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Chronic Recurrent Multifocal Osteomyelitis, A Case with A 12-Year-Old Girl

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Abstract

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare benign autoinflammatory skeletal disease characterized by unifocal or multifocal nonbacterial inflammatory bone lesions in the metaphysis of long bones. Due to its rarity and its unspecific clinical and imaging findings, it can be easily misdiagnosed. We report the case of a 12-year-old girl which symptomatology was similar to Ewing Sarcoma. In fact, the diagnosis of CRMO is a diagnosis of exclusion.

Keywords: chronic recurrent multifocal osteomyelitis; children; bone pain

Abbreviations

CRMO - Chronic Recurrent Multifocal Osteomyelitis.
CRP- C-Reactive Protein.
ESR - Erythrocyte Sedimentation Rate.
NSAIDs - Nonsteroidal Anti-Inflammatory Drugs.
DIRA - Deficiency of the Interleukin-1 Receptor Antagonist.
MRI - Magnetic Resonance Imaging.
TNF - Tumor Necrosis Factor.

Introduction

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a rare, benign, autoinflammatory skeletal disease characterized by unifocal or multifocal nonbacterial inflammatory bone lesions,[1]. Primarily affecting the metaphysis of long bones. Due to its rarity and nonspecific clinical and imaging findings, it is often misdiagnosed, leading to delays in appropriate management [1]. We report the case of a 12-year-old patient whose symptoms initially presented as mild bone pain.

Materials & Methods

Our case involves a 12-year-old girl who presented in February 2017 with pain in her right thigh. The pain had started three weeks earlier without any apparent cause. Initially, it was exertional, but it gradually became persistent. Notably, she had a fever three days before the onset of pain. Her medical history was unremarkable, except for bilateral metatarsalgia in September 2016, which had been treated with analgesics. On physical examination, she appeared healthy, walking normally without an antalgic gait. Her knee and hip joints were pain-free. A small swelling was noted in her right thigh, which was tender to palpation, but she was afebrile. X-rays of the right femur revealed a multilamellar periosteal reaction along the shaft (Figure 1). A CT scan confirmed this finding (Figure 2). MRI demonstrated a heterogeneous T1 hyposignal and T2 hypersignal mass infiltrating the muscles over a 27 cm length, accompanied by

a multilamellar periosteal reaction. Additional lesions were observed in the cervical and trochanteric region of the same femur and the left pubic rami, along with synovial effusion in the right hip and knee (Figure 3). Abdominal ultrasound and thoracic CT scan were unremarkable. Laboratory tests revealed an elevated C-reactive protein (CRP) level of 42 mg/L and an erythrocyte sedimentation rate (ESR) of 115 mm/h. Subsequent X-rays of the feet showed a multilamellar periosteal reaction in the 2nd and 4th metatarsals of the left foot and the 2nd metatarsal of the right foot (Figure 4). A whole-body MRI (Figure 5) revealed multiple lesions in the distal left humerus, right humeral shaft, proximal left humerus, left acetabulum, left pubic rami, right sacrum, 2nd and 3rd phalanges of the left ring finger, right femoral neck, and right femoral shaft, with an associated signal abnormality in the surrounding muscles. Given the high suspicion of Ewing sarcoma, a biopsy of the femoral lesion was performed. Histopathological examination showed nonspecific chronic inflammatory changes, with no evidence of malignancy. The patient was treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics, leading to a complete resolution of pain.

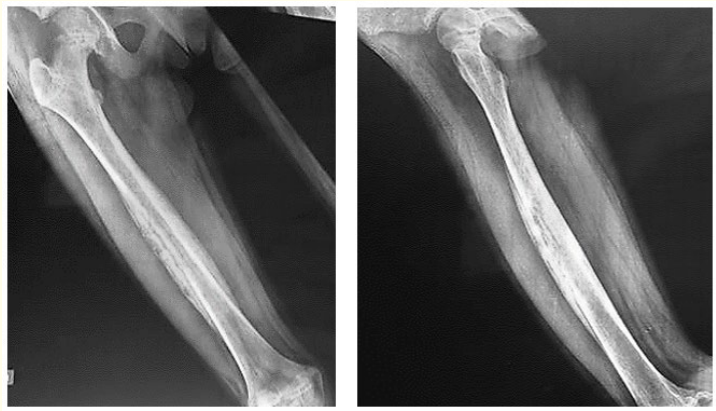

Figure 1: Figure 1: X-ray of the femur showing multilamellar reaction.

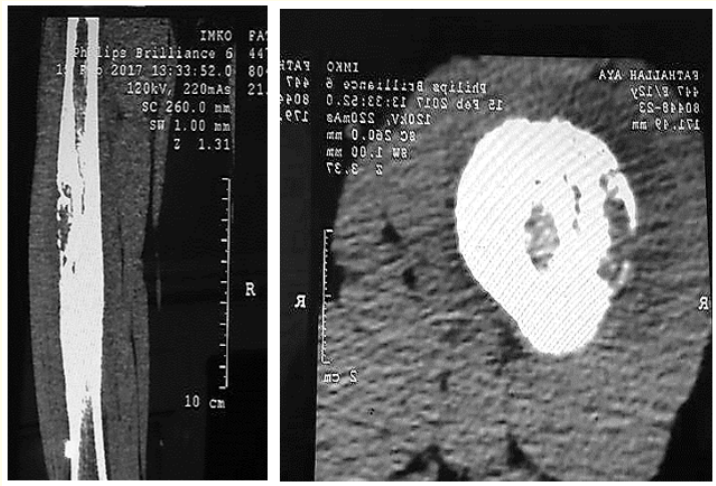

Figure 2: CT scan showing an multilamellar reaction.

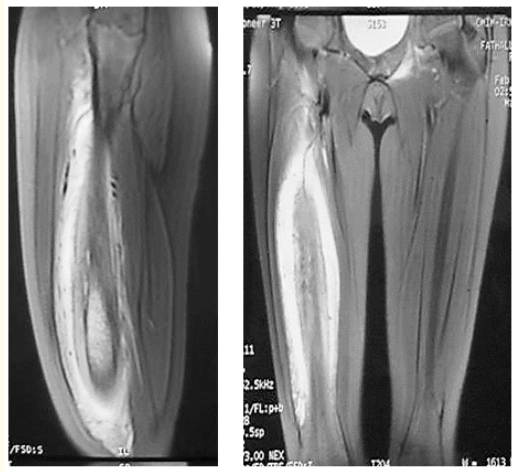

Figure 3: MRI of the right thigh.

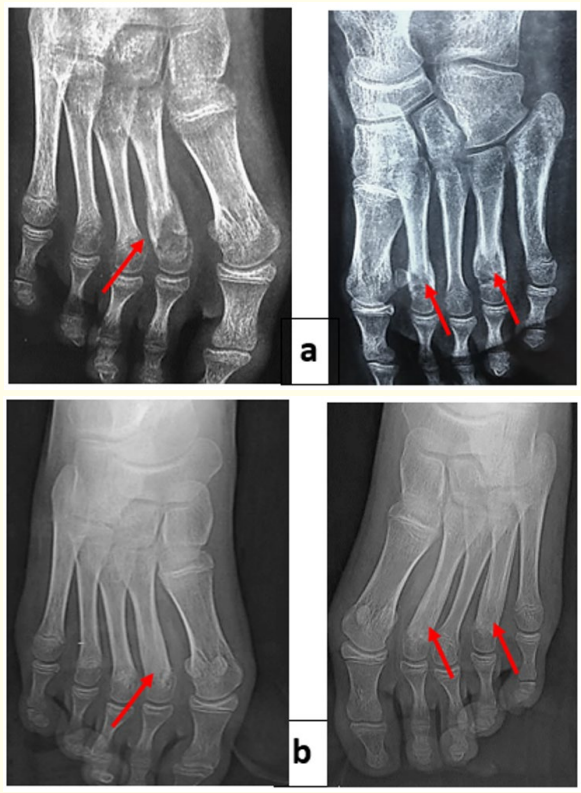

Figure 4: X-rays of both feet.
a. on 09/2016.
b. on 02/2017.

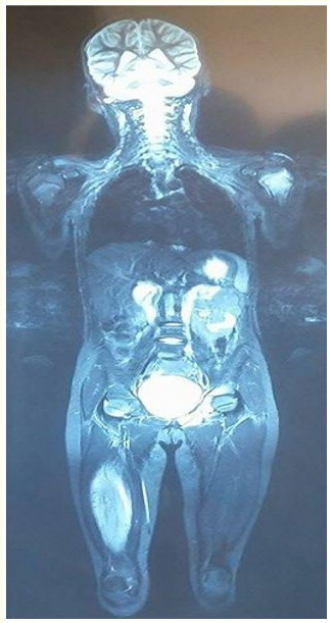

Figure 5: MRI of the whole body.

Discussion

Chronic Recurrent Multifocal Osteomyelitis (CRMO) is an autoinflammatory skeletal disease characterized by unifocal or multifocal nonbacterial inflammatory bone lesions in the metaphysis of long bones [1] It was first described in 1972 by Giedon et al [2] who called it "chronic symmetrical osteomyelitis", and later renamed CRMO by Gustavson et al. [3] and Probst et al. [4] in 1978. It has a Prevalence of around 1-2 per million [5] and an incidence of approximately 1:1,000,000. These numbers are probably higher, as not all the cases are reported as CRMO, as it is frequently misdiagnosed as tumors or bacterial osteomyelitis. CRMO mainly affects children and adolescents; the onset is usually around the age of 10 years with a range between the ages of 4-14 years [6], It most often corresponds to the pre-pubertal stage [7], It is found more in girls [6-8]. The pathogenesis of Chronic Recurrent Multifocal Osteomyelitis (CRMO) remains incompletely understood [9, 10]. While initial hypotheses suggested an infectious etiology involving organisms such as Staphylococcus aureus, Mycoplasma hominis, Propionibacterium acnes, and Chlamydia [6, 9], subsequent studies have not substantiated these claims, effectively ruling out infection as the primary cause [11-13]. The association of CRMO with dermatologic conditions like psoriasis and palmo-plantar pustulosis, as well as inflammatory bowel diseases such as Crohn's disease and ulcerative colitis, coupled with its responsiveness to corticosteroid therapy, has led to the hypothesis of an underlying autoimmune mechanism [11]. Notably, CRMO is a prominent feature in syndromes such as Majeed syndrome and deficiency of the interleukin-1 receptor antagonist (DIRA), implicating interleukin-1 in disease pathogenesis [14]. It predominantly affects the metaphyses of long bones [2, 7, 15], especially the proximal and distal regions of the tibia. Other commonly involved sites include the femur, clavicle, spine, pelvis, ribs, sternum, and mandible. Lesions may occur in any bone, including vertebrae [16, 17]. Clinically, patients often present with insidious onset of bone pain, which may be accompanied by tenderness, swelling, or limited range of motion. Notably, systemic symptoms such as fever are typically absent, distinguishing CRMO from infectious osteomyelitis [6, 11]. The disease can manifest as unifocal or multifocal lesions, with a propensity for bilateral involvement [9]. The patients with CRMO may experience symptoms for up to 10 years, with the average being 2 years [15] although Björkstén et al. have reported a case of a patient whose symptoms persisted for 15 years [12]. Our patient was 12 years old with no medical history. In patients with Chronic Recurrent Multifocal Osteomyelitis (CRMO), labo-

ratory findings can vary. Inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are often elevated, indicating systemic inflammation. However, these markers are not specific to CRMO and can be normal in some cases. Other laboratory tests, including complete blood counts and metabolic bone profiles, are typically within normal ranges. Blood cultures and serological tests are usually negative, reflecting the nonbacterial nature of the disease. Therefore, while laboratory tests can support the diagnosis by indicating inflammation and excluding infectious causes, they are not definitive for CRMO [18]. The radiological manifestations of Chronic Recurrent Multifocal Osteomyelitis (CRMO) are variable and non-specific, often leading to diagnostic confusion, particularly with neoplastic conditions. Lesions can appear purely osteolytic, osteolytic with a sclerotic rim, mixed (both lytic and sclerotic), or entirely sclerotic [4, 7, 9]. Standard radiographs commonly reveal lytic and sclerotic lesions in the metaphyses of long bones and the medial clavicles [19]. MRI is particularly useful in assessing disease extent, including transphyseal involvement, bone marrow edema, periostitis, and soft tissue inflammation. It also helps detect multifocal lesions, some of which may be asymptomatic, providing a comprehensive view of skeletal involvement [20], as it was with our case. For our patient, a full body MRI was indicated after finding several radiological lesions. The role of anatomopathology in diagnosing Chronic Recurrent Multifocal Osteomyelitis (CRMO) is primarily to exclude infectious or malignant causes, as there are no specific histopathological markers for CRMO. Bone biopsy is generally considered when there are constitutional symptoms, a solitary bone lesion, or an atypical presentation, as these may raise concerns for alternative diagnoses such as bacterial osteomyelitis or bone tumors [7, 13, 19, 21]. However, in cases where patients exhibit typical CRMO features—such as lesions in characteristic locations (clavicle, metaphysis of long bones, vertebral bodies), normal laboratory tests, absence of systemic symptoms, and the presence of associated inflammatory conditions (e.g., psoriasis, Crohn's disease),a biopsy may not be necessary due to the high clinical suspicion of CRMO.

Thus, while anatomopathology plays a crucial role in ruling out differential diagnoses, CRMO remains a diagnosis of exclusion, and biopsy should be reserved for cases where clinical and imaging findings are inconclusive or atypical.

Antibiotic treatments have not demonstrated efficacy in managing of CRMO. The initial therapeutic approach typically involves nonsteroidal anti-inflammatory drugs (NSAIDs), which have shown effectiveness in approximately 40-80% of pediatric cases [8]. In instances where patients exhibit systemic symptoms or present with highly active disease, corticosteroids may be considered. For cases unresponsive to initial treatments, particularly those with vertebral involvement, bisphosphonates are recommended. Additionally, tumor necrosis factor (TNF) inhibitors have been identified as a potential treatment option, especially for patients with concurrent immune-mediated conditions. The efficacy of interleukin-1 antagonists remains under investigation. Surgical interventions are generally deemed unnecessary in the management of CRMO [22]. CRMO is a chronic condition characterized by frequent relapses. A study by Andreasen et al. observed that patients with radiological lesions but no clinical symptoms experienced disease exacerbation upon discontinuation of treatment, with 60% relapsing in the first year and 71% in the second year. This underscores the importance of identifying risk factors for recurrence and implementing long-term monitoring strategies. Risk factors for relapse may include the presence of asymptomatic lesions detected by imaging, the extent of initial disease involvement, and the speed of treatment tapering. Therefore, a comprehensive follow-up plan, possibly involving regular imaging studies and cautious adjustment of therapy, is essential to manage CRMO effectively [23].

Conclusion

CRMO is rare and difficult to diagnose. A detailed history and a meticulous clinical examination should be performed to avoid misdiagnosing this disease. Whole body MRI is the gold standard today in the exploration of these patients.

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