Journal of Bone Research

OPEN ACCESS Freely available online

Short Communication

Chronic Recurrent Multifocal Osteomyelitis (CRMO): Pathogenesis, Clinical Features, Diagnostic Approaches and Management Considerations

Eduardo Gómez Muñoz*

Department of Traumatology and Orthopedic Surgery, Clínico San Carlos Hospital, Madrid, Spain

DESCRIPTION

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is an autoimmune inflammatory disease with recurrent bone lesions [1]. Although first described by Giedion [2], the term CRMO was adopted by Björkstén [3]. The term CRMO is used as a synonym for Chronic Nonbacterial Osteomyelitis (CNO), although CRMO is sometimes considered to be the most severe form of CNO, which is the global entity [1,4].

Epidemiology

There are barely half a thousand diagnosed cases worldwide, with an incidence of 1 case/1,000,000 population/year. However, it is thought to be an underestimated disease due to its rarity and low awareness among professionals. It mainly affects the pediatric population aged 7-12 years, with an average age of onset of around 10 years. Less than 6% of cases are diagnosed in people over 18 years of age [5]. Diagnosis in newborns and before the age of two is also rare, and cases are mainly associated with genetic forms of the disease [1,4,5], which can be divided into three pathologies. The prevalence is higher in females (3:2), with no association with race or social class [1].

Etiology and pathophysiology

The origin of the disease has been proposed to be auto-inflammatory, given the idiopathic nature of the disease, its association with other autoimmune diseases, and the absence of alterations in lymphocytes or antibodies [4-6].

The pathophysiology of the disease is also unknown. Monocytes from CRMO patients show reduced production of Interleukin-10 (IL-10), which triggers inflammasome activation and an imbalance of pro-inflammatory cytokines (IL-12, TNF-α, IL-20, IL-6) over anti-inflammatory cytokines (IL-10, IL-19, IL-1RN), leading to osteoclast activation and bone inflammation [4,6].

Genetic forms have specific genetic alterations and manifest before the age of two. There are three diseases or forms of genetic CRMO: Majeed syndrome (*LPIN2* mutations), deficiency of interleukin-1 receptor antagonist (DIRA, mutation in *IL1RN*), and pyogenic arthritis, Pyoderma

Gangrenosum and Acne syndrome (PAPA, mutations in *PSTPIP1*) [5,6].

Clinical characteristics

The main symptom in these patients is pain and inflammation at the level of the bone (osteitis), preferably in the metaphysis of the long bones of the lower limbs, and rarely at the level of the skull. Clinical manifestations and severity vary from patient to patient [1,4]. On physical examination, patients present with pain, swelling and increased temperature in the affected areas [1,5,6].

In addition to pain symptoms, patients may suffer from concomitant inflammatory diseases [1,4,6], like arthritis, Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis (SAPHO) syndrome, celiac disease, Takayasu's arteritis, pyoderma gangrenosum, Granulomatosis with Polyangiitis (GPA).

The onset of pain is often insidious and progressive, delaying diagnosis in the majority of patients [1,4,5].

Diagnostic approaches

The diagnosis in this pathology is one of exclusion, given the large number of pathologies it may resemble, based on clinical history, laboratory and imaging tests, and biopsy as the definitive test. Based on these four basis, two diagnostic criteria for CRMO/CNO, the Jansson [7], and Bristol [8], criteria, have been published.

Laboratory tests are usually non-specific, with no significant changes in cell counts and mild alterations in inflammatory markers. A complete radiograph of the affected area is always the first imaging study. Radiographic changes are usually seen in advanced stages of the disease, with lytic, sclerotic, or mixed lesions in the metaphyseal areas without evidence of periosteal reaction [4-6]. They may show progressive growth and a more sclerotic appearance as they become chronic. The use of magnetic resonance imaging allows better visualization of lesions in the early stages, assessment of soft tissue involvement and evaluation of response to treatment, making it

Correspondence to: Eduardo Gómez Muñoz, Department of Traumatology and Orthopaedic Surgery, Clínico San Carlos Hospital, Madrid, Spain, E-mail: edugomezm92@gmail.com

Received: 27-Mar-2024, Manuscript No. BMRJ-24-30515; **Editor assigned:** 29-Mar-2024, PreQC No. BMRJ-24-30515 (PQ); **Reviewed:** 12-Apr-2024, QC No. BMRJ-24-30515; **Revised:** 19-Apr-2024, Manuscript No. BMRJ-24-30515 (R); **Published:** 29-Apr-2024, DOI:10.35841/2572-4916.24.12.270

Citation: Muñoz EG (2024) Chronic Recurrent Multifocal Osteomyelitis (CRMO): Pathogenesis, Clinical Features, Diagnostic Approaches and Management Considerations. J Bone Res. 12:270.

almost mandatory in the differential diagnosis as it is a safe test in children [1,4,6].

The role of biopsy is particularly important in establishing a definitive diagnosis, especially in cases with an area of involvement that is unusual for this pathology, such as the diaphysis of long bones [1,4,5]. In CRMO, biopsies are sterile and show non-specific inflammatory changes in the affected areas, with infiltration of neutrophils, Polymorphonuclear Leukocytes (PMN) and multinucleated giant cells [4,5].

The differential diagnosis of this pathology is very broad and includes infectious processes (bacterial osteomyelitis, tuberculosis, spondylodiscitis), rheumatic pathology (hypophosphatasia, chronic arthritis), malignant neoplastic (leukemia, lymphoma, osteosarcoma) and benign (simple/aneurysmal bone wasting, osteoid osteoma, fibrous dysplasia, Langerhans cell histiosis, lymphoma, osteosarcoma) and benign (simple/aneurysmal bone cysts, osteoid osteoma, fibrous dysplasia, Langerhans cell histiocytosis), as well as other conditions such as vitamin C deficiency or complex regional pain syndrome [1,4,5].

Management strategies

Treatment decisions are based on evidence from case series because of the lack of strong evidence due to the small number of patients. Medications available for this condition include anti-inflammatories, corticosteroids, bisphosphonates and anti-TNFα1 [1,4-6].

Treatment is usually started with Non-Steroidal Anti-Inflammatory Drugs (NSAID) [6], of which indomethacin [9], has shown good results in disease remission. Systemic corticosteroids are added to the NSAID therapy, and the response evaluated over a period of 3 to 6 months in patients who do not respond to NSAID therapy alone [5,6]. If this combination fails to achieve complete remission, bisphosphonates and anti-TNFα are used as salvage therapy for refractory or severe forms [1,6].

Anti-TNFα agents (etanercept, infliximab, adalimumab) are particularly useful in patients with extraosseous involvement and high levels of TNFα [1,4,6]. The use of bisphosphonates in patients with CRMO has increased in recent years, with other types such as pamidronate or clodronate being added to zolendronate [10], with average doses of around 7 to achieve disease remission [6,10]. Anti-rheumatic medications (methotrexate and sulfasalazine), denosumab, anakinra (IL-1 receptor antagonist) and canakinumab (anti-IL-1β antibody) are also used to rescue these patients [1,6].

Prognosis and follow-up

The clinical course of the disease is variable, ranging from a single mild to moderate episode or very intermittent flares to severe cases with uncontrolled inflammatory activity, frequent highly destructive episodes and severe sequelae. Treatment leads to complete remission of the disease in 40%-80% of cases [1,4-6].

CONCLUSION

CRMO is a rare, low prevalence entity with an uncertain pathophysiology based on a regulatory and pro-inflammatory cytokine imbalance. There are no specific clinical findings or complementary tests. It requires a diagnosis of exclusion given the vast differential diagnosis. There is a need for higher quality studies in order to have more evidence-based management protocols.

REFERENCES

1. Buch K, Thuesen AC, Brons C, Schwarz P. Chronic non-bacterial osteomyelitis: A review. Calcif Tissue Int. 2019;104(5):544-553.
2. Giedion A, Holthusen W, Masel LF, Vischer D. Subacute and chronic "Symmetrical" osteomyelitis. Ann Radiol Paris. 1972;15(3):329-342.
3. Björkstén B, Gustavson KH, Nordström S, Eriksson B. Chronic recurrent multifocal osteomyelitis and pustulosis palmoplantaris. J pediatr. 1978;93(2):227-231.
4. Hofmann SR, Schnabel A, Rösen-Wolff A, Morbach H, Girschick HJ, Hedrich CM. Chronic nonbacterial osteomyelitis: Pathophysiological concepts and current treatment strategies. J Rheumatol. 2016;43(11):1956-1964.
5. Hofmann SR, Kapplusch F, Girschick HJ, Morbach H, Pablik J, Ferguson PJ, et al. Chronic Recurrent Multifocal Osteomyelitis (CRMO): Presentation, pathogenesis, and treatment. Curr Osteoporos Rep. 2017;15:542-554.
6. Ferguson PJ, Sandu M. Current understanding of the pathogenesis and management of chronic recurrent multifocal osteomyelitis. Curr Rheumatol Rep. 2012;14:130-141.
7. Jansson A, Renner ED, Ramser J, Mayer A, Haban M, Meindl A, et al. Classification of non-bacterial osteitis: Retrospective study of clinical, immunological and genetic aspects in 89 patients. Rheumatology. 2007;46(1):154-160.
8. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic Recurrent Multifocal Osteomyelitis (CRMO)-advancing the diagnosis. Pediatr Rheumatol. 2016;14:1-5.
9. Abril JC, Ramirez A. Successful treatment of chronic recurrent multifocal osteomyelitis with indomethacin: A preliminary report of five cases. J Pediatr Orthop. 2007;27(5):587-591.
10. Roderick M, Shah R, Finn A, Ramanan AV. Efficacy of pamidronate therapy in children with chronic non-bacterial osteitis: Disease activity assessment by whole body magnetic resonance imaging. Rheumatology. 2014;53(11):1973-1976.