treatment duration; however, the complication rate of surgical treatment could be greater compared with bracing treatment.

It should be noted that, to date, little data exists in the literature regarding the effectiveness of conservative treatment in CS.

In 2011, a comprehensive review was performed by Kaspiris et al., to support the assumption that early surgery is recommended in patients with congenital scoliosis. No supporting evidence for early surgical intervention was identified in this group of patients. The authors reported the effectiveness of spinal surgery in the control of deformities, but also remarked on relatively high rates of complications

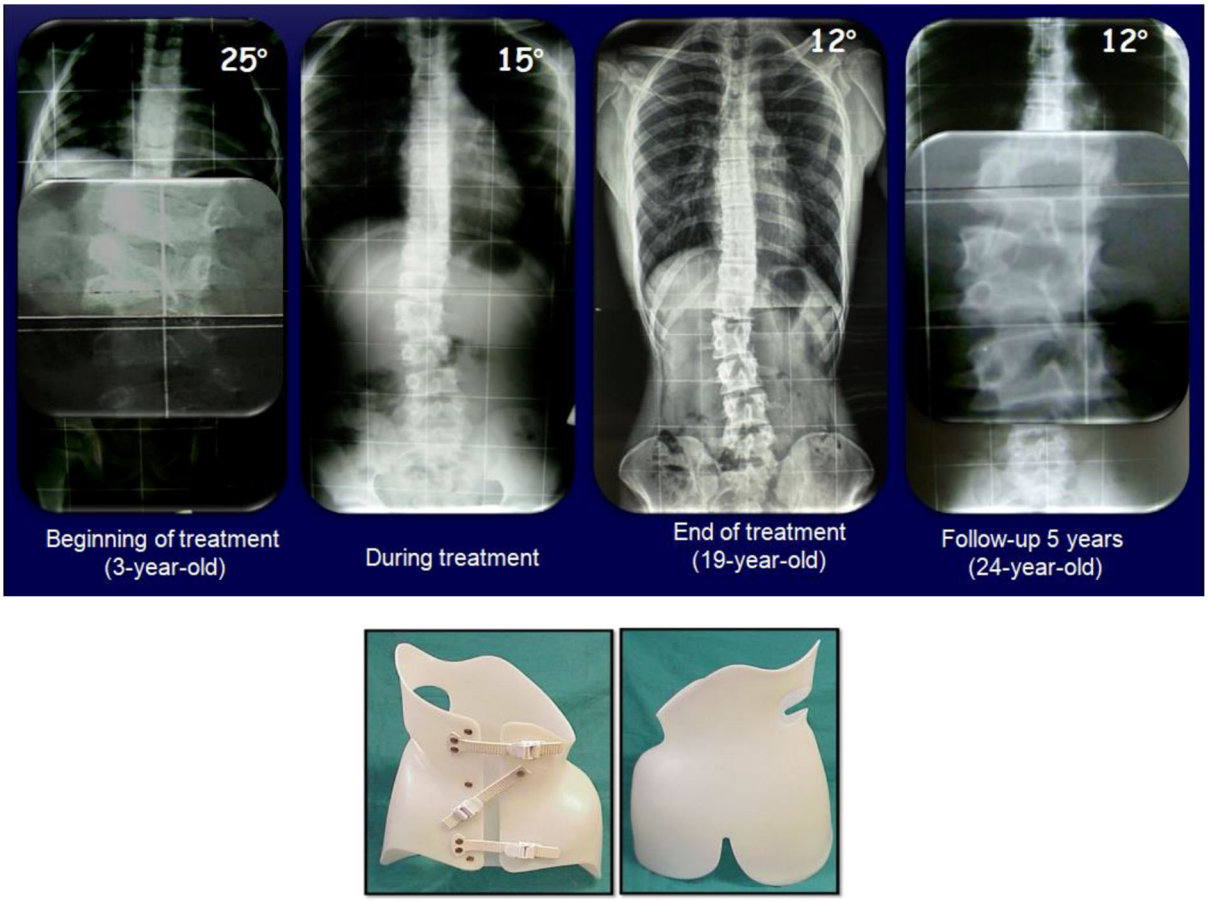

FIGURE 3
A 3-years-old male with a hemivertebra in L3 (in a 6 lumbar body) and a T12-L4 curve treated conservatively the PASB.

(up to 31%), such as implant failure, deep infection, low back pain, reduction of pulmonary function, and thoracic insufficiency syndrome (in early spinal fusion), pseudoarthrosis and neurological disorders such as neurapraxia.

Surgical indications for severe cases with rib synostosis and unilateral bar (failures of segmentation) are not in doubt. Nevertheless, formation failures frequently do not evolve and should not require surgical treatment first. For this reason, the authors concluded that, before contemplating a surgical procedure, consulting an expert in conservative management of congenital spinal malformations should be the first step looked at (2).

A Pub Med review published by Weiss in 2016 (15), as an update of the search made in 2011 with Kaspiris, was performed from 2011 to March 2015 searching for studies in support of congenital scoliosis early surgery. The Author concluded that there is no evidence (as regards randomized controlled or prospective controlled outcome studies) supporting the assumption that early surgical intervention in patients with congenital scoliosis is better than no treatment or bracing.

Chêneau et al. reported a case series of seven patients with congenital vertebral failure of formation treated conservatively with the Chêneau brace (16). They recorded an important correction of wedge angle, Cobb angle, and Chêneau index after 1 year of conservative treatment with a brace. At 2 years of follow-up, the radiographic findings had not changed significantly, but improved somewhat, concluding that bracing allows at least control and, in some cases, correction of congenital deformities of the spine.

In a case series published in 2008, Weiss reported three patients treated conservatively (two with failure of segmentation and one with failure of formation) with braces and Scoliosis In-Patient Rehabilitation (SIR) (14). In the two cases of segmentation defect, the brace treatment was at least able to avoid severe respiratory decompensation. The patient with formation failure showed balanced growth with no aesthetical or functional complaints to date, even though the curve

evolved because of final poor compliance. Weiss concluded that brace treatment can be at least in part helpful in failures of segmentation, while it should be recommended first in failures of formation.

A review of the literature from 2005 to 2016 focused on surgical and conservative management of congenital scoliosis was published by Pahys et al. (17). They selected several articles in which brace treatment was not used only as an alternative to surgery, but also as a delay-tactic to surgery. They reported that considering the potential complications of impaired pulmonary function and crankshaft phenomenon related to early long spinal fusions (18) together with the complications and concerns of growth-friendly surgery (19), serial derotational bracing was described as a valid "time-buying strategy" for the treatment of congenital scoliosis (20, 21).

Another more recent study with long-term follow-up published by Weiss et al. (22) reported an 18-month-old boy with relatively balanced formation failures (hemivertebra in T7 right and another one in L1 left) and the main curve in the thoracolumbar area measuring 52° of Cobb angle. Conservative treatment with a Chêneau spinal brace began promptly and the wearing time of the brace was 18 h/day, in the beginning, and between 7–11 years it was reduced to 12 h/day because of low growth dynamics and at the inception of puberty was increased again about 20 h/day. Until age seven, the main curve steadily decreased to an angle of 40° Cobb, at 13 years, it progressed back to 50° Cobb and at 15 years it further progressed to 58° Cobb after the loss of compliance. Sporadic clinical and radiological controls were performed during 22 years of follow-up and, at the final assessment at the age of 24, the main curve of 63° Cobb was calculated.

The patient's clinical appearance was satisfying, he was normally painless and reported a good quality of life. The authors concluded that, as opposed to the conventional surgical approach, early surgical intervention for vertebral formation failures is not imperative. Patients with disorders of vertebral formation should not undergo early surgical procedures before trying an adequate treatment with a brace.

As regards Juvenile Scoliosis (JS), Canavese et al., reported encouraging results with the Elongation, Derotation, and Flexion (EDF) casting technique, in particular, if performed under general anesthesia and neuromuscular blocking drugs (23). They reported that acting simultaneously in sagittal, frontal, and axial planes, EDF casting technique can control the evolution of the deformity and, sometimes, coax the originally curved spine to straighten up, demonstrating the effectiveness of conservative treatment even in older subjects.

Conclusions

Comparing our cases with those found in the literature we can confirm the ability of conservative treatment to change the natural history of congenital scoliosis due to failure of formation. In congenital scoliosis, aggressiveness can vary but the evolution of the congenital curve is certain. So, the treatment, given the natural progression, should be implemented as early as possible without waiting for the evolution of the curve, contrary to what occurs in lower idiopathic scoliosis. Conservative treatment, in fact, is to prevent the deformation of the adjacent vertebrae to hemivertebra that, if left to its potential deforming, induce a progressive deformation of the adjacent normal vertebrae. Once enlarged, and the deformity to the adjacent vertebrae occurs, the remodeling capacity of conservative treatment results tends to be low. Although conservative treatment with these guidelines is to be extended over time, the benefits, compared to the output and complications of surgical treatment, are evident.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Anterolateral congenital tibial bowing: case report

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Background: The treatment of congenital curvatures (bowing) of the tibia still represents a challenging problem for all pediatric orthopedic surgeons because of its unpredictable course, especially if pseudoarthrosis occurs after a pathologic fracture of the tibia.
Case presentation: We describe the case of a child affected by an isolated curvature of his left leg. The congenital malformation was discovered at birth and no other pathological clinical finding was present. The first x-ray showed the presence of a congenital curvature of the tibia of the antero-lateral type. He was born in another country (Romania) and when he first came to our clinical observation at the Orthopedic and Traumatology Department, Pediatric Hospital "Bambino Gesu'", Rome, the child was 14 months of age and had already started walking. Only a leg discrepancy of about 2 cm was present with consequent pelvis obliquity. At the beginning, we prescribed external lower limb orthoses and a simple shoe rise to prevent a tibial pathologic fracture and reduce pelvic obliquity. At periodical clinical follow-up visits and despite the external lower limb orthoses prescribed, a progressive worsening of the severe congenital tibial curvature was observed together with signs and symptoms, such as pain and limping, that suggested an objective "pre-fracture stage" of the tibial curvature; we decided to perform surgery. At the time of surgery, the child was three and a half years old. Surgery consisted of a double osteotomy, both of the fibula and of the tibia. Subtraction of the distal meta-diaphyseal portion of the fibula and tibial osteotomy in correspondence of the major anterolateral curvature. The tibial osteotomy was then stabilized by an internal Rush rod inserted proximally to the tibia under the cartilage growth plate and made it end inside the distal tibial epiphysis, crossing the distal tibial cartilage growth plate, preserving the ankle joint.
Results: The patient had an immediately excellent outcome. The tibial osteotomy site healed perfectly. At periodical orthopedic follow-up visits, the child was found to be always better. No clinical significative evidence of growth disturbances, due to the Rush rod that crossed the distal tibial cartilage growth plate, were noted. X-rays showed that the Rush rod progressively migrated with tibial growth together with the tibial bone growth, always getting further away from the distal tibial cartilage growth plate. Moreover, even the leg-length discrepancy and the pelvic obliquity improved. After an eight-year follow up, the patient, now a young boy of 11 and a half years, has an excellent outcome.

Conclusions: Our case report undoubtedly provides further important information for the treatment of these rare congenital disorders. In particular, it highlights the management of the "pre-fracture stage" in a severe congenital tibial antero-lateral curvature in a very young child and describes the surgical technique performed.

KEYWORDS

congenital tibial bowing, congenital tibial pseudarthrosis, lower limb defects in children, congenital long bone curvatures, intramedullary tibial nail in children

Introduction

Congenital bowing of the tibia is a rare condition, affecting one child every 140.000/190.000 births. It is usually noted at birth or shortly after and is considered the precursor of congenital pseudarthrosis of the tibia (CPT) (1, 2).

It is usually associated with genetic disorders such as neurofibromatosis type 1 (NF1), fibrous dysplasia, amniotic band syndrome, osteogenesis imperfecta, and bone fibromas (1).

Congenital bowing of the long bones can be more or less generalized or can regard a single bone segment, essentially the tibia point and in such last cases the condition is described as isolated curvature or "bowing" of the tibia. Several classification systems have been proposed to cover the spectrum of this condition; the most used is the one that describes three types of congenital curvatures of the tibia, referring to the convexity of the curvature always present at the distal third portion of the tibia: (1) antero-lateral, (2) posterior or posteromedial, and (3) anterior or anteromedial. The prognosis of these congenital disorders is very different (3).

The anterolateral bowing type is the one that often evolves into "secondary pseudarthrosis" of the tibia, although a benign form has been described (2–5). The prognosis of such congenital curvature must always be reserved since the surgical treatments are often very uncertain (4).

The posterior or posteromedial tibial curvature type is usually benign and presents a good prognosis. It is spontaneously regressive and surgical treatment can be considered without hesitation (4).

The anterior or anteromedial bowing type is often associated with congenital fibula defects, like aplasia or hypoplasia (6). The prognosis of this last type is also favorable.

The treatment for congenital curvatures of the tibia still represents a challenging problem for all pediatric orthopedic surgeons because of its unpredictable course if pseudarthrosis occurs after a pathologic fracture of the tibia.

Except for the resolving form, the natural history of anterolateral bowing, Crawford's type 2, is unfavorable if a fracture occurs and there is little tendency for the lesion to heal spontaneously despite the several surgical treatment options available, leading to amputation (5–7).

Because in the majority of cases, CPT is not present at birth, the term "congenital pseudarthrosis of the tibia" is somewhat inaccurate because only the underlying disease process and deformation of the tibia are usually present at birth, and is often just a question of time before a first fracture occurs (6).

Many treatment options are available for this disease, including both operative and non-operative options based on the severity of the condition (8–13).

Among the existing classification schemes that provide management guidance for these rare congenital disorders, Paley (2019) classified this condition based on severity, treatment, and prognosis (9).

In CPT, periosteal anomalies seem responsible for the curved dysplastic tibial bone that does not heal after a fracture. Thus, periosteal replacement addresses the pathogenesis of this disorder. As early as 1906, Codivilla proposed the concept of periosteal substitution (14, 15).

It is incredible that such a rare disorder still receives so much attention in the orthopedic literature. Pseudarthrosis of the tibia poses one of the most challenging treatment problems for all orthopedic surgeons because of the compounded difficulty of achieving and then maintaining union and simultaneously providing a functional extremity (6, 9).

There is a general pessimism as to the quality and longevity of any union that may be obtained, and the ultimate future function of the leg is uncertain. Although many treatment options exist, the fact that no one option has ever achieved long-lasting success with great frequency indicates that there is no single treatment for pseudarthrosis of the tibia (CPT) that will produce acceptable results in any predictable fashion (4, 9). The first step is to prevent fractures and give a normal alignment to the leg with or without fixation. There is no consensus on the appropriate age for surgery (16).

Initial treatment of tibial bowing deformity includes stretching, serial casting, or splinting. In many cases, a 50% correction of the deformity is usually observed by the age of two years, though a mild deformity often persists. Only significant deformity that interferes with growth may be an indication for tibial osteotomy, especially if little or no correction is seen by the age of two years or there is symptomatic and persistent deformity (17).

Many methods of treatment have been described for CPT, including mechanical (e.g., external fixators, nails), biological (e.g., free vascularized fibular graft, non-vascularized periosteum), and pharmacological (e.g., BMP, bisphosphonates) approaches as well as their combined use (18, 19). Together, these approaches have resulted in an amputation rate of 50% due to failure to achieve union in 20%–50% of cases and the occurrence of re-fractures in 30% of patients (18). The reported rate of bone union using several surgical techniques was 20%–50%, while bone union has been achieved in 100% of the cases treated with contralateral vascularized periosteal tibial graft transplantation (15). Longer follow-up for a refracture-free rate is needed to consider it safe enough to recommend it as a standard approach.

Another encouraging recently reported technique to treat CPT is the cross-union technique which also yielded excellent results with a 100% union rate with a seven-year mean follow-up (8, 9).

Short-term treatment for CPT is a serious weakness for any study regarding this topic. Furthermore, in another recent paper, contrary to much of the established practice, osteotomies may be safely performed in CPT (19).

All these techniques represent new tools for the surgical treatment of these congenital disorders and these recent papers are showing excellent outcomes in obtaining bone union and reducing amputation rates for these conditions.

All together, furthermore, provide more information to all pediatric orthopedic surgeons who deal with such biologically complex situations and can finally start choosing the best reconstructive strategy for any of these singular congenital rare cases.

Current treatment protocols focus primarily on combining intramedullary fixation with external or internal fixation to achieve union rates between 74% and 100% (20). Intramedullary devices should be retained as long as possible to prevent refracture. Cross-union techniques, though technically difficult, have a reported union rate of 100% with no refracture at mid-long-term follow-up. Vascularized fibular grafting and induced membrane techniques can be successful but at the cost of numerous surgical procedures. Growth modulation is a promising new approach to preventing fractures altogether, though further study with larger patient series is necessary (15–22).

In this paper, we will limit the description and considerations on CPT and focus on our case report that contributes further significative information regarding the treatment and management of these rare congenital disorders.

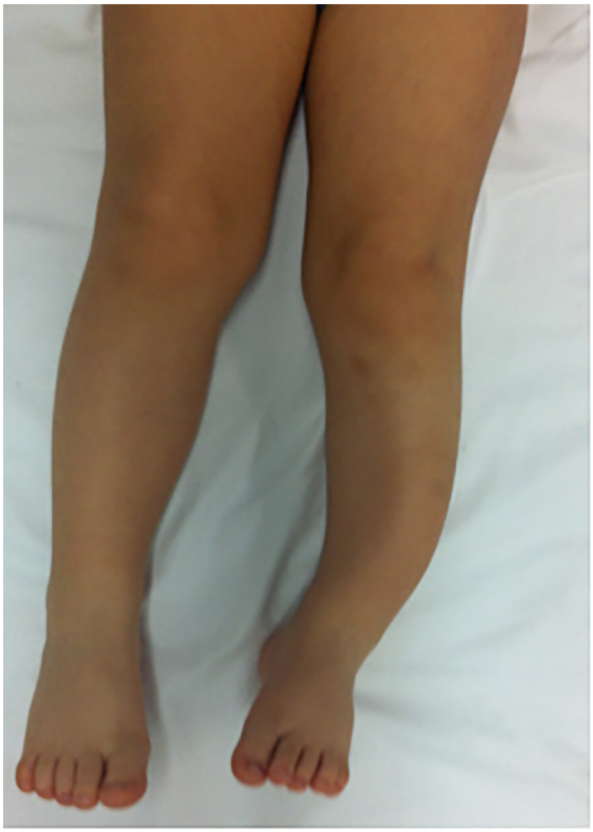

FIGURE 1
Congenital curvature malformation of the distal third portion of the left leg of a three and a half year old child. Anterolateral type of congenital tibial bowing. Leg-length discrepancy is present.

Case report

We describe a case of a young child affected by an isolated curvature of his left leg (**Figure 1**). The congenital malformation was discovered at birth and no other pathological clinical finding was present. The first x-Ray (**Figure 2**) showed the presence of a congenital curvature of the tibia of the anterolateral type. He was

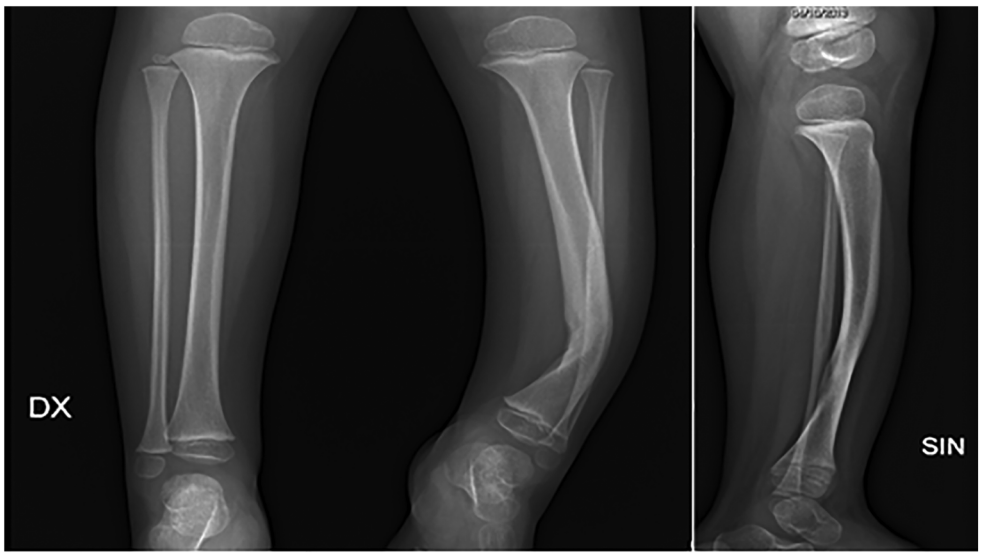

FIGURE 2
Initial x-rays (AP and LL view) of the anterolateral congenital tibial curvature.

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born in another country (Romania) and when he first came to our clinical observation at the Orthopedic and Traumatology Department, Pediatric Hospital "Bambino Gesu" in Rome, the child was 14 months of age and had already started walking. Only a leg-length discrepancy of about 2 cm was present with consequent pelvis obliquity.

In the beginning, we prescribed an external clamshell left limb orthoses and a simple shoe lift to prevent a tibial pathological fracture and reduce pelvic obliquity. After several months, despite the external orthoses, at a periodical clinical orthopedic follow-up visit, the child started to show clinical signs and symptoms such as pain and limping on his left leg together with an objective worsening of his congenital tibial curvature. The child's pain was primarily focused on the major convexity of the curvature of his left leg where we observed a little swelling beginning and his joints, left knee, and ankle were starting to suffer, for obvious biomechanical reasons, causing his limping. He did not manifest low-back pain and his leg-length discrepancy appeared to have worsened to about 2.5 cm. At that point, we understood that the child was headed towards the "pre-fracture stage" of his congenital severe tibial curvature and together with his parents we decided to perform surgery to prevent the pathological fracture (**Figure 3**). At the time of surgery, the child was three and a half years old.

Surgery consisted of a double osteotomy, both of the fibula and the tibia. Subtraction of the distal meta-diaphyseal portion of the fibula and tibial osteotomy in correspondence with the major anterolateral curvature. The tibial osteotomy was then stabilized by an internal Rush rod inserted proximally to the tibia under the cartilage growth plate and made it end inside the distal tibial epiphysis, crossing the distal tibial cartilage growth plate and preserving the ankle joint. The Rush rod was modified with a slight curvature of its distal portion to allow the correct proximal insertion and stabilization of the tibial osteotomy site.

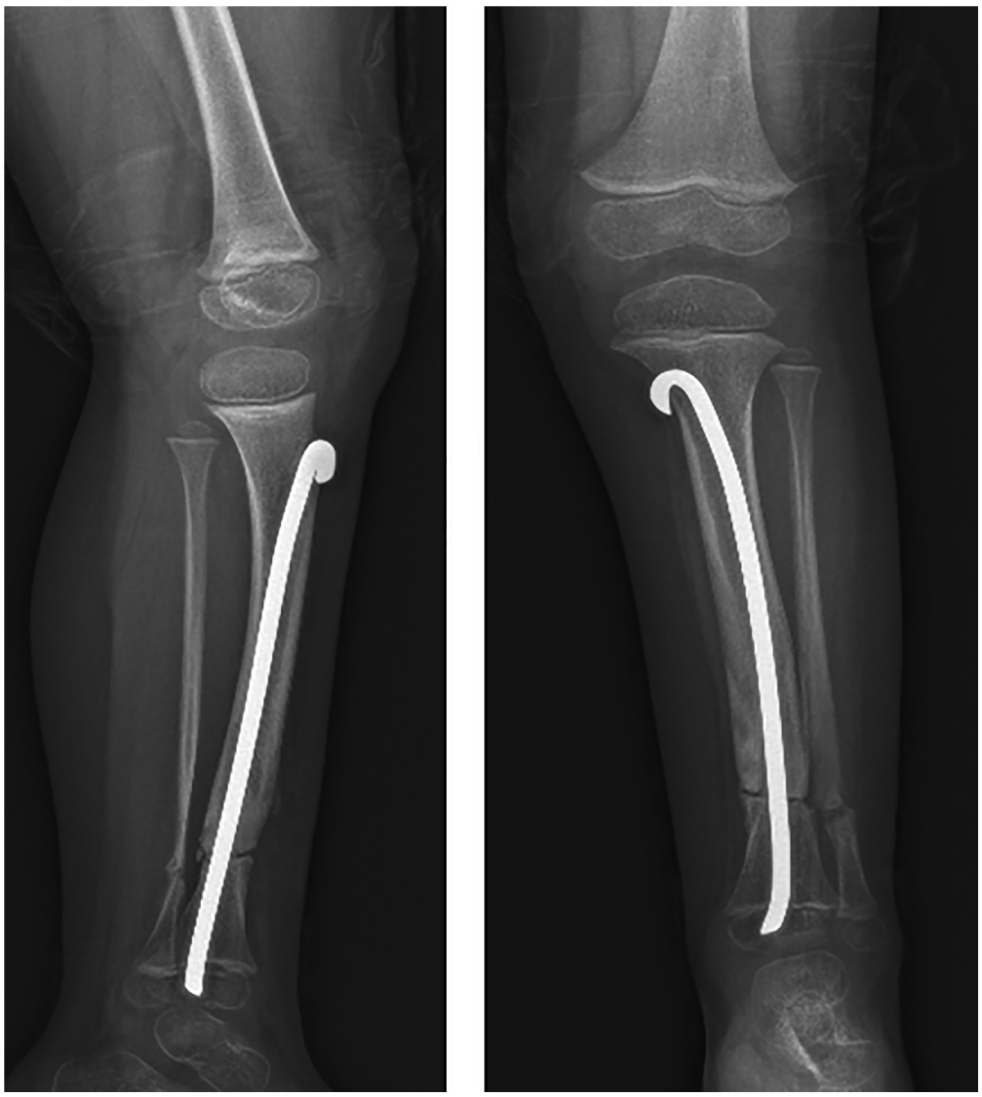

FIGURE 3
X-ray that shows the rush rod inserted across the distal tibial cartilage growth plate, preserving the ankle joint. Tibial and fibular osteotomy sites are evident.

After surgery, the child's left leg was immobilized with a "femur-foot cast" for 50 days and then with a "boot cast" for a further 30 days. After this period, we again prescribed external clamshell orthoses for the beginning of the walking phase. The child maintained the external orthoses for approximately one year from surgery until the osteotomy site appeared stable with an x-Ray showing advanced tibial bone healing process. The child was only allowed to swim without diving and was not allowed to jump or run for the first year after surgery.

Results

The patient a few months after surgery and from cast removal soon had an excellent clinical outcome. The tibial osteotomy site healed slowly and after six months from surgery was perfectly healed. At periodical orthopedic follow-up visits, it was found always to be better. Any clinical significative evidence of growth disturbances, due to the Rush rod inserted across the distal tibial cartilage growth plate, was noted; rather, x-rays showed that the Rush rod progressively migrated upwards together with tibial growth. Moreover, even the leg-length discrepancy and the pelvic obliquity improved, from the initial 2.5 cm to 0.5 cm. After eight years of follow-up, the patient, now a young boy of 11 and a half years, has an excellent clinical outcome without pain or lower limb dysfunction (**Figure 4**). We still did not remove the Rush rod because we were always afraid of having to deal with an unpredictable tibial pathological fracture, but we are now seriously considering removing it soon.

Discussion

Congenital pseudarthrosis of the tibia is a rare and challenging pediatric condition. The "pre-fracture stage", called congenital tibial dysplasia or anterolateral bowing of the tibia, presents a high fracture risk due to underlying bowing and dysplasia. After a fracture, there is a substantial risk of non-union (8, 9). Any union achieved may be complicated by re-fracture, deformity, leg-length discrepancy, stiffness, pain, and dysfunction (8, 9, 21).

The primary consideration in the treatment of CPT is the expected union rate and re-fracture risk. Combined intramedullary and external or internal fixation, especially with cross-union techniques, show the most promise. Perhaps most exciting is further research on preventing fractures through guided growth, which may reduce the morbidity of multiple surgical procedures which have been the mainstay of treatment for CPT thus far (19–22).

Our case report surely contributes further important information for the treatment and management of these rare congenital disorders. In particular, it prevented tibial fracture or pseudarthrosis, decreased tibial malalignment, improved the radiographic appearance of bone quality, and improved leg-length discrepancy. No growth disturbances were observed for the Rush rod inserted across the distal tibial cartilage growth plate. Instead, the preservation of the ankle joint from the Rush rod insertion determined a normal ankle joint, avoiding dealing with other problems such as stiffness, limping, chronic inflammation, and weight-bearing pain and dysfunction.

We modified the distal portion of a Rush rod, giving it a slight curvature that allowed us to proceed in a correct surgical manner

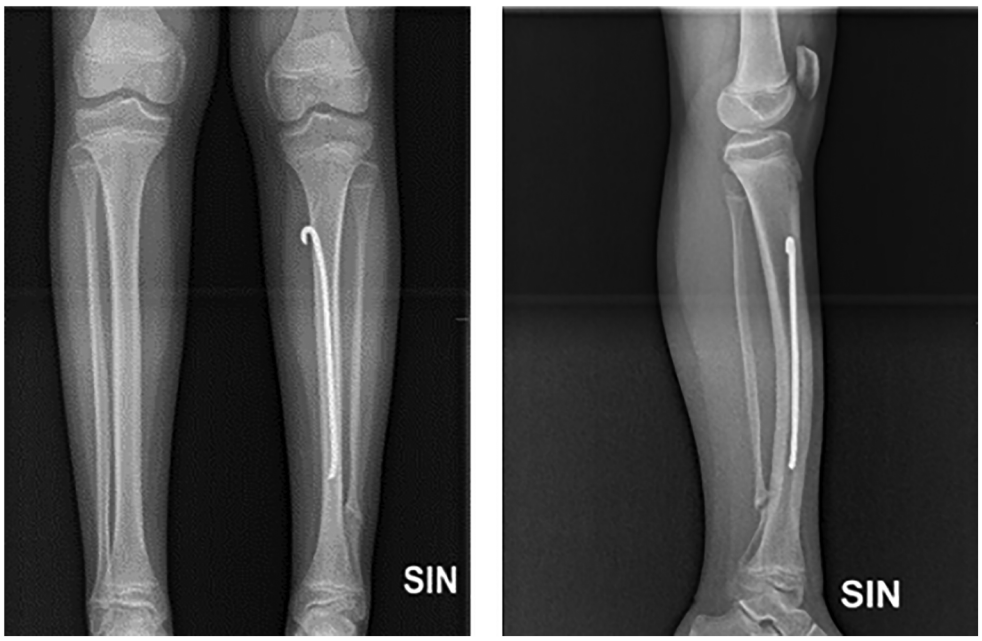

FIGURE 4
X-ray after eight-year follow-up. The rush rod is far away from the distal tibial cartilage growth plate. The tibial osteotomy site is perfectly healed. No growth plate disturbances are present.

for its proximal tibial insertion under the tibial cartilage growth plate. The Rush rod was then inserted into the endomedullary tibia, with a proximal-distally direction. The rod crossed the tibial osteotomy site and we made it end inside the distal tibial epiphysis, crossing the distal tibial cartilage growth plate, preserving the ankle joint.

Conclusion

Despite the rarity of this condition, a lot of work has been done in this area.

Initial treatment of tibial bowing deformity includes stretching, serial casting, or splinting. Indication for a tibial osteotomy may be justified only in a significant deformity that interferes with growth, especially in young patients, if no correction is obtained by the age of two years or if symptomatic and severe deformity persists (17).

Several recent studies on the surgical treatment for CPT are now available in the literature that are showing encouraging results, such as: "Congenital pseudarthrosis of the tibia: Rate of and time to bone union following contralateral vascularized periosteal tibial graft transplantation" (15); the "Cross-Union Technique" (8); "Distal Tibial Guided Growth for Anterolateral Bowing of the Tibia: Fracture may be prevented" (21); and "Does An Osteotomy Performed in Congentital Pseudarthrosis of the Tibia Heal?" (19).

In our case report, no metal changes due to the steel Rush rod utilized for the intramedullary tibial nailing were observed and, as mentioned above, we are seriously considering removing it soon. In addition, we did not use other adjunctive treatment options like preoperative bisphosphonates and/or BMP-2, as reported in recent papers (19).

We suggest the method described in this paper only for severe cases of congenital tibial curvatures that clinically appear to undergo a pathological fracture that can lead to CPT.

The surgical treatment method described gave us an excellent outcome at an eight-year follow-up, even if we had to wait, in the beginning, about six months to achieve a good bone union at the osteotomy tibial site, which was perfectly in line with recent papers (19).

All these techniques represent new tools for the surgical treatment of these congenital rare disorders and recent papers are showing excellent outcomes in obtaining bone union and reducing amputation rates for these conditions.

We are all confident and hopeful for the other existing surgical trends that are all showing excellent outcomes for CPT and its complications, achieving bone union, reducing re-fracture and the morbidity of multiple surgical procedures, and not least the decreasing of the percentage of amputation rate (15, 19, 20).

Altogether, this undoubtedly provides much information to all pediatric orthopedic surgeons who deal with such biologically complex situations and who can finally start choosing the best reconstructive strategy in each of these singular congenital rare cases.

Our case report described together with the relative surgical technique performed could be considered as an initial surgical treatment option for these severe anterolateral congenital tibial curvatures during the "pre-fracture stage" and that all the other surgical treatments available can be considered in later phases.

The management of the "pre-fracture stage" in severe congenital tibial curvature disorder together with the surgical technique performed, as described in our case report, to our knowledge, has never been reported in the literature.

It produced a satisfactory long-term functional outcome and adds further important information to keep in mind for the management of such congenital rare disorders, even during the "pre-pathological fracture stage".

Written informed consent for the publication of this case report, with all data and images, was obtained from the child's parents, and the Scientific Committee of "Bambino Gesu'" Pediatric Hospital, Rome, gave the approval for its publication.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics Statement

Written informed consent for the publication of this Case Report, with all data and images, was obtained from the child's parents.

Author contributions

All authors contributed, improved and reviewed the article. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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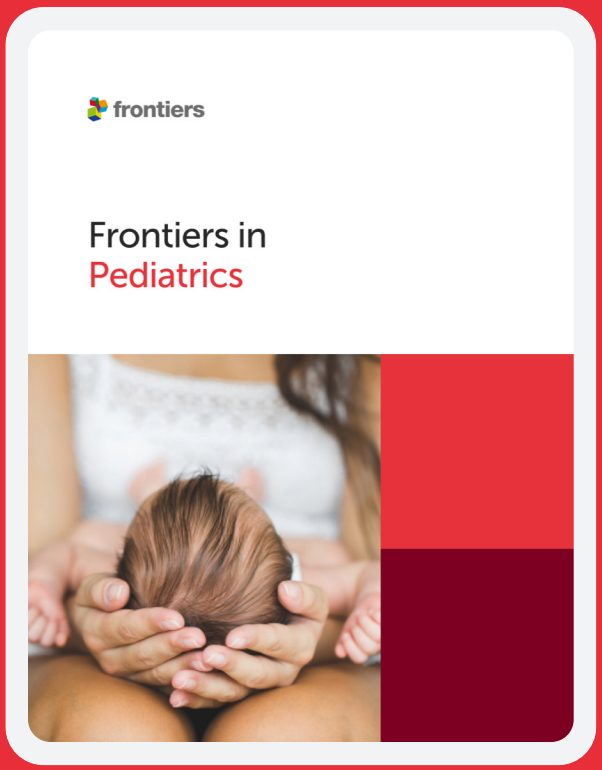

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