

Metachondromatosis: A Confusing Disease

Metacondromatose: Uma doença confusa

Alejandro Blasco¹ Marta Salom² Francisco Giner³ Emilio Baixauli¹ Francisco Baixauli⁴

¹Upper Limb and Peripheral Nerve Unit, La Fe Polytechnic University Hospital, Valencia, Spain

²Pediatric Orthopedics and Trauma Unit, La Fe Polytechnic University Hospital, Valencia, Spain

³Anatomic Pathology, La Fe Polytechnic University Hospital, Valencia, Spain

⁴Musculoskeletal Tumors and Joint Infection Unit, La Fe Polytechnic University Hospital, Valencia, Spain

Address for correspondence Alejandro Manuel Blasco González, MD, Upper limb and peripheral nerve unit, La Fe Polytechnic University Hospital, Fernando Abril Martorell, 106, Valencia, Spain (e-mail: ablasgon@gmail.com).

Rev Bras Ortop 2024;59(Suppl S1):e26–e30.

Abstract

Metachondromatosis is a rare autosomal dominant genetic disease with incomplete penetrance that involves abnormal function of the *PTPN11* gene. Differentiation between chondrogenic tumors is a challenge for orthopedists. We report a case of a 5 year-old girl with metachondromatosis, a disease that shares attributes with osteochondromas and enchondromas. We found multiple osteochondroma-like lesions with the atypical characteristic of guiding its growth toward the neighboring joint (epiphysis) instead of moving away from it. Furthermore, columnar enchondroma-like lesions were clearly visible in the right distal radius, in the proximal femoral cervix and in the iliac crests. The patient reported that some other tumor had disappeared or downsized with time. This case was debated between a multidisciplinary skeletal dysplasia group. The aforementioned clinical and radiographic findings reinforced the hypothetical diagnosis of metachondromatosis. Definitive diagnosis of metachondromatosis requires a combination of clinical, radiographical and histopathological findings. Differential diagnosis between enchondromas, osteochondromas and metachondromatosis is vital due to differences in malignization and natural history. When a patient has multiple enchondromas and osteochondromas with regression of some lesions and atypical radiographical characteristic of the osteochondroma-like lesions pointing toward the epiphysis, metachondromatosis, a rare disease, must be considered. Surgical treatment is reserved for painful lesions Risk of malignization is insignificant and genetic advice must be given due it is an autosomal dominant disease.

Keywords

- ▶ bone neoplasms/pathology
- ▶ child
- ▶ enchondromas
- ▶ exostoses, multiple hereditary
- ▶ osteochondromas

Study carried out at La Fe Polytechnic University Hospital, Valencia, Spain.

received
December 15, 2020
accepted
July 8, 2021

DOI <https://doi.org/10.1055/s-0041-1736614>.
ISSN 0102-3616.

© 2021. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution 4.0 International License, permitting copying and reproduction so long as the original work is given appropriate credit (<https://creativecommons.org/licenses/by/4.0/>).

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Palavras-chave

- ▶ criança
- ▶ encondromas
- ▶ exostose múltipla hereditária
- ▶ neoplasias ósseas/patologia
- ▶ osteocondromas

Metacondromatose é uma doença genética autossômica rara com penetração incompleta que envolve função anormal do gene *PTPN11*. A diferenciação entre tumores condrogênicos é um desafio para os ortopedistas. Relatamos um caso de uma menina de 5 anos com metacondromatose, doença que compartilha atributos com osteocondromas e encondromas. Encontramos múltiplas lesões semelhantes a osteocondromas com a característica atípica de guiar seu crescimento em direção à articulação vizinha (epífise) em vez de se afastar dela. Além disso, as lesões semelhantes a encondromas colunares eram claramente visíveis no raio distal direito, no colo uterino femoral proximal e nas cristas ilíacas. A paciente relatou que algum outro tumor tinha desaparecido ou reduzido com o tempo. Este caso foi debatido entre um grupo multidisciplinar de displasia esquelética. Os achados clínicos e radiográficos acima mencionados reforçam o diagnóstico hipotético da metacondromatose. O diagnóstico definitivo da metacondromatose é uma combinação de achados clínicos, radiográficos e histopatológicos. O diagnóstico diferencial entre encondromas, osteocondromas e metacondromatose é vital devido a diferenças na malignização e na história natural. Quando um paciente tem encondromas múltiplos e osteocondromas com regressão de algumas lesões e característica radiográfica atípica das lesões semelhantes ao osteocondroma apontando para a epífise, a metacondromatose, uma doença rara, deve ser considerada. Tratamento cirúrgico é reservado para lesões dolorosas. O risco de malignização é insignificante e conselhos genéticos devem ser dados por se tratar de uma doença autossômica dominante.

Introduction

Osteochondromas are the most common benign cartilaginous tumor. Osteochondromas are typically metaphyseal tumors of the long bones (proximal humerus, tibia, and distal femur). They usually grow as pedunculated or sessile lesions composed of cortical tissue and with medullary bone tissue covered by a cartilaginous cap.¹

Enchondromas are the second most common benign cartilaginous tumor after osteochondroma. They are commonly found within the medullary cavity of the bones of the appendicular skeleton (more frequent in the hands than in the feet, particularly in the phalanges) and they are characterized by the formation of mature hyaline cartilage in the medullary cavity.²

Metachondromatosis is a rare autosomal dominant genetic disease with incomplete penetrance that involves abnormal function of the *PTPN11* gene.¹

Differentiation between chondrogenic tumors is a challenge for orthopedists. We report the case of a patient with metachondromatosis, a disease that shares attributes with osteochondromas and enchondromas.

Case Report

A 5-year-old girl was referred to our Pediatric Orthopedics Unit asking for evaluation of multiple osteochondromas. Physical examination revealed multiple painful tumor compatible with osteochondromas on radiography. Impairment for proximal interphalangeal (PIP) and distal interphalangeal

(DIP) flexion of the fourth finger of the right hand was evidenced, which correlated with a middle phalanx osteochondroma. Previous history of skeletal hereditary diseases could not be confirmed. Surgical excision was performed without complications.

However, an anatomopathological examination showed multiple osseous and cartilaginous pieces compatible with the outer cap of a benign enchondroma. Eight months later, she was also operated for a growing and painful osteochondroma in the third left metacarpal and in the fourth right metacarpal. Paradoxically, in this case, the anatomopathological examination showed a 2.3 × 2 cm osseous lesion covered with a pearly-white smooth cap compatible with benign osteochondroma (► Fig. 1).

Previous radiographies were examined to find out a reason for this unexpected paradox. What we found was multiple osteochondroma-like lesions with the atypical characteristic of guiding its growth toward the neighboring joint (epiphysis) instead of moving away from it. Furthermore, columnar enchondroma-like lesions were clearly visible in the right distal radius, in the proximal femoral cervix and in the iliac crests (► Figs. 2 and 3). The patient reported that some other tumor had disappeared or downsized with time. This case was debated between a multidisciplinary skeletal dysplasia group. The aforementioned clinical and radiographic findings reinforced the hypothetical diagnosis of metachondromatosis.

After 8 years of follow-up, the patient is 13 years old, and new lesions in the right ankle, the hip, and the middle phalanx or the fourth left finger have grown, while others

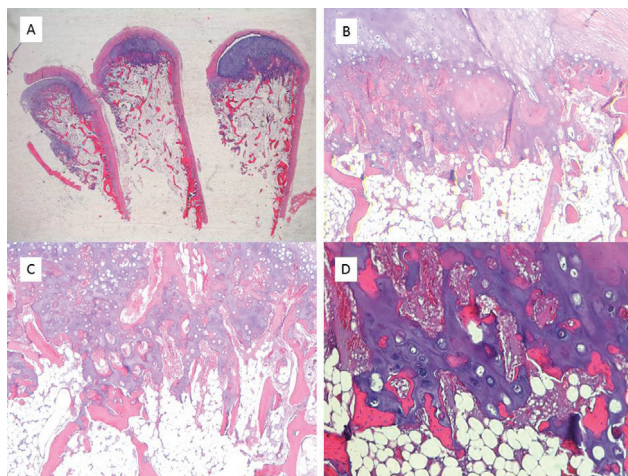


Fig. 1 Images of different histological sections stained with hematoxylin-eosin. A) Sample of the exostotic lesion constituted by a cartilaginous cap with an osteoid central trabecular matrix, 2.5X. B) The chondral matrix shows mature characteristics with endochondral ossification, 4X. C) Transition zone between the peripheral cartilaginous component and trabecular bone resembling a slightly disorganized growth plate, 4X. D) Chondrocytes are arranged in isogenic groups, larger in the central portion, without atypia or atypical mitoses, 10X.

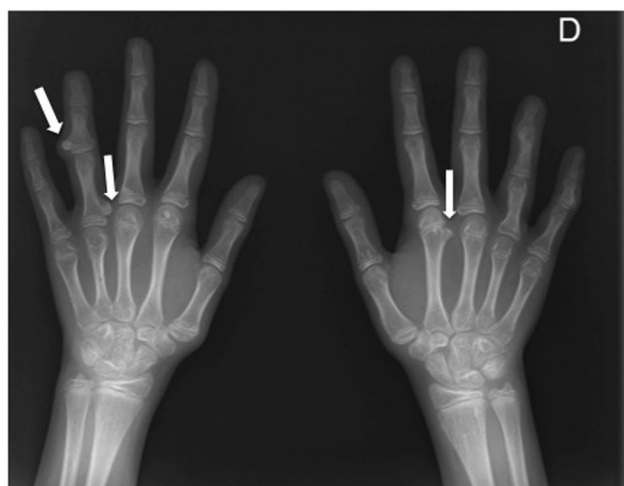


Fig. 2 Anteroposterior view of both hands showing multiple osteochondroma-like lesions with the atypical characteristic of guiding

have regressed. However, she is asymptomatic, and she leads a normal life.

Discussion

Metachondromatosis combines multiple metaphyseal juxtaepiphyseal exostoses, metaphyseal enchondromas, periarticular calcifications, and frequent unilateral or bilateral Legg-Calvé-Perthes-like changes in the femoral head resembling osteonecrosis.³⁻⁵

Classification: Metachondromatosis is a subtype of enchondromatosis without spinal affection, autosomal dominant transmission and osteochondroma-like lesions.⁶

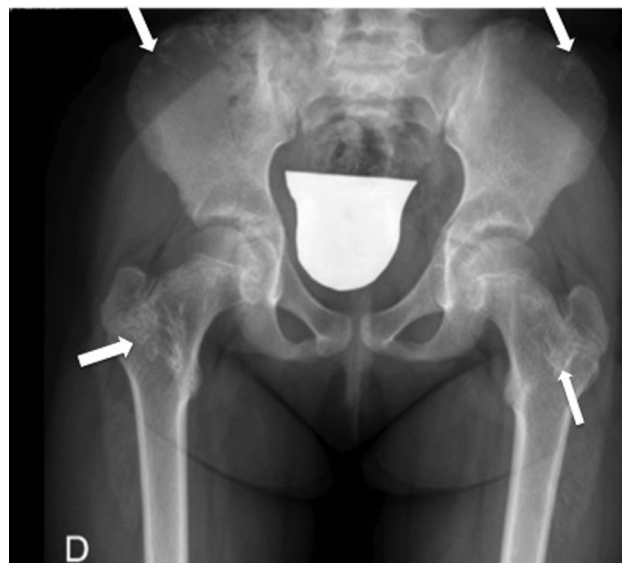


Fig. 3 Anteroposterior view of the pelvis. In metachondromatosis, enchondromas distribute mainly around the iliac crest and metaphyseal regions of the long bones.

Etiology: Metachondromatosis is related with genetic abnormalities. Fisher et al. found 31 cases published.¹ Mutation of the *PTPN11* gene (protein tyrosine phosphatase non-receptor type 11) and lack of production of the tyrosine phosphatase SHP2 is related with the pathogenesis of metachondromatosis, as well as of other developmental diseases (Noonan syndrome, Noonan syndrome with multiple lentiginos) and malignant diseases (juvenile myelomonocytic leukemia).⁷ Mutation of the *PTPN11* gene is inherited in an autosomal dominant pattern with incomplete penetrance and parents must be advised of it. Unlike enchondromatosis, EXT-1 and EXT-2 mutation (exostosin protein) is not observed in metachondromatosis.^{1,7}

The definitive diagnosis of metachondromatosis requires a combination of clinical, radiographical, and histopathological findings (► **Table 1**).⁸

Clinical findings: The combination of multiple enchondromas and osteochondromas raises suspicion of metachondromatosis.^{3,4} Metachondromatosis has characteristically epiphyseal-pointing osteochondroma-like lesions that can spontaneously regress, in contrast with conventional osteochondromas.^{3,4}

Radiographical findings: In metachondromatosis, enchondromas distribute mainly around the iliac crest and the metaphyseal regions of the long bones (► **Fig. 3**). In contrast, osteochondroma-like lesions are mainly distributed in the hands and feet (► **Fig. 2**).⁶ In our case, we saw that these lesions can distribute in both the axial skeleton (pelvis, spine, scapula, and hip) and the appendicular skeleton (hands and feet). The hands were the most frequently affected locations in our case, which is in line with Fisher et al.¹ Metachondromatosis is not related with shortening and deformity of the long bones, a common feature of hereditary multiple exostosis.⁴ As with osteochondromatosis and enchondromatosis, new lesions do not appear after skeletal maturation.¹

Table 1 Differential diagnosis between enchondromas, osteochondromas and metachondromatosis

	Enchondromas	Osteochondromas	Metacondromatosis
Frequency	10% of benign osseous tumors. ⁸ The prevalence of Ollier disease is 1/100,000. ¹	20–50% of all benign bone tumors and 10–15% of all bone tumors. ⁷ The prevalence of multiple osteochondromas is estimated to be 2/100,000. ¹	< 1/1,000,000, < 30 cases described. ²
Location	Frequently found in the hands more than in the foot and ankle bones, particularly in the phalanges. ¹	Proximal humerus, tibia, and distal femur. ¹	Enchondroma-like lesions: Metaphyseal regions of the long bones and iliac crest Osteochondroma-like lesions are mainly distributed in the hands and feet. ⁶
Genetics	Does not follow a clear Mendelian transmission pattern	HMO is an autosomal dominant inherited trait. ⁷ EXT-1 and EXT-2 mutation (exostosin protein; endoplasmic reticulum transmembrane glycosyltransferase necessary for the heparan sulfate synthesis and physeal growth)	Autosomal dominant <i>PTPN11</i> gene mutation, lack of tyrosine phosphatase SHP2
Radiology	Formation of hyaline cartilage in the medulla of a bone. ² Well-defined, expansile, lytic lesions with varying degrees of stippled or punctate calcifications in the diaphysis or metaphyseal-diaphyseal regions of the bone. ¹	Cartilage pedunculated or sessile lumps outside the metaphyseal region of the long bones. ²	Epiphyseal-pointing osteochondroma-like lesions combined with calcified enchondroma-like lesions (→ Figs. 1 and 2). They can spontaneously regress. ³
Anatomopathological examination	On gross visual inspection, an enchondroma will appear as a bluish, semi-translucent, hyaline cartilage with a distinctly lobular arrangement. These lobules will vary from a few millimeters to a few centimeters in diameter. Cytologically, an enchondroma will appear as small chondrocytes that lie in the lacunar spaces, with a small, round, regular nucleus, and no significant atypia. No mitoses will be seen. Occasional binucleate cells will be seen. Some enchondromas can contain foci of ossification within this cartilage ¹	Bony lesion covered with a pearly-white smooth cap	42% as osteochondromas, 33% as enchondromas, 17% combined. ¹
Natural history	New lesions do not appear after skeletal maturation	New lesions do not appear after skeletal maturation	New lesions do not appear after skeletal maturation
Malignization	5% in solitary enchondromas, >20% multiple enchondromatosis. ¹	Between 0.4% and 2% in patients with solitary osteochondroma and between 1 and 4% in patients with HMO. ⁷	No malignization

Histopathological findings: Histopathological examination reported first multiple osseous and cartilaginous pieces compatible with the outer cap of a benign enchondroma and, second, a bony lesion covered with a pearly-white smooth cap compatible with benign osteochondroma (–Fig. 1). However, sample size and location might determine a different diagnosis from the pathologist because they are difficult to differentiate. The histopathological analysis described by our pathologists is comparable to others that have been published.¹ After a review of the current literature on metachondromatosis, Fisher et al. found that 12 biopsies were studied; 42% (5/12) of the biopsies were diagnosed as osteochondromas, 33% (4/12) as enchondromas, and 17% (3/12) had multiple biopsies, some diagnosed as osteochondromas while some as enchondromas, as in our case.¹

Treatment

Conservative treatment is the treatment of choice, because of the regressive potential and the near absence of malignization.^{2,5} Metachondromatosis is an autosomal dominant disorder, so genetic advice must be given to patients. We recommend periodical monitoring of the lesions.

Surgical treatment is reserved for painful lesions: neurovascular compression (for example, equinus secondary to nervus fibularis communis compression in the peroneal head) and avascular necrosis of the femoral head.^{1,4,5}

Differential diagnosis between enchondromas, osteochondromas and metachondromatosis is vital due to differences in malignization and natural history. When a patient has multiple enchondromas and osteochondromas with regression of some lesions and osteochondroma-like lesions with atypical radiographical characteristics pointing toward

the epiphysis, metachondromatosis, a rare disease, must be considered. Risk of malignization is insignificant and genetic advice must be given due it is an autosomal dominant disease.

Financial Support

No financial support was received for the present study.

Conflict of Interests

The authors declare that they have no conflict of interests.

References

- 1 Fisher TJ, Williams N, Morris L, Cundy PJ. Metachondromatosis: more than just multiple osteochondromas. *J Child Orthop* 2013;7(06):455–464
- 2 McFarlane J, Knight T, Sinha A, Cole T, Kiely N, Freeman R. Exostoses, enchondromatosis and metachondromatosis; diagnosis and management. *Acta Orthop Belg* 2016;82(01):102–105
- 3 Wittram C, Carty H. Metachondromatosis. *Pediatr Radiol* 1995;25(Suppl 1):S138–S139
- 4 Wenger DR, Birch J, Rathjen K, Tobin R, Billman G. Metachondromatosis and avascular necrosis of the femoral head: a radiographic and histologic correlation. *J Pediatr Orthop* 1991;11(03):294–300
- 5 Mavrogenis AF, Skarpidi E, Papakonstantinou O, Papagelopoulos PJ. Chondrosarcoma in metachondromatosis: a case report. *J Bone Joint Surg Am* 2010;92(06):1507–1513
- 6 Pansuriya TC, Kroon HM, Bovée JV. Enchondromatosis: insights on the different subtypes. *Int J Clin Exp Pathol* 2010;3(06):557–569
- 7 Bowen ME, Boyden ED, Holm IA, et al. Loss-of-function mutations in PTPN11 cause metachondromatosis, but not Ollier disease or Maffucci syndrome. *PLoS Genet* 2011;7(04):e1002050
- 8 Chun KA, Stephanie S, Choi JY, Nam JH, Suh JS. Enchondroma of the Foot. *J Foot Ankle Surg* 2015;54(05):836–839