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ORIGINAL CLINICAL ARTICLE

Metachondromatosis: more than just multiple osteochondromas

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Abstract
Introduction Metachondromatosis is a rare genetic disease of osteochondroma and enchondroma formation, caused by loss of function of the PTPN11 gene. It is distinct from other similar conditions such as multiple osteochondromas and hereditary multiple exostoses by the distribution and orientation of lesions, and pattern of inheritance. Lesions typically occur in hands, feet, femora, tibiae and the pelvis. Lesions are typically reported to regress in adulthood.
Methods We reviewed the current literature on metachondromatosis, and present four new cases in a family with metachondromatosis.
Results Long-term follow up data reveal spontaneous regression of lesions by skeletal maturity. Complications may include nerve palsy due to the mass effect of lesions, avascular necrosis of the femoral head and angular deformity of long bones. Histopathological analysis has demonstrated that lesions in metachondromatosis are a mix of osteochondromas and enchondromas; however, one case of chondrosarcoma has been reported.
Conclusion Lesions associated with metachondromatosis may cause a variety of complications due to mass effects; however, they are often asymptomatic, cause cosmetic concerns and, importantly, most regress spontaneously. Regular clinical review with selective imaging to monitor for such complications is appropriate, but uncomplicated lesions are unlikely to require surgical intervention.

Keywords Metachondromatosis · Review · Case report · Osteochondroma · Enchondromatosis

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Introduction

Metachondromatosis is a rare hereditary disorder involving the formation of enchondromas and osteochondromas, first described by Maroteaux [1]. There have been approximately 50 cases reported worldwide [1–19]. It is distinct from multiple osteochondromatosis (MO), also known as hereditary multiple exostoses (HME), as the orientation of lesions in metachondromatosis is towards rather than away from the epiphysis, and there is a predilection for the hands and feet [8]. Loss of function of the protein tyrosine phosphatase non-receptor type 11 (PTPN11) tumour suppressor gene has been identified as a cause [20, 21], and the condition is inherited in an autosomal dominant pattern with incomplete penetrance [21], unlike other enchondromatoses, such as Ollier's disease and Maffucci syndrome, which are sporadic in nature [3, 21–24]. Lesions in metachondromatosis are reportedly not associated with axial deformity or disruption to the growth of bones [11, 23, 24]; however, case reports have documented deformities in fingers [11, 15] and the distal tibia [11]. Periarticular soft tissue calcifications are often present [3] and appear similar to those seen in Trevor's disease, also known as dysplasia epiphysealis hemimelica. Lesions are typically present in the hands and feet [24]; however, the iliac crest

[8], spine [1] and long bones such as the proximal femur [12, 13, 15, 16] are also affected.

The natural history of metachondromatosis is described as one of spontaneous regression during childhood [3], although some lesions persist into adulthood. As with other enchondromatoses and MO, new lesions do not appear after skeletal maturation [24]. Taking a thorough family history of spontaneously regressing lesions is, therefore, vital in the diagnosis of metachondromatosis.

This condition is also considered to differ from other enchondromatoses due to its lack of potential for malignant transformation; however, a recent paper reports a grade 2 chondrosarcoma arising in an enchondroma in a patient with metachondromatosis [19].

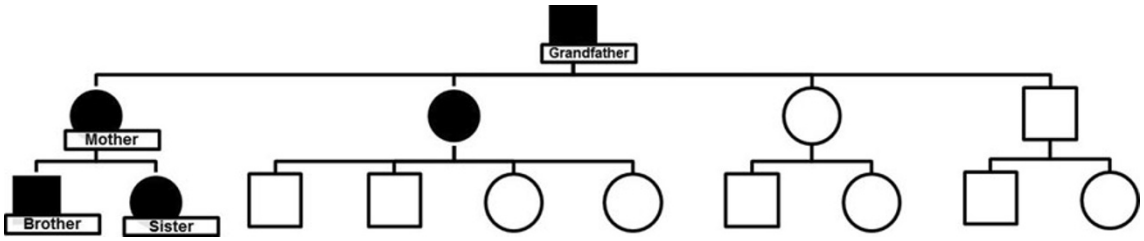

Fig. 1 Maternal family tree

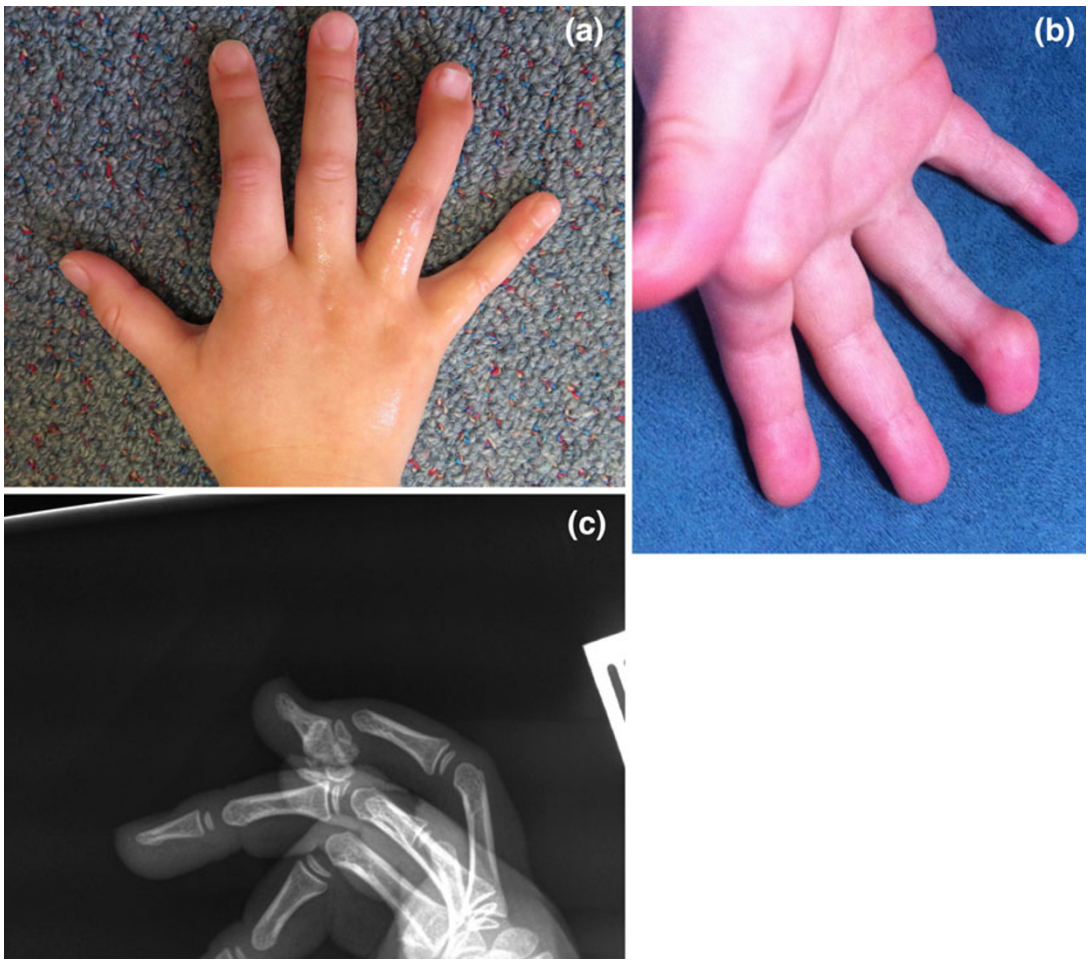

Fig. 2a–c Exostosis at the base of the right ring finger distal phalanx causing hyperextension deformity and subluxation of the distal interphalangeal joint

Other reported complications of metachondromatosis include common peroneal nerve palsy secondary to compression by exostoses near the fibular head, resulting in numbness and footdrop [11]. Nerve function usually recovers completely with excision of the offending lesion. Avascular necrosis of the femoral head has also been described in patients with lesions around the femoral neck [12–15, 18]. This is thought to be due to the disruption of lateral epiphyseal vessels in the femoral neck [13]. Necrosis of skin overlying a large lesion has occurred in at least one case [11].

Methods

We reviewed the current literature on metachondromatosis with regards to complications, natural history and treatment strategies. Thirty-one case reports of metachondromatosis in 14 journal articles published in English were identified in a Medline search of PubMed [2–4, 6, 8, 11–19].

We also present four cases of metachondromatosis occurring in a single family.

Consent was obtained from the family and ethics approval for the publication of case reports was obtained from our institutional review board (Audit 615A).

Case reports

Four cases of metachondromatosis in a single family are presented (Fig. 1). A sister of the third case was also reported to have had a disorder of bony growths during childhood with complete regression of lesions and no residual abnormality, but they were not available for interview or examination. There was no history of similar disorders in the children's father or his family. Genetic testing was not performed due to a positive family history of lesion regression, lesion appearance and distribution all being consistent with a diagnosis of metachondromatosis.

Sister

The first case is a female, 2 years and 11 months of age. She presented initially for review of lumps on her hand and ankle. A prominence on the volar aspect of her right ring finger distal interphalangeal joint was noted, which produced a hyperextension deformity (Fig. 2). There was a moderate sized lump on the dorsum of her left middle finger metacarpophalangeal joint (Fig. 3) and another on her left little finger. She did not have any noticeable restriction in function of either hand. Both left and right ankles had palpable lumps on the anterolateral aspects (Fig. 4), but, again, these did not appear to interfere with function and range of motion was intact.

Radiographs of the upper limbs showed exostoses of the distal left second metacarpal, base of the left middle finger proximal phalanx (Fig. 3b), distal left fifth metacarpal and right distal radius. Lower limb films showed exostoses on the left and right proximal (Fig. 5) and distal femora, proximal left third metatarsal and distal right fifth metatarsal. Enchondromas were apparent on the left and right iliac crests (Fig. 5), as well as bony spurs on the anterior aspect of the L1 vertebral body, proximal humeral metaphyses, base of the left first metacarpal,

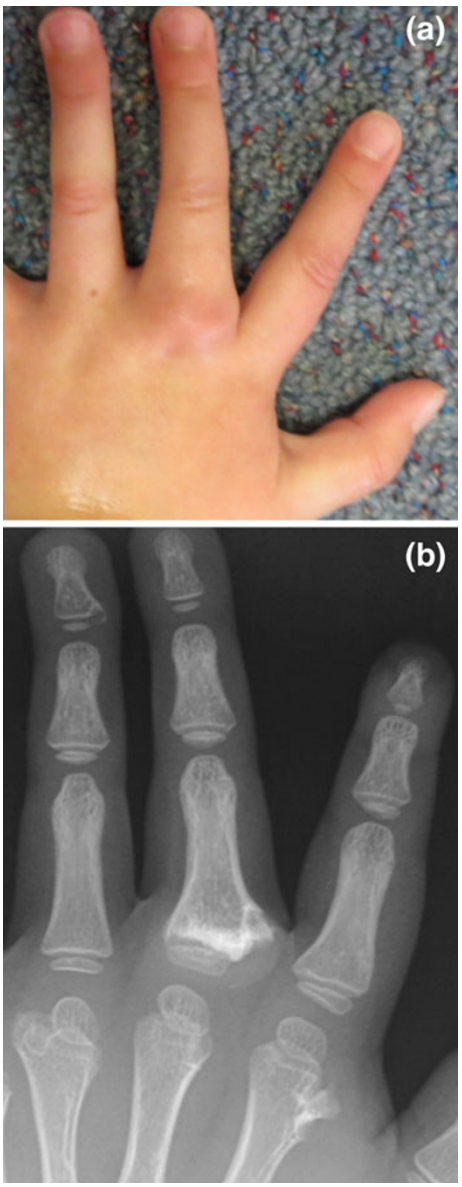

Fig. 3a, b Exostosis of the left middle finger proximal phalanx and enchondroma at the base of the left ring finger distal phalanx

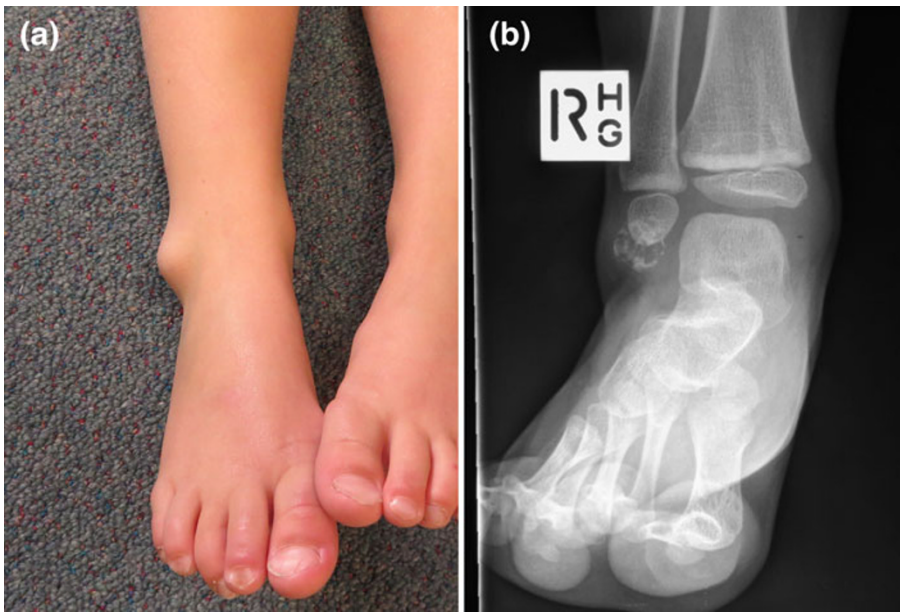

Fig. 4a, b Calcification of the distal right fibula

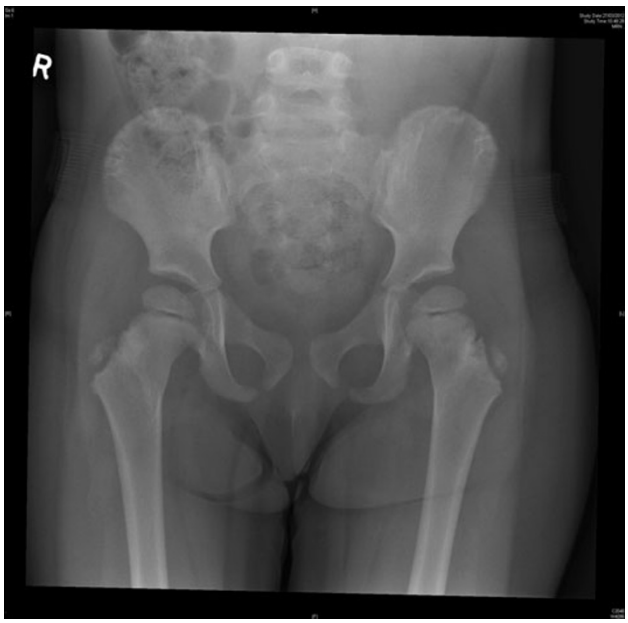

Fig. 5 Enchondromas of bilateral iliac crests and proximal femora

base of the left ring finger distal phalanx (Fig. 3b), left fourth metacarpal and right index finger proximal phalanx. Clavicles were not affected. Periarticular soft tissue calcification was noted around the distal right fibula (Fig. 4b), base of the right index finger proximal phalanx, base of the right third metatarsal, lateral right cuboid and left fourth toe proximal phalanx. An exostosis of the base of the right ring finger distal phalanx was present, causing subluxation of the distal interphalangeal joint (Fig. 2c).

Brother

The second case is the male sibling of the first case, aged 4 years and 8 months. He was examined for similar lesions following the radiographic findings in his sister.

The only significant clinical finding was a prominent but non-tender lump on the left scapula. He was otherwise well and growing normally.

Upper limb radiographs revealed exostoses of the left ring finger proximal phalanx and base of the left middle finger proximal phalanx (Fig. 6). Lower limb films showed enchondromatous changes of the left and right femoral necks (Fig. 7), exostoses of the left and right distal femora, left and right proximal fibulae, and right proximal tibia (Fig. 8). Bony spurs were also noted on the inferior aspect of the left scapula (Fig. 9), anterior aspect of the L2 vertebral body, distal left and right tibial metaphyses, distal left radial metaphysis, right middle finger proximal phalanx, left and right proximal metatarsals, and the distal right first metatarsal. Periarticular soft tissue calcification was present around the left ring finger proximal phalanx (Fig. 6b), head and base of the left index finger proximal phalanx, between the first and second metacarpals on the right hand and between the bases of the fourth and fifth metacarpals on the right hand. Calcification was also extensively present around the tarsal bones of the left and right feet (Fig. 10).

Mother

The third case is a 34-year-old female, and mother of the first and second cases. She recalled developing palpable lumps in a similar distribution to that of her daughter

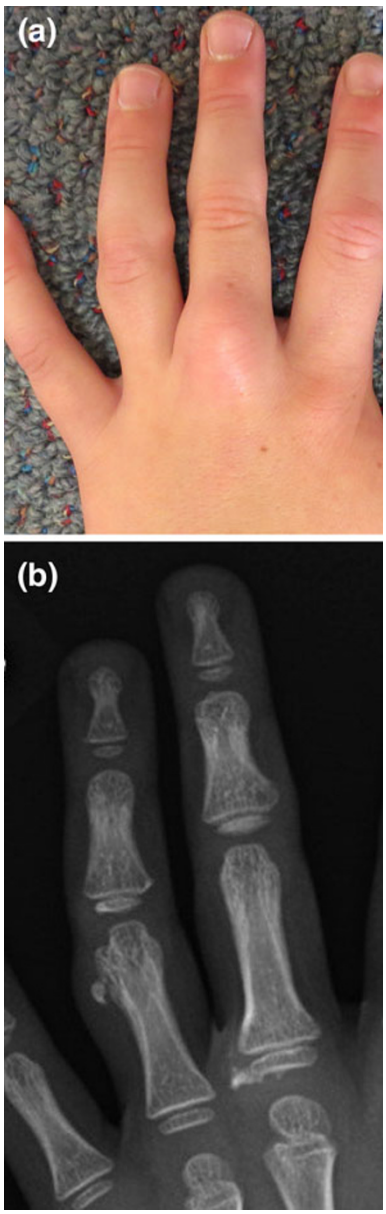

Fig. 6a, b Exostoses of the base of the left middle finger proximal phalanx, and body of the left ring finger proximal phalanx with associated soft tissue calcification

during childhood, the majority of which regressed in adolescence. A mild valgus deformity of the proximal interphalangeal joint of her right index finger remained (Fig. 11a). Radiography of her right hand showed the angular deformity but no evidence of persistent exostosis or enchondroma (Fig. 11b). There was no previous imaging available for comparison.

Grandfather

The fourth case is a 69-year-old man who was the maternal grandfather of the first two cases and father of the third. He reported a history of similarly distributed lumps developing in his hands and ankles during childhood. His lesions regressed completely during his adolescent years; however, a valgus deformity of the proximal interphalangeal joint of his right ring finger persisted (Fig. 12a). Radiography of this region showed angulation of the distal joint surface, likely reflecting growth disturbance during childhood; however, there was no evidence of persistent exostosis or enchondroma (Fig. 12b). No radiographs of lesions during childhood were available for review.

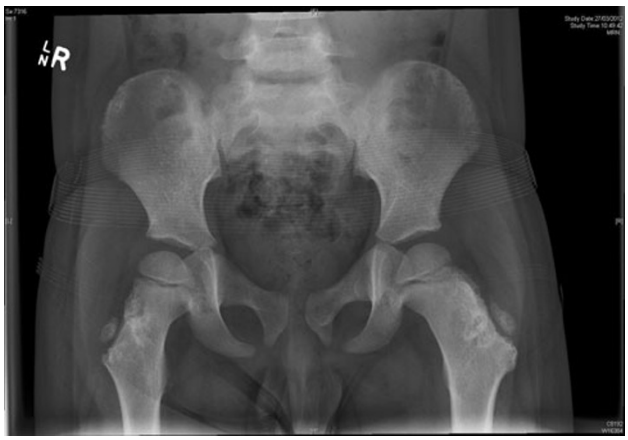

Fig. 7 Enchondromas of bilateral iliac crests and proximal femora

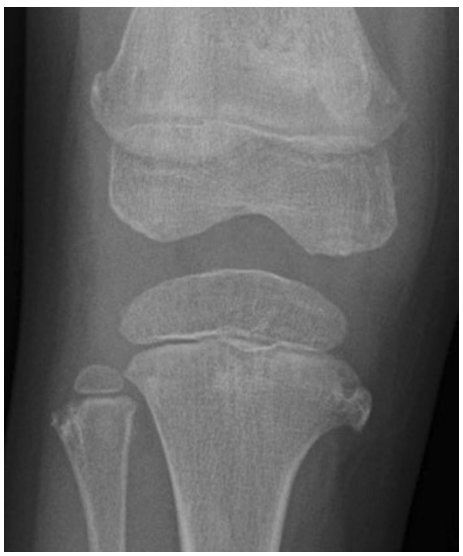

Fig. 8 Exostoses of the right distal femoral metaphysis, proximal fibular metaphysis and proximal tibial metaphysis

Literature review

Regression of lesions

The natural history of metachondromatosis is described as one of spontaneous regression of lesions; however, very

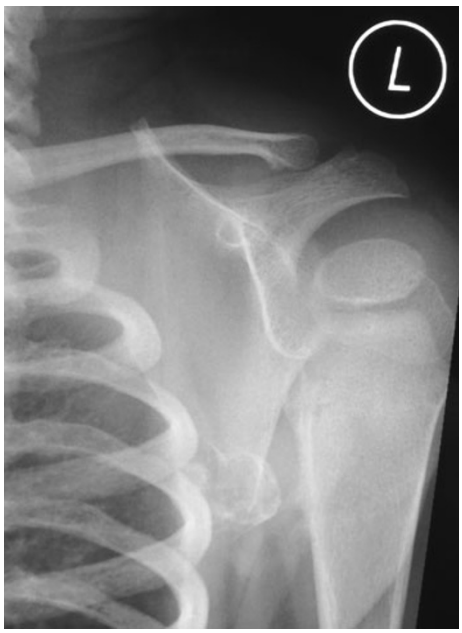

Fig. 9 Osteochondroma arising from the inferior aspect of the left scapula, with associated soft tissue calcification

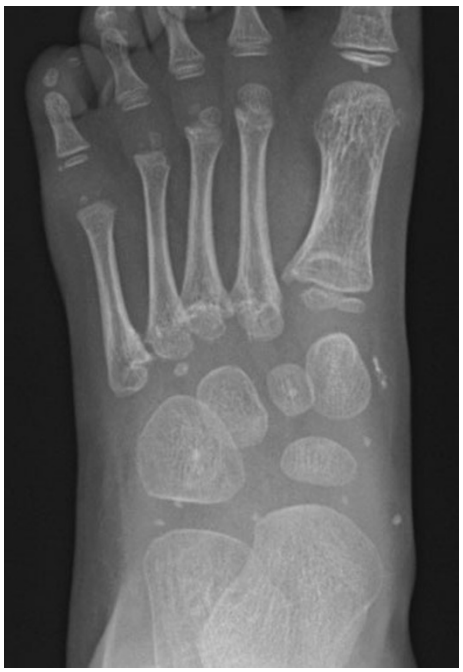

Fig. 10 Soft tissue calcification in the tarsal region

few cases have had prolonged follow up or serial examination, making objective assessment of regression difficult. Frequently, the parents of affected children have had the diagnosis made in retrospect and reported as cases in tandem with their children. Ten [2, 4, 8, 13–15, 17, 18] of 31 case reports (32 %) described evidence of at least partial regression of lesions either on serial examination, radiographs or both (Table 1). A further five [3, 8, 11, 13] cases (16 %) in family members of children with a diagnosis of metachondromatosis reported regression of nodules; however, no serial examination or radiographic evidence was available. The remaining sixteen cases (52 %) either made no mention of regression of lesions, or showed no signs of regression at most recent follow up. Six [3, 8, 11, 14, 18] of seven cases (86 %) where examination was completed as an adult noted at least partial regression of lesions in adulthood; however, of the cases which did not report any evidence of regression, 15 [3, 6, 11, 15, 16, 18] of 16 (94 %) were followed only to the age of 14 years or younger. Bowen et al. [21] also presented radiographic evidence of complete regression of three lesions around the knee joint between the ages of 6 and 16 years.

Histopathology

Histopathological analysis was performed on lesions excised in 12 cases [2, 4, 6, 11, 13, 14, 16–19]. Biopsies in five [4, 11, 16–18] cases (42 %) were found to be osteochondromas, four [2, 6, 14] (33 %) were identified as enchondromas and two [6, 13] cases (17 %) had multiple biopsies, which included both osteochondromas and enchondromas. Mavrogenis et al. [19] reported a patient with metachondromatosis who developed a grade 2 chondrosarcoma. No other cases of malignant transformation were identified.

Bowen et al. [21] reviewed the histopathologic features of 30 exostoses excised from patients with MO and compared them with 15 lesions excised from children with metachondromatosis. They found lesions in MO to be comprised of cartilaginous caps overlying enchondral bone immediately beneath, whereas lesions in children with metachondromatosis had a fibrous cap, a disorganised cartilaginous core and surrounding trabecular bone.

Genetic studies

Two studies have attempted to identify the gene responsible for metachondromatosis. Sobreira et al. [20] studied two families, finding an 11 base pair deletion in one and a nonsense mutation in the other, both (100 %) resulting in loss of function of the PTPN11 gene. Bowen et al. [21] studied 17 families, of which frameshift, nonsense, deletion and splice-site mutations of PTPN11 were identified in 11 (65 %). This is distinct from the EXT-1 and EXT-2 gene mutations that cause MO [25]. Cells appear to undergo a "second hit", as in MO, resulting in two non-functioning PTPN11 genes, leading to absence of the production of the SHP2 protein. The mechanism by which SHP2 deficiency

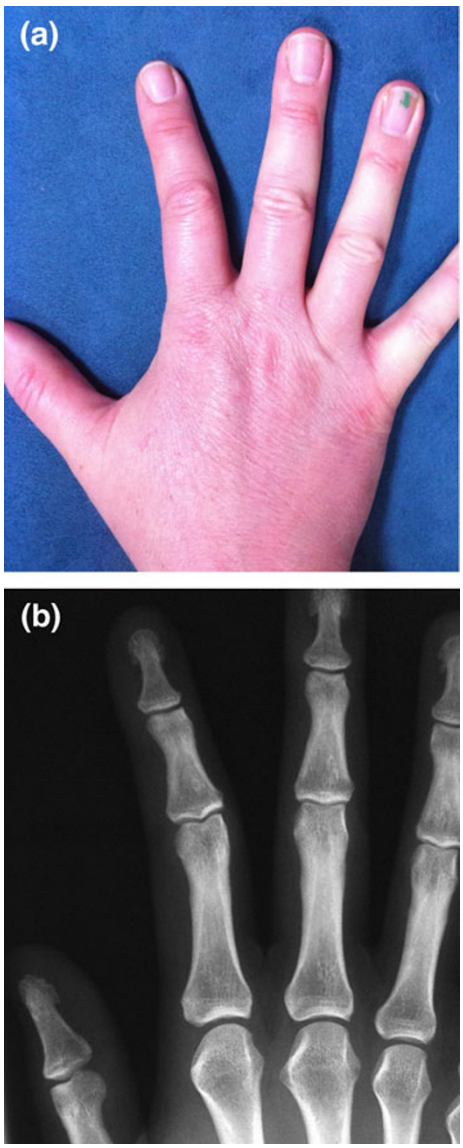

Fig. 11a, b Residual valgus deformity of the right index finger proximal interphalangeal joint despite regression of a previously palpable lump

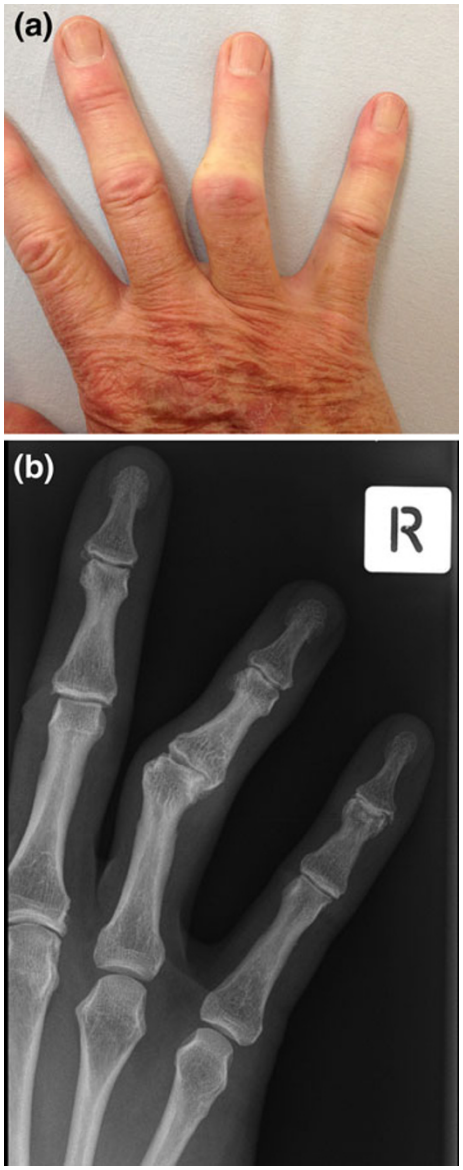

Fig. 12a, b Residual valgus deformity of the right ring finger proximal interphalangeal joint

leads to the development of enchondroma or osteochondroma is yet to be determined.

Complications

Eight [12–15, 18] of 31 cases (26 %) reported the presence of avascular necrosis of the femoral head, identified radiologically. In one case, a core biopsy of the femoral head was taken during a Chiari osteotomy, confirming the diagnosis of avascular necrosis [13].

Necrosis of skin overlying a lesion has been reported in one [11] case (3 %). Two [11, 15] cases (6 %) developed angular deformities of the fingers and one [11] (3 %) of the distal tibia. Two [11] cases (6 %) of peroneal nerve palsy have been identified secondary to compression. In both cases, excision of lesions resulted in full nerve recovery.

Discussion

Metachondromatosis is a rare genetic disorder causing a combination of osteochondromas and enchondromas in the hands, feet, long bones, iliac crests and spine [1]. The differential diagnosis includes MO and multiple enchondromatosis (Ollier's disease). The orientation of lesions towards rather than away from epiphyses helps distinguish metachondromatosis from MO. Lesions associated with Ollier's disease are almost always unilateral, and there is

Table 1 Summary of case reports reviewed

Date	Author, reference	Case	Initial age (years)	Final age at follow up (years)	Locations	Regression	Histopathology	Complications
1974	Lachman et al. [2]	Case 1	2 + 6	6	Shoulders, hands, pelvis, knees, ankles, feet	Y	Exostosis, enchondroma	Excisions performed for cosmesis
1975	Giedion et al. [3]	Case 1	1	9 + 4	Hands, knees, ankles, feet	N	N	Nil
		Case 2	1 + 3	5 + 8	Hands, knees, ankles, feet	N	N	Nil
		Case 3	10	36	Hands	Y	Nil	Nil
1975	Kozlowski and Scougall [4]	Case 1	5 + 2	6 + 3	Wrists, hands, pelvis, knees, feet, thoracic and lumbar spine	Y	Exostosis, osteochondroma	Nil
1982	Beals [6]	Case 1	13	N/A	Hands, ankles, feet	N	Enchondroma	Nil
		Case 2	4	9	Hands, knees, feet	N	Enchondroma	Nil
		Case 3	5	9	Hands, hips, knees, ankles	N	Enchondroma, osteochondroma	Nil
1983	Kennedy [8]	Case 1	8	9 + 6	Hands, pelvis, knees, feet	Y	Nil	Nil
		Case 2	?	N/A	Wrists, hands, knees, feet	Y	Nil	Nil
		Case 3	?	N/A	Hands, knees, feet	Y	Nil	Nil
1985	Bassett and Cowell [11]	Case 1	1 + 5	16	Hands, pelvis, hips, knees, feet	Y	Osteochondroma	Axial deformities of fingers, peroneal nerve compression, skin necrosis
		Case 2	52	N/A	Hands, ankles, feet	Y	Nil	Nil
		Case 3	2	14	Wrists, hands, pelvis, hips, knees, ankles	N	Nil	Peroneal nerve palsy, angular deformity of distal tibia
		Case 4	4	N/A	Shoulders, hands, pelvis, knees, ankles	N	Nil	Nil
1990	Keret and Bassett [12]	Case 1	4 + 4	8 + 3	Shoulders, hands, pelvis, knees, ankles	N	Nil	AVN
1991	Wenger et al. [13]	Case 1	9 + 7	13 + 7	Hands, pelvis, hips	Y	Nil	AVN
		Case 2	8 + 10	N/A	Hands, pelvis, hips, knees, ankles, feet	Y	Osteochondroma, enchondroma	AVN
1992	Ikegawa et al. [14]	Case 1	10 + 8	N/A	Hands, pelvis, hips, knees, ankles, feet	Y	Enchondroma	AVN
		Case 2	42	N/A	Scapula, hands, hips, knees, feet	Y	Nil	Nil
1995	Hunter et al. [15]	Case 1	6 + 3	16	Shoulders, wrists, hands, pelvis, hips, knees, ankles, feet, lumbar spine	Y	Nil	AVN
		Case 2	2	8	Wrists, hands, hips, knees, ankles, sternum	N	Nil	Angular deformities of fingers
		Case 3	5	10	Hands, pelvis, hips, lumbar spine	N	Nil	Nil
		Case 4	3	8	Hands, hips, cervical and thoracic spine	N	Nil	Nil
		Case 5	1 + 10	N/A	Wrists, hands, knees, ankles	N	Nil	Nil
1995	Wittram and Carty [16]	Case 1	1 + 6	2 + 8	Shoulders, hips, knees, feet	N	Osteochondroma	Nil
1996	Shaw [17]	Case 1	1 + 7	3 + 7	Wrists, pelvis, hips, feet	Y	Osteochondroma	Nil
1997	Herman et al. [18]	Case 1	0	7	Hands, hips, knees	N	Nil	AVN
		Case 2	0 + 6	5	Hands, hips	N	Nil	AVN
		Case 3	4	5	Shoulders, hands, ankles, feet	N	Osteochondroma	Nil
		Case 4	7	26	Hands, hips	Y	Nil	AVN
2010	Mavrogenis et al. [19]	Case 1	29	29 + 7	Knees	N	Grade 2 chondrosarcoma	Nil

N/A represents cases where a single encounter was described with no observation over time and no follow up recorded

no familial inheritance of the condition, unlike metachondromatosis. The prevalence of multiple osteochondromas is estimated to be 2/100,000 [26] and Ollier's disease 1/100,000 [27]. Both conditions are, therefore, significantly more prevalent than metachondromatosis.

Two studies have independently identified loss of function of the PTPN11 gene as a cause of metachondromatosis in 13 of 19 families [20, 21], further distinguishing this disorder from MO and Ollier's disease. Several other overlapping but phenotypically distinct disorders, including Noonan syndrome, Noonan-like disorder with multiple giant cell lesion syndrome and LEOPARD syndrome, are caused by gain of function mutations of PTPN11 [28, 29].

Histopathological findings differ between authors. Several papers found typical enchondromas and osteochondromas with cartilaginous caps [2, 4, 6, 11, 13, 14, 16–18]; however, one paper reported lesions with fibrous caps overlying cartilaginous cores [21]. The reason for the difference in these findings is unclear.

Diagnosis is made based on the distribution and orientation of lesions; however, a recently published case report describes a family with radiographic features of both metachondromatosis and MO, and a mutation of EXT-2 [22]. This is suggestive of a diagnosis of MO, but raises doubt over the reliability of distinction based on clinical and radiological factors, and suggests that the two may lie on a spectrum.

We present four family members with metachondromatosis, with a further family member having a likely diagnosis. The children had a typical distribution of lesions involving hands and feet, as well as the pelvis, spine and long bones. None of these reported cases had significant symptoms related to their lesions; however, the second case (brother) will be monitored regularly for development of peroneal nerve palsy and both children for avascular necrosis of femoral heads. The third case (mother) had no functional disability related to the angular deformity of the finger, and the fourth case (grandfather), despite significant angulation of his ring finger, described only minimal interference with activities of daily living. While it has been suggested that axial deformities do not occur in metachondromatosis, three such cases were identified in our review, noting that persistent valgus deformity of a finger was found on examination of both the children's mother and grandfather.

Given the small number of cases reported, estimation of complication rates is difficult; however, femoral head avascular necrosis, peroneal nerve palsy and malignant transformation are important considerations. Our review demonstrated that the regression of lesions appears, to some extent, to be typical.

Formal treatment and surveillance recommendations are difficult to make in the absence of a larger number of case reports in the literature. A conservative approach, however, appears to be warranted. Indications for surgical excision are predominantly symptomatic, relating to pain and nerve compression. Malignant transformation has only recently been described, but should be considered an indication for intervention. Based on observations of other conditions causing the formation of enchondromas and osteochondromas, regular bi-annual clinical review, skeletal survey of regions not examinable clinically (chest, pelvis, scapula) and repeat imaging of lesions that grow larger or become painful appears appropriate, with a view to minimising unnecessary irradiation [24].

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