

# Hereditary Multiple Osteochondroma with Incomplete Penetrance in a Lebanese Family: A Case Report

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## Abstract

**Background:** Hereditary multiple osteochondroma (HMO) is a rare autosomal dominant disease with high penetrance reaching 95 to 100%. It manifests during childhood in most of the times. The spectrum of the disease is wide. It is classified into 2 types depending on the number of cases and the penetrance in the same generation. The most feared complication of this disease is the malignant transformation. Establishing a screening protocol requires the identification of the true prevalence and penetrance of the disease.

**Case Report:** A 17-year-old girl presented with multiple painful lesions in the lower extremities. Physical examination of the patient and her siblings allowed the diagnosis of HMO with incomplete penetrance, and the construction of a pedigree of the family. Surgical treatment was sufficient to control the patient's symptoms.

**Conclusion:** Being the first case in Lebanon, this report adds more awareness about this rare disease. By increasing awareness, this report can have an impact on the transmission and the number of affected cases in the country. Furthermore, these data, when added to the available evidence worldwide, can be used in the determination of true penetrance of the disease, and the creation of accurate classification and screening protocol.

**Keywords:** Hereditary multiple osteochondroma; Bone tumor; Genetic disease; Multiple exostosis; Case report

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## Introduction

Hereditary multiple osteochondroma (HMO), also known as diaphyseal aclasis, Bessel-Hagen disease, or multiple congenital exostosis, is a complex rare disease of the musculoskeletal system that usually manifests during childhood [1]. HMO is an inherited autosomal dominant disease caused mainly by loss-of-function mutation of exostosin gene 1 and 2, with a high penetrance reaching 96% in females and 100% in males [2].

Its true prevalence is unknown, but it is thought that 1 per 50000 Caucasians is affected by the disease [3]. HMO results in the formation of multiple benign tumors in the metaphyseal area of long bones mainly in the distal femur (90%), proximal tibia (84%), fibula (76%), and humerus [4].

The spectrum of clinical presentation can range from a mild asymptomatic disease, to a more debilitating phenotype associated with pain, restriction of range of motion of the near joints, interference with growth potential, and other neurovascular complication [4]. Malignant transformation was also reported in literature, ranging from 1% to 25% in some papers [4].

The diagnosis is mostly made by the typical radiological appearance of the lesions. Genetic testing is only needed in rare cases with atypical presentation. Symptomatic lesions are treated with surgical excision [5].

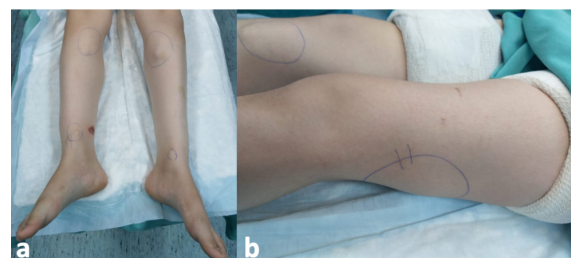
We present herein, a very rare case of a family with HMO with incomplete penetrance, in which the index case had disease free parents. To our knowledge, this is the first case to be reported in Lebanon.

## Case Presentation

This is a case of 17-year-old female Lebanese patient who presented to our clinic for bilateral lower limb painful lesions in the last year prior to presentation. The patient has no past medical or surgical history. She reported having progressively growing bony prominences since

childhood in her right proximal and distal tibia, and her left distal femur and tibia. A year ago, some of these lesions started to become painful.

On physical examination, the patient had short stature, no facial dimorphism, and no syndromic features. Her lower limb inspection was relevant for limb length discrepancy (taller left lower limb), with evidence of bony prominences in the right proximal and distal tibia, left proximal and distal tibia, and left distal femur (Figure 1). The most painful lesions were the ones located on the right and left distal tibia, and the left distal femur.



**Figure 1:** Inspection of lower limbs (a) limb length discrepancy with bony prominences in the right proximal and distal tibia, and left proximal and distal tibia, (b) bony prominence of the left distal femur.

With palpation of the upper limb, we identified 1 painless bony prominence in the posterior aspect of the left proximal humerus.

Radiographs of the upper and lower extremity were done. Starting with the left lower limb, radiographs showed a small exostosis of the femoral neck, a medial exostosis of the distal femur, a widening of the anteroposterior metaphyseal diameter of the distal femur, a long anteromedial exostosis of the proximal tibia, a proximal tibo-fibular synostosis, medial small exostosis of the distal tibia, and a large posterolateral exostosis of the distal tibia deforming the fibula in proximity to it (Figure 2).

Radiographs of the right lower limb showed a small exostosis of the femoral neck, a posterolateral exostosis of the distal femur along with widening of the metaphyseal diameter of the distal femur, a long posteromedial exostosis of the

proximal tibia, a small exostosis of the distal fibula, a medial small exostosis of the distal tibia, and a distal tibio-fibular synostosis (Figure 3).



**Figure 2:** Radiographs of the right lower limb. (a, b) anteroposterior and lateral radiographs of the femur showing a small exostosis of the femoral neck in addition to a medial exostosis of the distal femur along with a widening of the anteroposterior metaphyseal diameter of the distal femur, (c, d) anteroposterior and lateral radiographs of the tibia showing a long anteromedial exostosis of the proximal tibia, proximal tibiofibular synostosis, a medial small exostosis of the distal tibia, and a large posterolateral exostosis of the distal tibia deforming the fibula in proximity to it.



**Figure 3:** Radiographs of the left lower limb. (a, b) anteroposterior and lateral radiographs of the femur showing small exostosis of the femoral neck in addition to posterolateral exostosis of the distal femur along with widening of the metaphyseal diameter of the distal femur, (c, d) antero-posterior and lateral radiographs of the tibia showing a long posteromedial exostosis of the proximal tibia, a small exostosis of the distal fibula, a medial small exostosis of the distal tibia, and distal tibio fibular synostosis.

Radiographs of the left upper limb showed a small exostosis of the anterolateral proximal humerus, a posterolateral exostosis at the proximal metaphyseal diaphyseal junction of the humerus, a small exostosis of the distal radius, a shortening of the ulna, and a short second phalange of the 5th finger leading to its shortening (Figure 4). Radiographs of the right upper limb showed a small exostosis of the proximal humerus, a small exostosis of the distal ulna, and a short 4th

metacarpal bone leading to a short 4th digit (Figure 5).



**Figure 4:** Radiographs of the left upper limb. (a, b) anteroposterior and lateral radiographs of the arm showing small exostosis of anterolateral proximal humerus in addition to posterolateral exostosis at the proximal metaphyseodiaphyseal junction (c, d) anteroposterior and lateral radiographs of the forearm and hand showing small exostosis of the distal radius, shortening of the ulna along with a short second phalange of the 5th finger leading to a short digit.



**Figure 5:** Radiographs of the right upper limb. (a, b) anteroposterior and lateral radiographs of the arm showing small exostosis of proximal humerus (c) anteroposterior radiograph of the forearm and hand showing small exostosis of the distal ulna, along with a short 4th metacarpal bone leading to a short digit.

According to these findings, a diagnosis of HMO was made and the parents were asked again about their family history. They denied any history of bony disorders or syndromes in both of them. However, the mother recalled that her brother in law had multiple bone excision surgeries during his childhood. She added that her grand-mother had short stature and multiple asymptomatic bony prominences. Careful anamnesis and examination of all family members lead to the construction of the family pedigree of the disease (Figure 6). Examination of the patient's sister showed multiple lesions in upper and lower extremities.

The patient underwent surgical excision of the lesions of the lower extremity (Figure

7). She had a smooth post-operative stay, and was discharged on the third day. Pathology results confirmed the benign nature of the disease.

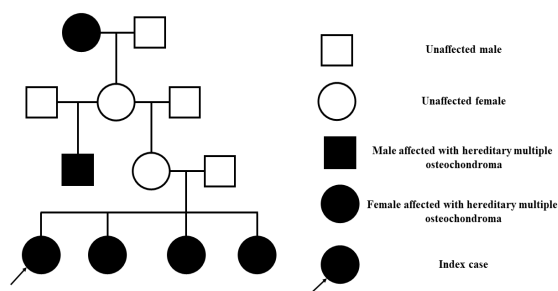


Figure 6: Family pedigree of 4 generations.

The patient was then followed on yearly basis, where physical examination did not reveal any recurrence at the surgical site, and the patient was still free of symptoms. Magnetic resonance imaging for screening of spinal lesion was offered, but refused by family. Her sisters remain asymptomatic.

## Discussion

HMO is an autosomal dominant benign bone tumor, characterized by the formation of multiple cartilage capped bone tumors [6]. It affects 1 in 50,000 Caucasians with a male to female ratio of 1.5:1 [3].

The main causes of HMO are two gene mutations, exostosin-1 (EXT1) and exostosin-2 (EXT2), located on chromosome 8 (locus 8q24.1), and chromosome 11 (locus 11p11-13) respectively. These genes are responsible for heparan sulfate proteoglycans synthesis. Most of these mutations are

familial, with a percentage of 78% for EXT1 mutation and 87% for EXT2 mutation [7, 8].

HMO that affects only one child in the proband is considered type I, while that affecting more than one child in the generation is considered type II [9].

The penetrance of these genes was the subject of many studies in the literature. One of the largest cohort studies to assess penetrance of the disease was conducted by Legeai-Mallet et al. over a period of 40 years, and involved 175 families. They found that families with type I HMO have incomplete penetrance, while families with type II HMO tend to have a complete penetrance of 100% [9].

Other studies that did not use grouping (type I versus type II) when assessing HMO penetrance, found a “complete” penetrance of 95 to 100% [1]. Our case is a type II HMO, but has features of type I since it showed incomplete penetrance.

According to the literature, the main location of these tumors is the metaphysis of long bones, mainly in the distal femur (90%), proximal tibia (84%), fibula (76%) and humerus (72%). Interestingly, it is absent in the calvaria of skull, the mandible, and facial bones, which have an intramembranous ossification origin [10, 11].

The appearance of these bony protuberances occurs shortly after birth, and continues to grow throughout childhood and into puberty [4].

Pain is the main clinical presentation; it is caused by compression of neurovascular

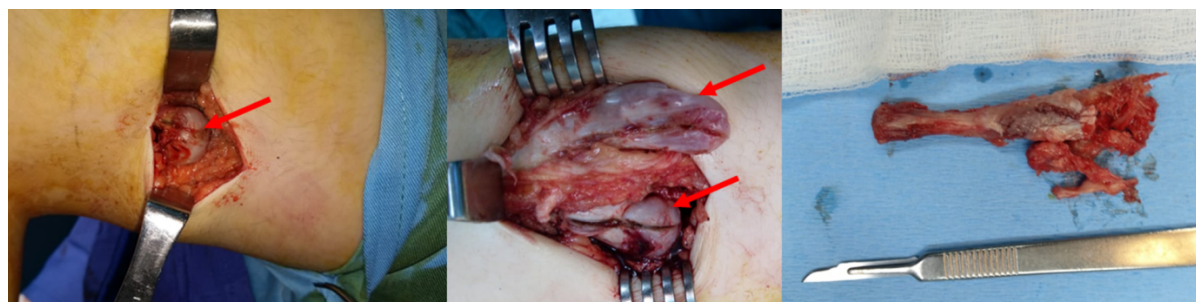


Figure 7: Intraoperative photographs of multiple lesions: (a) intraoperative photograph of the lesion of the left distal femur, (b) intraoperative photographs of the lesion of the left proximal tibia, (c) intraoperative photograph of the excised lesion from the right proximal tibia.

and tendinous structures. Some documented areas of major neurovascular compression are the superficial peroneal nerve and popliteal artery thrombosis or pseudo aneurysm [12].

Serial upper and lower extremities radiographs are the main diagnostic tool. MRI can help measure the thickness of the cartilage cap which can be suspicious for malignant transformation if its more than 2 cm thick [13].

Genetic testing could be helpful for the diagnosis of HMO in atypical presentations. However, these tests should not be done systematically. In fact, the typical radiological aspect of the lesions is often enough to make the diagnosis [5].

Like our case, surgical excision of symptomatic bony osteochondromas is the treatment of choice with a favorable outcome for pain relief and correction of associated limbs' deformity. However, the medical treatment remains at an experimental stage. A recent study by Huegel et al. highlighted the role of a potent heparanase inhibitor in chondrogenesis inhibition [14].

Because of its rarity, screening protocols for this disease are not available. All family members of an index case should be examined for the possibility of the disease.

## Conclusion

We presented a case of an adolescent female presenting with symptomatic HMO diagnosed by physical examination and radiological appearance and treated with surgical excisions. The most feared complication of this disease is malignant transformation. Establishing a screening protocol requires the identification of the true prevalence and penetrance of the disease. This data can be used in the determination of true penetrance of the disease, and the creation of more accurate classification and screening protocol. Being the first case in Lebanon, this report increases clinicians' awareness of this rare disease, and adds more data allowing for

screening of affected families.

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