



Exostoses, enchondromatosis and metachondromatosis; diagnosis and management

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We describe a 5 years old girl who presented to the multidisciplinary skeletal dysplasia clinic following excision of two bony lumps from her fingers. Based on clinical examination, radiographs and histological results an initial diagnosis of hereditary multiple exostosis (HME) was made. Four years later she developed further lumps which had the radiological appearance of enchondromas. The appearance of both exostoses and enchondromas suggested a possible diagnosis of metachondromatosis. Genetic testing revealed a splice site mutation at the end of exon 11 on the PTPN11 gene, confirming the diagnosis of metachondromatosis. While both single or multiple exostoses and enchondromas occur relatively commonly on their own, the appearance of multiple exostoses and enchondromas together is rare and should raise the differential diagnosis of metachondromatosis. Making this diagnosis is important as the lesions in metachondromatosis may spontaneously resolve and therefore surgical intervention is often unnecessary. We discuss the diagnostic findings, genetic causes, treatment and prognosis of this rare condition of which less than thirty cases have previously been reported.

Keywords: skeletal dysplasia ; enchondromas ; metachondromatosis.

INTRODUCTION

Exostoses are the most common benign bone tumours, they typically arise in the metaphyseal

region of long bones and are composed of a cartilage lump outside the bone which may be pedunculated or sessile, the knee is the most common site (1,10). An isolated exostosis is a common incidental finding rarely requiring treatment. Disorders associated with exostoses include HME, Langer-Giedion syndrome, Gardner syndrome and metachondromatosis.

Enchondroma are the second most common benign bone tumour characterised by the formation of hyaline cartilage in the medulla of a bone. It occurs most frequently in the hand (60%) and then the feet. The typical radiological features are of a well-defined lucent defect with endosteal scalloping and cortical expansion in the metaphysis of the bone. The most common disorder associated with enchondromas is Ollier disease, Maffucci syndrome being much rarer, with fewer than 200 cases having been reported in the literature (9,10).

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While both exostoses and enchondromatosis occur relatively commonly on their own, it is rare for both of these to develop in the same person and a diagnosis of metachondromatosis should be considered in such cases (3).

CASE REPORT

A 5 years old girl presented to the multidisciplinary skeletal dysplasia clinic following excision of two bony lumps, one from her right index finger and one from her right ring finger, she also had a palpable lump on the right side of her skull, which was asymptomatic but she was otherwise in good health. There was no family history of bone deformity, skeletal dysplasia or joint problems. The radiograph of the right index finger showed a benign cartilaginous lesion of periosteal origin. The histology of the second lump also suggested an exostotic lesion and a diagnosis of HME was made. At a twelve month follow up appointment further painless, asymptomatic palpable lumps had developed at the proximal end of the left humerus and at the right sterno-clavicular joint. Radiographs showed areas of patchy sclerosis at the proximal humerus. She continued to be reviewed annually and at the age of nine had developed mild valgus deformity of both ankles. Interestingly radiographs of the right ankle showed an osteochondroma arising from the posterior aspect of the tibial metaphysis with the exostosis pointing towards the joint, a feature that can be associated with metachondromatosis (Fig. 1). A radiograph of the pelvis showed some bilateral destruction of the cortex in the metaphysis of the femoral neck, it was difficult to determine whether these lesions were osteochondromas or enchondromas. The iliac crest metaphyses demonstrated similar lesions but we considered them to be more suggestive of enchondromas (Fig. 2).

Due to the new clinical findings and X-ray changes, the diagnosis was no longer felt to be in keeping with HME and was more likely to be metachondromatosis. Genetic tests were organised by way of PTPN11 testing for the loss-of-function mutations that are associated with metachondromatosis and found in 60% of cases. The PTPN11 gene consists of 15 exons. Loss-of-function mutations in exons



Fig. 1. — Sessile tibial metaphyseal osteochondroma pointing towards the joint, typical of metachondromatosis.

3,4,6,10,11 and 13 are associated with metachondromatosis. Analysis of the gene showed a splice site mutation at the end of exon 11, consistent with the diagnosis. We have recommended regular monitoring of the bone tumours and explained that metachondromatosis is usually a self-limiting condition. We have advised a genetic review for the patient when she is older to discuss off-spring risks, as metachondromatosis is an autosomal dominant disorder.

DISCUSSION

Hereditary multiple exostoses (HME) is a relatively common hereditary disorder presenting to the Joint Orthopaedics and Genetic clinic (5). The reported prevalence of HME ranges from as high as one in 100 in a small population in Guam to approximately one in 100,000 in European populations (5,7). It is an autosomal dominant disorder

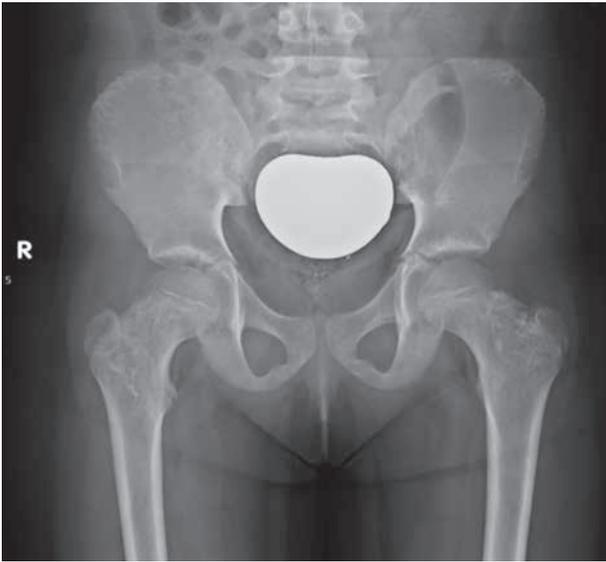


Fig. 2. — AP pelvis radiograph showing bilateral sclerotic regions in the metaphyses of the femoral neck and iliac crest.

which may be associated with mutations in one of two genes known as EXT1 and EXT2. Diagnosis is typically dependent on clinical examination, histology and x-rays. Surgical excision of the tumours is rarely necessary and only indicated if causing significant discomfort, neurological problems secondary to nerve compression or impaired function of a joint. Increasing pain or increase in size of an exostoses, typically post puberty are signs of malignant transformation and is an indication for biopsy and or excision. HME has a risk of transformation to chondrosarcoma of between 0.6 to 8.3% (4,6,8).

Enchondromatous disorders are less frequent, but potentially have a larger differential diagnosis including Ollier disease, Maffucci syndrome, metachondromatosis, genochondromatosis (small symmetrical lesions of the upper humerus, knee and clavicles), spondyloenchondromatosis, (platyspondyly with small metaphyseal lucencies that do not cause deformities) cheirospondyloenchondromatosis also known as metaphyseal chondromatosis (platyspondyly with enchondromatosis, markedly involving hands and feet) and dyssspondyloenchondromatosis (enchondroma-like metaphyseal lesions and mild irregularities of vertebral bodies) (9).

Ollier disease is non-hereditary and has an estimated prevalence of 1 in 100,000 although it is sig-

nificantly less common than HME. It is characterized by the presence of multiple enchondromas with asymmetric distribution and may involve the entire skeleton. The skull and vertebral bodies are only rarely involved. It is usually non-familial and affects both sexes equally. Clinical problems caused by the enchondromas include skeletal deformity, limb-length discrepancy and malignant transformation. The risk of malignant transformation of one or more enchondromas is variable but may occur in up to 37% of patients, most frequently in long tubular bones which can present as a pathological fracture with chondrosarcoma formation (10). Ollier disease patients also have an increased risk of developing non-skeletal visceral and brain malignancies such as astrocytoma, gliomas, pancreatic, liver and breast in approximately 25% of patients (11). Prognosis is dependent on the extent of joint deformity and malignant transformation.

Maffucci syndrome is a rare condition in which multiple enchondromatosis is associated with soft tissue haemangiomas, and less commonly lymphangiomas. It is also non-hereditary and less than 200 cases have been reported. The enchondromas are asymmetrically distributed. The haemangiomas can be found anywhere in the body and can sometimes be seen on X-ray due to calcification. Both the enchondromas and the vascular lesions may progress to malignancy. The syndrome may be associated with other benign or malignant tumours (goiter, parathyroid adenoma, pituitary adenoma, adrenal tumour, ovarian tumour, breast cancer and astrocytoma). Management aims at relief of symptoms and early detection of malignancies. Surgical treatment is not indicated in asymptomatic patients unless there is evidence of malignant transformation. Patients with Maffucci syndrome may have a normal life span but have a very significant malignancy risk at 53% and regular examinations by an orthopaedic surgeon and dermatologist to evaluate changes in the skin and bone lesions are mandatory (10). The diagnosis of both Ollier disease and Maffucci syndrome is based on clinical and radiological evaluation. Histology is usually only required if malignancy is suspected.

The incidence of metachondromatosis is thought to be less than 1 in 1 000,000, fewer than 30 cases

have been reported. It is characterized by a combination of multiple exostoses and enchondromas (2). The first signs of metachondromatosis occur during the first decade of life. Exostotic lesions in metachondromatosis occur frequently in the digits and involve the metaphyses and epiphyses. Exostotic lesions may decrease in size and spontaneously regress. Enchondromas in metachondromatosis are common in the metaphyses of long bone and the pelvis. The clinical course of metachondromatosis is unpredictable as there may be simultaneous growth of some of the lesions and regression of others. It does not generally cause bowing of the long bones, joint deformity or joint subluxation. In asymptomatic and uncomplicated cases, no treatment is required. For severe functional limitation or deformity of the fingers and toes surgical intervention can be considered to remove the exostoses. No malignant transformation has been reported in the literature to date. Nerve paralysis or vascular complications may occur and avascular necrosis of the femoral head due to enchondromas has been a frequent complication in patients with metachondromatosis. It is an autosomal dominant condition and loss-of-function mutations, including deletions, non-sense mutations and splice sites mutations of the PTPN11 gene have been linked to metachondromatosis in some families although in some patients with metachondromatosis no PTPN11 mutations have been detected, suggesting heterogeneity (3). Diagnosis is based on clinical signs, radiographic findings and familial history ; if a molecular diagnosis is confirmed then this can be used to aid diagnosis in other family members.

CONCLUSION

This case study highlights that when both exostoses and enchondromas are found together diagnoses other than HME and simple enchondromatous dis-

orders need to be considered. Metachondromatosis although rare, is a differential diagnosis and molecular confirmation should be sought as it will change the advice given regarding disease progression, management and malignancy risk. Furthermore the genetic advice given to individuals with Metachondromatosis is very different to that for Ollier or Maffucci syndrome, as well being much more reassuring when counselling about the risk of malignant transformation.

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