

Chondrosarcoma in Metachondromatosis: A Rare Case Report

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Abstract- Metachondromatosis which was first described in 1971 by Maroteaux is a rare genetic disease consisting of osteochondromas and enchondromas, caused by loss of function of the PTPN11 gene. It is distinct from other cartilaginous tumors such as multiple osteochondromas and hereditary multiple exostosis by the distribution and orientation of lesions, and pattern of inheritance. In Metachondromatosis osteochondromas typically occur in hands, feet, femur, and tibia while enchondromas commonly affect the pelvic bones and femurs. Both tumors are generally reported to regress in adulthood. To the best of our knowledge only one case of Chondrosarcoma has been reported, and our case is the second reported case of Chondrosarcoma in metachondromatosis.

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Introduction

Metachondromatosis, (MC), is a rare genetic disease characterized by the formation of enchondromas and osteochondromas. There have been approximately 50 cases reported in the literature since the first reported case in 1971 (2). It is distinct from hereditary multiple exostosis (HME), as the orientation of lesions in metachondromatosis is towards rather than away from the epiphysis, and exostosis is commonly seen in the hands and feet (4). Loss of function of the protein tyrosine phosphatase non-receptor type 11 (PTPN11) tumor suppressor gene has been reported as a cause of this disease (5). Metachondromatosis is inherited as an autosomal dominant disease with incomplete penetrance (5) and is different from other enchondromatosis, such as Ollier's disease and Maffucci syndrome, which are sporadic in nature (5,6).

The metachondromatosis consists of multiple exostosis which is true osteochondromas with cartilaginous caps and characteristically points toward the adjacent joint rather than away from it. This exostosis, which often involve the bones of the hands and feet, do not produce shortening or growth disturbance of the affected bone (7) however, case reports have documented deformities in the distal part of tibia and fingers (8,9) and tibia (8).

Soft tissue calcifications in periarticular areas are often present (10) and appear similar to those observed in Trevor's disease, which is also known as dysplasia epiphysealis hemimelica. The periarticular calcifications are due to peripheral enchondral ossification within exophytic enchondromas (3).

The enchondromas in MC in contrast of those of multiple enchondromas, most often affect the iliac crests and the metaphyses of long bones with the similar radiographic picture. These enchondromas may appear as metaphyseal enchondromas, have a flowery appearance around joints (8,9,11), or be similar to lytic metastatic bone lesions (7,8).

The natural history of metachondromatosis is reported as one of spontaneous regression during childhood (10), although some lesions may remain into adulthood. Like other enchondromatoses and multiple exostosis, new lesions do not appear after skeletal maturity (6). This condition is different from other enchondromatoses due to its lack of potential for malignant transformation; however, there is a case report regarding a grade 2 Chondrosarcoma arising in an Enchondroma in a patient with metachondromatosis (3).

There are some reported complications of metachondromatosis which are attributable to pressure effect of osteochondromas, or enchondromas. These include common peroneal nerve palsy secondary to

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Chondrosarcoma in metachondromatosis

compression by exostosis near the fibular head, resulting in numbness and footdrop (8) with later recovery after excision of the exostosis, avascular necrosis of the femoral head in patients with lesions around the femoral neck (12,13) due to the disruption of lateral epiphyseal vessels (7), and skin necrosis overlying a large lesion (8). The pathological fracture may also be present in metachondromatosis (14). The aim of this study was to report on a very rare case of chondrosarcoma which happened in metachondromatosis, and to the best of our knowledge is the second reported case in the English literature.

Case Report

A forty-two-year-old man was admitted to our hospital complaining of left leg pain for two years. The pain had been worse and was accompanied by a mass two months before the admission. Pain and mass were localized to the upper third of the leg. The pain had been worse at night but was also present during the daytime. The patient report having multiple bony protrusions (exostosis) in his hands and feet since the age of 11,

long before he was visited by us. Our patient did not report any family member as having metachondromatosis, enchondromas, or osteochondromas.

Physical examination showed a tender mass at the anterolateral aspect of the proximal part of the left tibia. He had also a hard mass on the lateral aspect of his right arm.

Anteroposterior and lateral plain radiographs of the left knee showed a radiolucent lesion in proximal tibial epiphysis and metaphysis accompanied with a flocculent calcification. Lateral cortex of the tibia was eroded and showed sunburst periosteal reaction at the level of the metaphysis (Figure 1a and b). All these features were consistent with an aggressive chondroid tumor. There were multiple enchondromas in metaphysis, and diaphysis of left femur, and left tibia (Figure 1c). Radiographies of his right humerus showed an osteochondroma of the shaft of the humerus, and an osteochondroma of the right scapula (Figure 1d). Other exostoses and enchondromas were also present in his right hand, and both feet (Figure 1e and f).

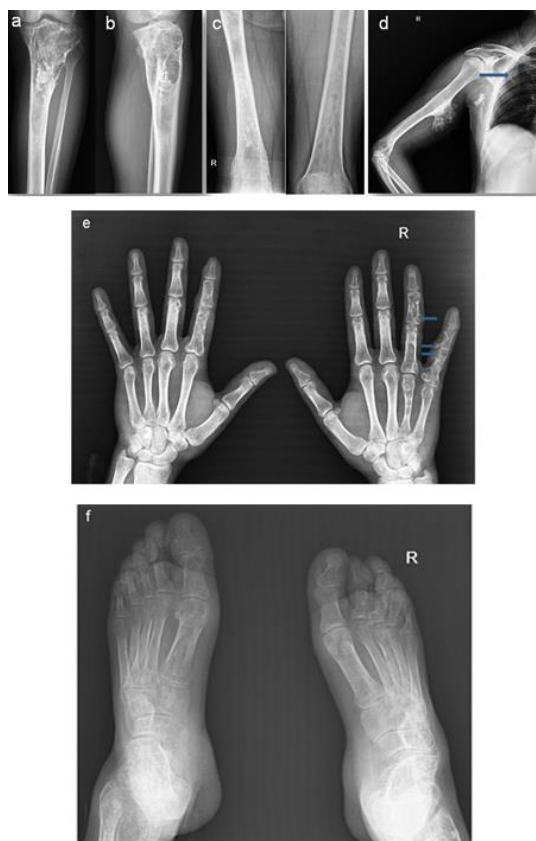


Figure 1. (a) and (b) Lytic lesion of the proximal part of the tibia, and erosion of the lateral cortex, Anteroposterior, and lateral views respectively;(c) Enchondromas in the metaphyses, and shafts of both femurs;(d) Osteochondroma of the shaft of the humerus, and right scapula (arrow), with soft tissue classification in axilla;(e) Exostoses (arrows) and enchondromas of the hands ; (f) Exostosis and enchondromas of both feet

T1 weighted magnetic resonance imaging revealed a low intense lobulated lesion involving the left proximal tibial epiphysis, metaphysis, and upper part of the diaphysis, with soft tissue component around the lateral

aspect of the proximal tibia. On T1 weighted MRI, the lesion was iso signal as compared to muscle (Figure 2a). On T2 weighted MRI images, the tumor had bright signal (Figure 2b).

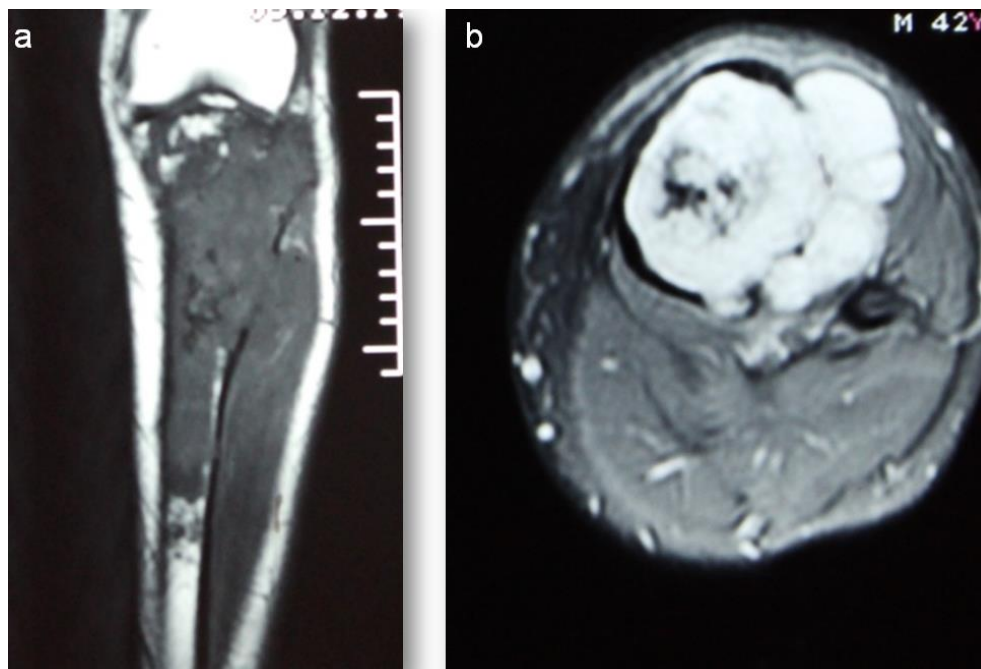


Figure 2. (a) Coronal T1-weighted magnetic resonance imaging of the left tibia shows a lesion involving epiphysis, metaphysis, and upper part of the diaphysis, with soft tissue component. The lesion has iso-intense signal as compared to muscle. (b) Axial T2-weighted magnetic resonance imaging with fat suppression of the left tibia illustrates a high signal intensity lesion in proximal tibia with a soft tissue component

A biopsy was planned for this patient and was performed through an anterolateral incision to the proximal tibia. Histological examination showed a moderately cellular to hyper cellular cartilaginous neoplasm with features suggestive of Chondrosarcoma including cellular atypia (Figure 3). The reported diagnosis by our hospital's bone pathologist was Chondrosarcoma grade II/III of the WHO classification. Due to the presence of soft tissue component in this tumor, and considering the histopathology report, we decided to perform a wide excision. Through an anterolateral approach, wide excision of the proximal tibia was performed, and MUTARS prosthesis was used for reconstruction of the defect. Gross examination of the specimen showed a nodular, translucent, whitish tissue which completely filled intramedullary space of the tibial epiphysis, metaphysis, and proximal diaphysis down to a distance of about fifteen centimeters from the

knee joint line, and was accompanied with a soft tissue component at its proximal extent (Figure 3a). Histological examination of the resected proximal tibia showed a cartilaginous neoplasm consistent with an intermediate-grade to high-grade (grade II/III) Chondrosarcoma (Figure 3b and c). Surgical margins were declared as free in the histopathology exam, and the nearest surgical margins were reported 1.5 centimeters. Follow-up visits were scheduled every three months for the first two years after surgery. In each follow-up, we performed a physical examination and asked for plain radiographies of the chest, the operated leg, and any symptomatic areas of his skeleton. At two years after the operation, this patient was alive, and there was no evidence of local recurrence or distant metastases. The last radiography of the left knee was consistent with a well-fixed prosthesis (Figure 4).

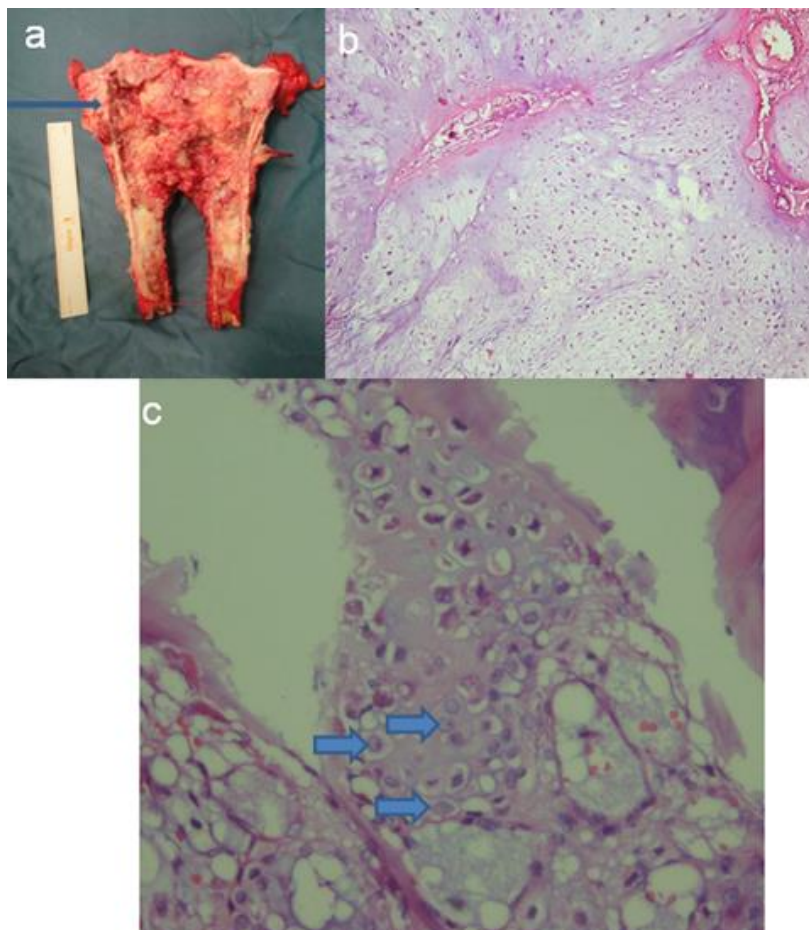


Figure 3. (a) Sagittally bisected resection specimen of the proximal tibia showing a destructive nodular, whitish cartilage mass inside tibia with a soft tissue component outside of it (arrow); (b) photomicrograph of the tumor showing a myxoid cartilage neoplasm with diffuse proliferation of spindle and satellite cells with lobular pattern, (H and E 100X); (c) Photomicrograph of the tumor showing a cellular hyaline cartilage with mild nuclear atypia of chondrocytes. Vesicular nuclei with prominent nucleoli are seen (arrows), (H and E 400X)

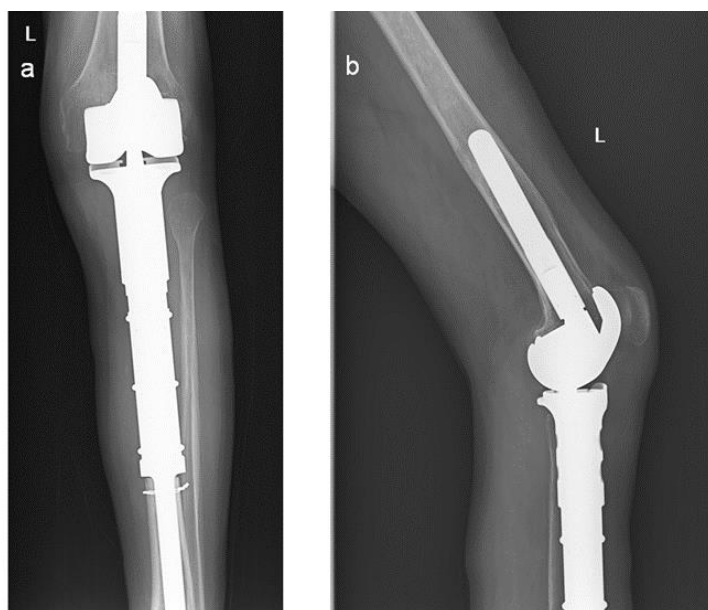


Figure 4. Postoperative radiography of the patient showing MUTARS prosthesis in good condition

Discussion

Metachondromatosis is a rare genetic disorder which is described as a combination of osteochondromas and enchondromas in the hands, feet, long bones, iliac crests, and spine (1).

Metachondromatosis is usually noticed during the first decade of life (15). Exostoses in metachondromatosis commonly occur in the digits, and toes, and involve the metaphyses and epiphyses (15). Exostoses may decrease in size and spontaneously regress. Enchondromas in metachondromatosis are commonly found in the pelvis and the metaphyses of long bone (15). They may be similar to lesions seen in a lytic metastatic disease (7,8) and have a periarticular flowery appearance (8,9,11). The reported locations of enchondromas include the iliac crest, proximal and distal end of the femur, the proximal portion of the fibula, and humerus, the distal end of the tibia, and the radius, and hands and feet (4,7,9,11) periarticular calcifications were also reported in metachondromatosis (3). Our patient had some enchondromas in the metaphysis, and diaphysis of both femurs, and one exostosis in the shaft of the right humerus, and right scapula each, as well as many enchondromas elsewhere (Figure 1). He had also soft tissue calcifications in his right axilla. Our patient did not recall any family member as having metachondromatosis, enchondromas, or osteochondromas, but he reported having multiple bony protrusions (exostosis) in his hands and feet since the age of 11. The clinical course of metachondromatosis is unpredictable because there may be the simultaneous growth of some of the lesions and regression of the others. It does not generally cause bowing of the long bones, joint deformity or joint subluxation (7). Nerve paralysis or vascular complications may occur, and unilateral or bilateral Legg-Calvé-Perthes-like changes in the femoral head, resembling osteonecrosis has been reported (7,8,11).

The differential diagnosis includes multiple osteochondromas, (MO), and multiple enchondromatosis (Ollier's disease). The fact that the lesions are oriented towards rather than away from epiphyses helps distinguish metachondromatosis from multiple exostosis. Enchondromas in Ollier's disease are almost always unilateral, and this disease is not a hereditary condition like metachondromatosis. The prevalence of multiple osteochondromas is estimated to be 2/100,000(16) and Ollier's disease 1/100,000 (17), and both are significantly more prevalent than

metachondromatosis (2,16,17). Loss of function of the PTPN11 gene has been reported as a cause of metachondromatosis in two studies (5,18), a fact that further distinguishes this disorder from multiple exostosis and Ollier's disease. There are other overlapping syndromes, including Noonan syndrome, LEOPARD syndrome, and Noonan-like disorder with multiple giant cell lesion syndrome, which are caused by gain of function mutations of PTPN11(19,20).

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 (15). There are some differences between authors regarding the histopathology of metachondromatosis. Several reports found typical enchondromas and osteochondromas with cartilaginous caps (7,8,13,21,22); however, there is a report regarding the presence fibrous caps overlying cartilaginous cores (5).

On the basis of histological parameters, Chondrosarcoma are divided into three grades. Grade I Chondrosarcoma is described as a cartilage neoplasm with the exclusive presence or marked preponderance of small, densely-straining nuclei. Multiple nuclei (two or more) within one lacuna is commonly seen in grade I tumors (23). Grade II Chondrosarcoma represents histologically as areas in which a significant proportion of the nuclei are at least of moderate size, but the mitotic rate is low (23). The principal criteria of Chondrosarcoma Grade III are the presence of two or more mitoses per 10 high power field in the most active areas of the tumor (23). Grade I Chondrosarcoma is considered as low-grade and grades II and III as high-grade (24). The therapeutic options for different grades of Chondrosarcoma are thorough curettage, in the case of grade I tumors, or complete resection, for grade II and III cases (25).

Primary Chondrosarcoma arises de novo, whereas secondary Chondrosarcoma develops in association with a predisposing condition such as an enchondroma or osteochondroma (26,27). Malignant transformation of an osteochondroma or an enchondroma to Chondrosarcoma is rare. The risk of Chondrosarcoma is greater in patients with multiple enchondromas, such as Ollier's disease and Maffucci syndrome, and in those with hereditary multiple exostosis. In Ollier's disease, this risk was first estimated to be around fifty percent while new reports suggest a lower risk around twenty-five to thirty percent (28,29). The risk of malignant transformation in Maffucci syndrome is even higher with estimates around

one hundred percent (29). In hereditary multiple exostosis the risk of malignant change is lower than the risk in multiple enchondromas and is reported to be around five to twenty-five percent (30). The risk of malignant degeneration with other cartilaginous disorders such as metachondromatosis is not totally unexpected. To the best of our knowledge, however, this is the second case of the malignant transformation of a metachondromatosis-associated enchondroma to a Chondrosarcoma.

Treatment and surveillance recommendations in MC are difficult to make in the absence of a larger number of reported cases in the literature. In asymptomatic and uncomplicated cases, no treatment is warranted. For functional limitation or deformity of the fingers and toes which are severe, surgical intervention can be considered for removing of the exostoses. Other Indications for surgical intervention are predominantly symptomatic and are related to pain and nerve compression. Malignant transformation has only been observed in one case but should be considered as an indication for intervention. Based on observations of the natural history of other conditions causing the formation of enchondromas and osteochondromas, regular bi-annual clinical examination, skeletal survey of regions with lesions difficult to examine clinically (chest, pelvis, scapula) and repeat imaging of lesions that enlarge or become painful appears appropriate, with a view to minimize unnecessary irradiation (6).

Although many reports shows that the regression of lesions appears to be the usual fate (2), Some complications are important to notice in metachondromatosis. These include femoral head avascular necrosis, peroneal nerve palsy and most importantly, malignant transformation.

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