STUDENT ARTICLE

Chronic Recurrent Multifocal Osteomyelitis: A Forgotten Diagnosis

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ABSTRACT

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare condition characterized by longstanding inflammatory bone lesions. Often initially misdiagnosed as infectious osteomyelitis, the time to accurate diagnosis is frequently lengthy and may lead to unnecessary diagnostic studies and ineffective treatment strategies. We discuss a case of a seven-year-old male who initially presented with right knee pain, followed by intermittent left ankle and hip pain, who was subsequently diagnosed with CRMO eight months later. This case report highlights to primary care providers the importance of considering CRMO as a potential diagnosis in children with recurrent bone pain.

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is an uncommon auto-inflammatory condition generally found in pediatric populations. The disease consists of skeletal lesions, most commonly involving metaphyseal regions of long bones, clavicles, and vertebral bodies. However, CRMO is also closely associated with other inflammatory conditions of the skin and gastrointestinal system, such as inflammatory bowel disease, acne, and psoriasis. The pathophysiology behind CRMO is not yet entirely understood, but is thought to have a genetic component based upon an imbalance between pro- and anti-inflammatory cytokines.[1]

Patients generally present due to refractory bone pain with or without any physical findings such as erythema or swelling. Diagnostic evaluation usually begins with x-rays, then progression to Magnetic Resonance Imaging (MRI) and/or bone scans.[2] When the medical history, physical and radiologic findings are typical, the diagnosis can be made without a biopsy. However, since CRMO is primarily a diagnosis of exclusion, thus biopsies may be required to distinguish CRMO from infectious or malignant pathologies when presentation is unclear.[3]

We discuss a case of a seven-year-old male who initially presented with right knee pain, followed by intermittent left ankle and hip pain, who was subsequently diagnosed with CRMO eight months later.

CASE PRESENTATION

A seven-year-old male presented to his pediatrician with right knee pain after a fall off his bike. Over time, the knee pain improved, but he began experiencing intermittent pain in his left ankle and hip that worsened with activity. His pediatrician recommended ibuprofen and heating pad as needed. However, he continued experiencing refractory pain.

He was fully immunized with no significant past medical history or family medical history. He experienced no joint swelling, erythema of skin overlying joints, fever, weight loss or night sweats. He had no significant travel, exposure to wooded areas, or sick contacts.

Due to refractory pain, x-rays of the left hip and ankle were obtained and were normal except for soft tissue swelling. Laboratory tests were mostly within normal limits with the exception of a slightly elevated platelet count (523 K/mcL), an elevated erythrocyte sedimentation rate (ESR) (43 mm/h), and a slightly elevated peripheral blood neutrophil percentage (64%). MRI of the left ankle and pelvis was performed and demonstrated multiple focal bone lesions and areas of marrow edema and contrast enhancement (figures 1-3). The MRI findings led to concern for the possibility of osteomyelitis, histiocytosis, or malignancy.

Biopsies of the left proximal femur and the left distal tibia lesions were performed. Pathology of the left proximal femur showed hypocellular subcortical marrow without any evidence of inflammation or neoplasia. The left distal tibia, however, showed hypocellular subcortical marrow with histological features associated with chronic osteomyelitis. The lesions were negative for findings of neoplasia (figures 4-5). Tissue cultures for bacteria, fungi and mycobacteria were negative. The patient was referred to Pediatric Infectious Diseases. He was subsequently diagnosed with CRMO and was treated with naproxen with excellent response.

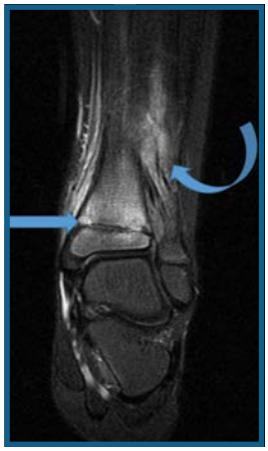

Figure 1

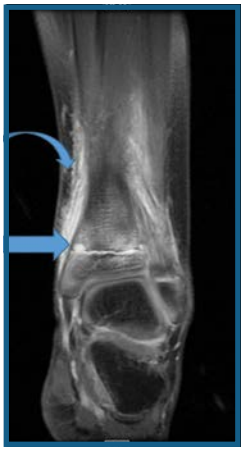

Figure 2

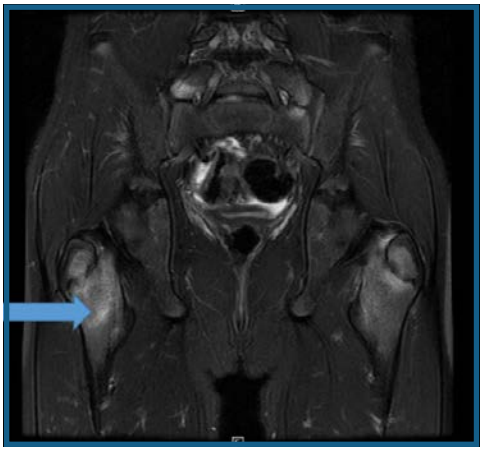

Figure 3

Figure 1: Coronal T2-weighted iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) MRI image of the left ankle shows focal hyperintense signal just superior to distal tibial physis (straight arrow) and within the soft tissues above the ankle (curved arrow).

Figure 2: Coronal T1-weighted MRI image of the left ankle after injection of intravenous gadolinium contrast shows increased focal enhancement just superior to distal tibial physis (straight arrow) and within the soft tissues above the ankle (curved arrow).

Figure 3: Coronal T2-weighted iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) MRI image of the pelvis and hips shows patchy hyperintense signal in the right proximal femur (arrow) representing marrow edema.

DISCUSSION

When a child presents with the primary symptom of refractory bone pain, the initial differential generally includes infectious osteomyelitis, benign bone tumors, and primary bone malignancies. The differential expands depending on other features of the history and clinical presentation. When coupled with leukocytosis, fever and weight loss, possibilities such as leukemia and lymphomas must be considered. In patients with a history of chronic steroid use, avascular necrosis must be ruled out. In patients with malnourishment concerns, the possibility of vitamin deficiencies, particularly vitamin C deficiency leading

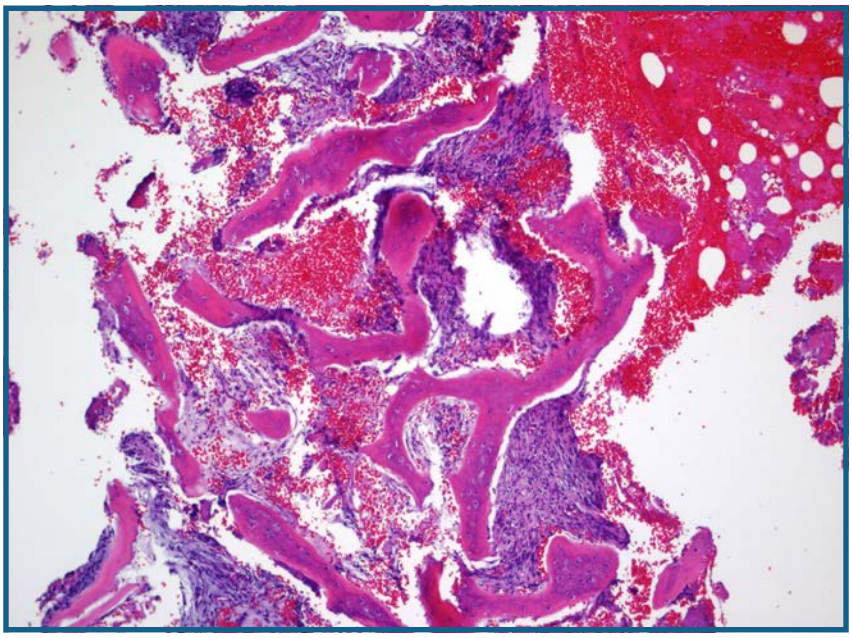

Figure 4: Histopathology of the left distal tibia on low power

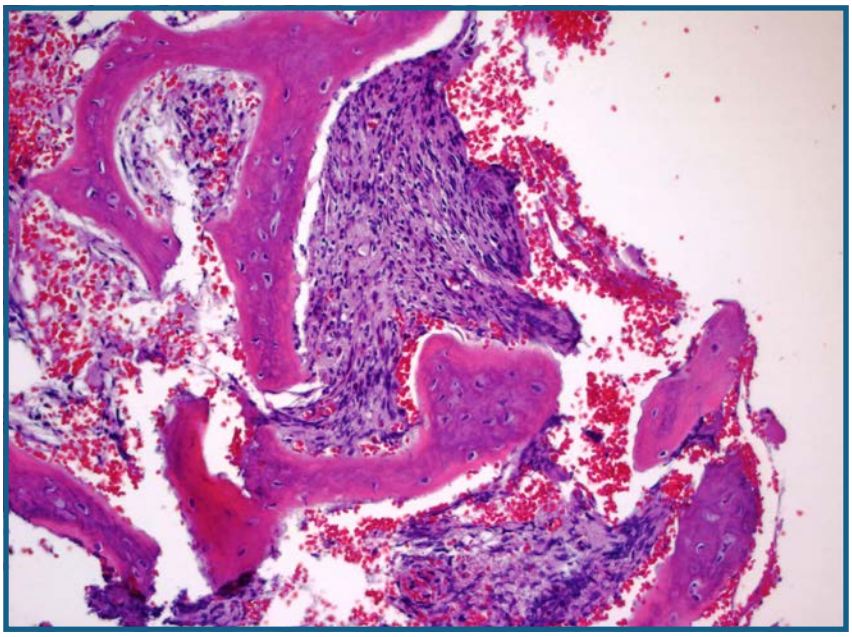

Figure 5: Same on high power, showing hypocellular subcortical marrow with features associated with chronic osteomyelitis, and no evidence of neoplasia.

to scurvy, must be considered. CRMO can be a particularly elusive diagnosis. Laboratory studies such as peripheral white blood cell counts, ESR and C-reactive protein (CRP) are often normal or only slightly elevated.[1]

X-rays are frequently the first imaging step in the diagnosis. While they are often normal in early disease, they may reveal areas of lytic changes surrounded by sclerosis. In the past, x-rays were often followed by a technicium-99 bone scan to survey the extent of involvement, but bone scan has now been mostly supplanted by use of MRI. This is a much more sensitive study and can often reveal changes earlier on, such as edema and soft tissue involvement of the surrounding area.[2] When biopsy is indicated, the histopathologic findings generally include an inflammatory infiltrate consisting of lymphocytes, plasma cells, histiocytes, and occasional neutrophil granulocytes.[4]

The patient in this particular case had a diagnostic delay of almost eight months. Unfortunately, this length of delay in diagnosis is typical in CRMO, since it is very uncommon condition not often considered in a physician's differential diagnosis in a patient complaining of bone pain. Indeed, the average time of symptom onset to CRMO diagnosis is 15 months.[5] In order to avoid delays in diagnosis, physicians must be diligent in including CRMO in the differential for such cases. Because CRMO is so often presumed to be infectious osteomyelitis, the work-up must be focused on discriminating between the two entities. The diagnostic modalities of choice for both infectious osteomyelitis and chronic recurrent multifocal osteomyelitis are generally an MRI followed by bone biopsy if deemed necessary. However, in infectious osteomyelitis, bone cultures from biopsy typically are positive for a specific organism, whereas in CRMO cultures are be negative by rule. Thus, providers may waste significant time and costs by repeating cultures in CRMO in what are futile attempts to identify an infectious etiology. The presence of typical MRI findings coupled with a negative culture is highly suspicious of CRMO, and further work-up is often not required.

Antibiotics have been proven to play no role in the management of CRMO. Nonetheless, a study published in 2018 reported that one-third of 284 surveyed patients with CRMO received antibiotics prior to their diagnosis, and one-fourth of those patients received them for greater than six months.[6] Such antibiotic courses are lengthy, expensive, and entirely unhelpful for CRMO and also come with significant side effect profiles, increased risk for *Clostridium difficile* infection, and potential to contribute to overall antimicrobial resistance.

Treatment of CRMO typically begins with nonsteroidal anti-inflammatory drugs (NSAIDs), which have been associated with a response rate of up to 80%.[2] In patients who fail to respond to NSAIDs, trials of temporary or chronic oral corticosteroids have been used, often with great benefit. In refractory patients, various agents such as methotrexate, TNF-alpha inhibitors, bisphosphonates, and IL-1 receptor blocking agents have been attempted with mixed results.[3]

The intent of this report is twofold – to share an interesting case of an uncommon disease, and to remind medical practitioners to consider CRMO as a potential diagnosis in chronic and/or recurrent bone pain in children. While CRMO is infrequent, it is important to keep the disease in mind in patients with confounding refractory bone pain and the characteristic imaging findings. With greater awareness of this condition, perhaps medical providers will be able to prevent unnecessary diagnostic evaluations, reduce unneeded courses of antibiotics, and shorten the time to effective treatment.

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