Case Report
Characterization of a rare case of a bone bridge formed by osteochondromas associated with a novel EXT2 mutation in a patient with hereditary multiple osteochondromas

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Abstract: Hereditary multiple osteochondromas (HMO) is an autosomal dominant bone disorder that presents as multiple benign cartilage-capped tumors. The major morbid genes EXT1 and EXT2 account for 90% of HMO cases. In HMO patients, osteochondromas appear adjacent to the physis and remain in the metaphyseal lesion of the long bones. Consequently, it is uncommon for osteochondromas to form a bone bridge in the inferior tibiofibular syndesmosis. We present a rare case of a 20-year-old female patient with HMO with limited flexing range in her left ankle joint. Based on plain radiographs, a bone bridge formed by osteochondromas was situated in the distal tibiofibular syndesmosis of her left ankle. A novel nonsense mutation, c.67C>T p.Arg23X in exon 2 of the EXT2 gene, was discovered; we inferred that this mutation was the cause of HMO.

Keywords: Hereditary multiple osteochondromas, EXT2, bone bridge, nonsense mutation

Introduction

Osteochondromas, also called osteocartilaginous exostoses, are benign growths capped with hyaline cartilage; they represent the majority of bone tumors. Solitary osteochondromas are not inborn, but develop in a single bone. Hereditary multiple osteochondromas (HMO), is an autosomal dominant disorder characterized by the abundant duplication of a solitary exostosis [1]. Genetic studies have demonstrated associations between HMO and three loci, EXT1 [2], which maps to 8q24.1, EXT2 [3], which maps to 11p13, and EXT3 [4], which is located on the short arm of chromosome 19 (the exact position is unknown). An estimated half of all HMO patients have EXT1 mutations, and one-third have EXT2 mutations [5].

The size and number of osteochondromas often increase during childhood and adolescence. In fact, these tumors can occur on almost every bone, including the short bones, flat bones, and irregular bones, though they are preferentially located at the juxta-epiphyseal region of the long bones [6]. Patients with HMO typically have no symptoms, unless the pressure exerted by the osteochondroma affects the adjacent muscles, tendons, nerves, or blood vessels [7]. The clinical manifestation is often related to this pressure and includes pain, angular deformities, short stature, restricted joint motion, fracture of the lesion itself, inflammatory changes of the bursa exostotica covering the cartilaginous cap, and even malignant transformation [8].

Osteochondromas generally develop in the growth plate of the long bones of children and subsequently grow toward the diaphysis [9]. Bone bridges formed by osteochondromas are a rare phenomenon. In these cases, patients can experience pain and discomfort as well as a restricted range-of-motion.

In this study, we performed clinical, imaging, histological, and genetic analyses of a patient with typical HMO with a bone bridge formed by
osteochondromas located in the distal tibiofibular syndesmosis of her left ankle. To the best of our knowledge, this is the first reported incidence of a HMO patient with a bone bridge formed by osteochondromas. Based on a genetic analysis of the patient and her family members, we detected a novel nonsense mutation, c.67C>T p.Arg23X, near the EXT2 exostosis domain that results in a protein truncation of 705 C-terminal amino acids.

Case report

Five and half years ago, a 20-year-old, short-statured female patient presented at our clinic with multiple elevated bony prominences and a limited ability to bend her left ankle for approximately 1 year. She had no history of trauma. The bony prominences and shape anomalies were asymptomatic and were initially observed when she was 4 years old. They progressively increased in size and extent. She first experienced pain when her left ankle was at its maximum bending angle seven years prior to visiting our clinic, and she experienced progressive limitation in vigorous activity. The patient was also uncomfortable with the appearance of the multiple osteochondromas.

The patient had a family history of HMO on the paternal side. Her father, aunt, and paternal grandfather also had short statures and multiple elevated exostoses in various locations, but they had no limitations in joint mobility and no notable symptoms. The pedigree of this Chinese family is shown in Figure 7.

A physical examination revealed multiple bony prominences around her right knee and wrist, with hard, clear boundaries, no activity, and no tenderness. However, there was significant pain in the left ankle joint during loaded flexion. Although the left ankle was capable of activity, the maximum dorsiflexion was 10° and the maximum plantar flexion was 30°. The circumference of the left ankle was 4.5 cm longer than that of the right ankle. The function of her left ankle was normal. Plain radiographs revealed exostoses in the right distal radius, bilateral distal femur, and bilateral proximal tibia, and a bone bridge in the distal tibiofibular syndesmosis of the left ankle (Figure 1).

Surgical excision was performed owing to the pain and limited motion experienced by the patient and the unknown nature of the lesion. Under general anesthesia, the patient was
placed in a supine position on the operating table. Sandbags were placed under the ipsilateral hip to easily reveal lateral and forward positions. We observed a decreased bending range, with a maximum dorsiflexion angle of 10°. We make a lateral fibular incision of approximately 10 cm to reveal the fibula. We stripped the periosteum of the leading edge of the fibula and exposed the bone tumors at the distal tibiofibular syndesmosis. We observed a bone tumor compressing the fibula at the distal tibiofibular syndesmosis, and cut the fibula at the distal tibiofibular syndesmosis. After the complete resection of the tumor, we reset the fibula using nickel clad and screws. During surgery, C-arm fluoroscopy revealed that the fibula was well-positioned on the line and the fixed position was good. A dramatic improvement was observed in the bending range, with a maximum dorsiflexion angle of 20°, which indicated that the bone bridge was preventing the right knee from bending fully. For aesthetic reasons, the protuberant extra-articular osteochondromas in the tibia and the femur around her right knee were resected via small incisions.

Pathological analyses of the bone tumors indicated typical HMO (Figure 5B). After surgery, the pain during loaded flexion in the left ankle was dramatically relieved. Two years after the removal, the knee was symptomless and no signs of recurrence were detected in a radiograph analysis. Two years later, the patient removed the internal fixation of fibula devices. Six months ago, the patient felt soreness, pain, and limited mobility in the left ankle. A physical examination revealed decreased activity of the ankle. Plain radiographs and CT showed that a bone was protruding in the left tibia near the ankle (Figure 3). Surgical excision was performed, using the original approach, owing to the pain and limited motion experienced by the patient and because the exact nature of the lesion was not known. We detected the bony fusion at the distal tibiofibular syndesmosis, which then we resected completely and sent to pathology (Figure 5A). We used a plate and screw at the outside of the fibula and fixed the distal tibiofibular syndesmosis by syndesmosis screw fixation.

To identify the genetic basis of HMO in our patient, each exon of EXT1 and EXT2 was sequenced in the patient and three affected family members (I1, II2, II3, and III1) as well as four unaffected family members (I2, II1, II4, and III2). After data filtering procedures, we discov-
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Figure 5. A: Pathological analyses revealed mostly mature bone tissue and local cartilage ossification. B: Pathology revealed hereditary multiple osteochondromas with three layers (i.e., fibrous perichondrium, cartilage cap, and bone).

Figure 6. The heterozygous nonsense mutation c.67C>T (p.Arg23X) was detected in the EXT2 gene of HMO patients, but not in the healthy controls.

Discussion

Most osteochondromas are not hereditary and occur singly [10, 11]. However, approximately 15% of patients have two or more osteochondromas [12, 13], and the vast majority of these patients (over 70%) have a family history indicating HMO. Although they are benign tumors, there are common complications in patients with HMO, including abnormal skeletal growth, bone deformities, and short stature (37%), limited joint mobility and early-onset osteoarthritis (14%) [13], pain due to nerve compression (22.6%), blood circulation disorders caused by vascular compression (11.3%), and so on. Hand deformities caused by short metacarpals are also common [5, 14]. There are also more serious complications; osteochondroma can become chondrosarcoma or osteosarcoma, and the rate of malignant transformation is approximately 0.5% to 2% [12, 15, 16].

Bone bridges formed by osteochondromas are rare in patients with HMO and have not been described previously. The bone bridge not only made the fibula diastrophic, but also injured the distal tibiofibular syndesmosis, affecting ankle function. The syndesmosis maintains the structural stability of the ankle joint. Ankle fractures are often combined with varying degrees of tibiofibular joint damage, resulting in chronic ankle instability and traumatic arthritis.

For orthopedic or functional reasons, approximately 75% of patients with HME accept one or more osteochondroma surgical procedures [15]. The patient in our case study accepted surgery to resect the osteochondroma and correct the force line of the fibula. Injury of the distal tibiofibular syndesmosis without fracture is uncommon [17-22]. Our understanding of the disruption of the distal tibiofibular syndesmosis is insufficient, and it was not resolved during the first operation. After removing the fixation, instability of the ankle may have caused hyperostosis at the distal tibiofibular syndesmosis. There is still no gold standard for the treatment of chronic disruption of the distal tibiofibular syndesmosis, although several relevant techniques have...
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been reported [23-32]. Harper used a similar surgical technique to ours for an external rotation stage 4 fracture and evaluated the performance of syndesmosis screw fixation with or without syndesmosis debridement in 6 patients with chronic disruption after pronation [24]. The efficacy of arthroscopic debridement of the distal tibiofibular syndesmosis and medial gutter with percutaneous fixation of the syndesmosis using screws, which is a less invasive technique, has also been described [25]. Some researchers have recommended arthrodesis of the distal tibiofibular joint for chronic cases [30-32]. Katznelson et al. [30] performed arthrodesis of the distal tibiofibular joint in 5 patients, among whom 4 had no pain and full range of motion of the ankle joint at one year after surgery. We fixed the distal tibiofibular syndesmosis by syndesmosis screw fixation. After 6 months, pain in the left ankle was dramatically relieved and we observed a notable improvement in the bending range. Usually, osteochondroma growth occurs over time and eventually stops, then the likelihood of its new small osteoma body [1]. Figures 2B, 3A, 3B and 4 show images of our patient with no evidence of recurrence. After 20 years, patients have no new osteochondroma, and existing osteochondromas do not increase.

The osteochondroma system is composed of three different tissue types: the substrate and tumor made of bone, fibrous cap made of hyaline cartilage, and envelope made of fibers. The deep envelope is cartilage tissue that produces hyaline cartilage. Disordered cartilage growth plates shift to the outside and proliferates along the long diagonal axis, away from the adjacent joint bone, forming cartilaginous, fibrous cartilage or bony cartilaginous bodies. Osteochondroma occurs by calcification or ossification to form bone-like bodies [9, 33].

EXT1 is approximately 250 kb, containing 11 exons and encoding 746 amino acids [34], and EXT2 is approximately 110 kb, containing 14 exons and encoding 718 amino acids [35]. They have an amino acid similarity of 30.9% [36]. Both EXT1 and EXT2 are widely expressed, and the proteins encoded by EXT1 and EXT2 are localized to the endoplasmic reticulum. EXT1 and EXT2 can form a heterodimer. Glycosyltransferase activity of heterologous oligomeric complexes is much higher than that of EXT1 or EXT2 alone [37]. The heterodimer is a biological form of heparan sulfate polymerase, which explains why different EXT mutations can lead to very similar clinical phenotypes. Mutations in either EXT1 or EXT2 can lead to the insufficient synthesis of heparan sulfate and HSPG [39-41], and disrupt signaling of growth plate IHH and FGF [42-44]. Accordingly, signaling involved in normal bone development is interrupted, promoting early cartilage differentiation and increased chondrocyte proliferation. The bone in adjacent regions grows abnormally [45], leading to the occurrence of HME.

In China, EXT2 mutations are more common than EXT1 mutations [46]. Nonsense mutations, frameshift mutations, and splice site mutations, which result in truncated proteins, explain HME in 80% of patients [47]. EXT1 mutations are broadly distributed and have been detected in each exon [48, 49]. EXT2 mutations are rare in the final third of the coding region [47].

The 23R>X nonsense mutation resulted in a truncated EXT2 protein lacking 705 amino acids at the C-terminus (Figure 3B). Although the glycosyltransferase and exostosin domains play significant roles in HS biosynthesis, the loss of the C-terminus may have an important impact on EXT2 function, especially with respect to HS biosynthesis.
References


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Disclosure of conflict of interest

None.

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