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CLINICAL CASE

Chronic recurrent multifocal osteomyelitis in a pediatric patient, a case report

Osteomielitis crónica multifocal recurrente en paciente pediátrico, reporte de caso

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Abstract

Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a very rare disease, of unknown origin that affects primarily the metaphysis of long bones. It is characterized by an insidious onset of symptoms and multiple remissions. The chronicity of symptoms, the diagnostic imaging and the lack of response to first line antibiotic treatment, should be helpful for diagnostic. **Objective:** Present a clinical case, based on clinical, laboratory, radiologic imaging and histopathological results, that ultimately led to the diagnostic of CRMO. **Case report:** 9 year old, female patient, with one month of bilateral knee and left ankle arthralgia. Bone Gammagraphy and full body MRI, showed multifocal bone inflammation. These findings led to a biopsy, that turned negative for malignancy and infection. Given all the information available from the laboratory test results, radiologic imaging and histopathological findings, CRMO diagnosis was made. NSAID treatment was order, with good results. **Conclusions:** CRMO is a rare disease that even to date and with cutting edge technology, still represents a diagnostic challenge that primarily relies on a high level of suspicion, for a timely and correct treatment.

Keywords:
Chronic recurrent multifocal osteomyelitis, children

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Introduction

Chronic recurrent multifocal osteomelytis (CRMO) is a rare disease, which mainly affects children and adolescents, predominating in the female gender. In 1972 it was first described as a subacute to chronic and symmetric osteomyelitis, and back in 1986 it received the name of CRMO[1,2]. Although it has an unknown etiology, it is believed that it may have an autoimmune, infectious or genetic origin.

CRMO is a disease of insidious onset, presenting frequently some exacerbations and relapses. From a clinical point of view it mainly manifests with inflammatory symptoms such as bone pain, paresthesias, erythema, edema and local functional limitation, and usually targets the metaphysis of long bones, mainly the femur and the tibia, as well as other places such as the clavicle, mandible, sternum and vertebrae[3,4]. In some cases, fever may occur, usually followed by skin disorders[1,2].

When thorough blood test screening is performed, it is common to find elevated erythrocyte sedimentation rates, and the blood count may be normal or leukocytosis may be present. As for antinuclear antibodies and rheumatoid factor, both are negative, and some patients may be positive for HLA-B27 antigen[5].

On the X-ray imaging, lytic lesions with progressive sclerosis are the likely findings. The magnetic resonance imaging (MRI) and the Bone Scintigraphy could help to better characterize focal lesions and determine their extent. Furthermore, both of them can potentially highlight hidden lesions previously unseen with x rays[2].

As bone multifocal lesions are a common finding in a wide variety of diseases, both tissue culturing and biopsy are tools of great importance, since the histopathological findings play a determining role in the diagnosis and help rule out other diseases[1].

Regarding treatment options, the best choice are those non-steroidal anti inflammatory drugs (NSAID), which have shown a response rate of over 80%. There are other options, which are corticosteroids, interferon, calcitonin, azithromycin, sulfasalazine and bisphosphonates, to name but a few[1].

The purpose of this article is to report a clinical case of CRMO, in order to outline the clinical manifestations, laboratory, and radiological findings, as well as the histopathological study, which led to the final diagnosis.

Clinical Case

A female patient of 9 years old, with a background of 1 month presenting arthralgia in both knees and left ankle, along with fever of 39 ºC (102.2 ºF), without other symptoms. At the moment of physical examination, her general appearance was not compromised; there was claudication, left ankle edema, slight erythema and pain on palpation, without limitation in the joints movement arches, she felt pain when bending the left knee, but without inflammatory signs or any compromise in mobility.

The patient had normal blood count and C-reactive protein (CRP) within expected values for her age, when she was admitted to the Hospital, with a slightly elevated erythrocyte sedimentation rate (ESR). In the comparative ankle x-rays, soft tissue edema was observed, as well as periosteal lifting and bone marrow involvement, with a possible cystic lesion close to the left distal fibula.

Subacute osteomyelitis was diagnosed with these findings, blood cultures were taken and antibiotic treatment with clindamycin was the physicians first line choice, which was administered for 21 days. Microbial cultures yield no microbiological isolation.

During the treatment, inflammatory symptoms were observed in other joints, thus a total Bone Scintigraphy was performed, showing inflammatory areas in the right distal femur, both knees, left distal tibia-fibula (figure 1). Given this result, it was decided to extend the scope of the diagnostic imaging with a full body MRI, which reported multifocal infiltrative or inflammatory bone changes with impaired signal in-

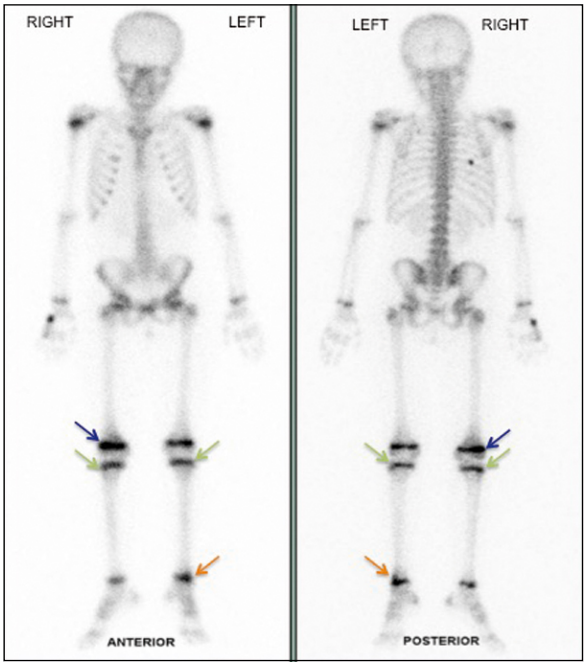

Figure 1. Inflammatory areas in the right distal femur (blue arrows), both knees (green arrows), left distal tibia-fibula (orange arrows).

tensity, compromising the distal metaphyseal region of the right femur, observing a lobulated lesion, with relatively well defined borders and with a continuous periosteal reaction of approximately 14 mm in diameter (figure 2). The damage continued all the way to the metaphyseal region with extension to the physis of the left distal tibia. Some lesions were also found in the metaphysis of the left fibula, of up to 10 mm in diameter, presenting similar characteristics and with a hyperintense image in the distal metaphyseal region of the ulna on the right side, without vertebrae, pelvis or other bone structures involvement.

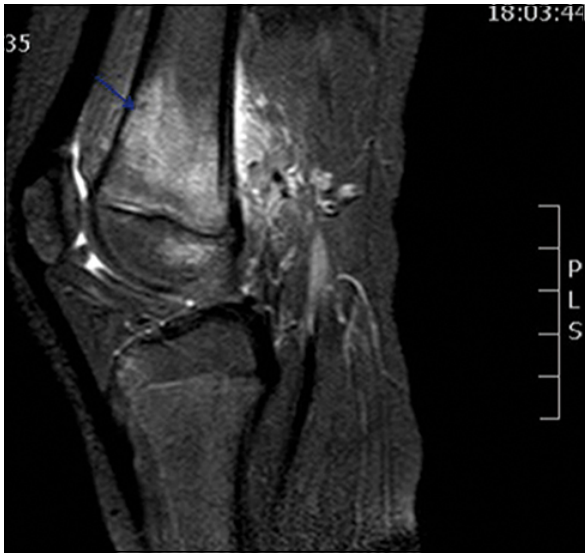

Figure 2. Multifocal infiltrative bone changes compromising the distal metaphyseal region of the right femur, observing a lobulated lesion, with relatively well defined borders and with a continuous periosteal reaction (blue arrow).

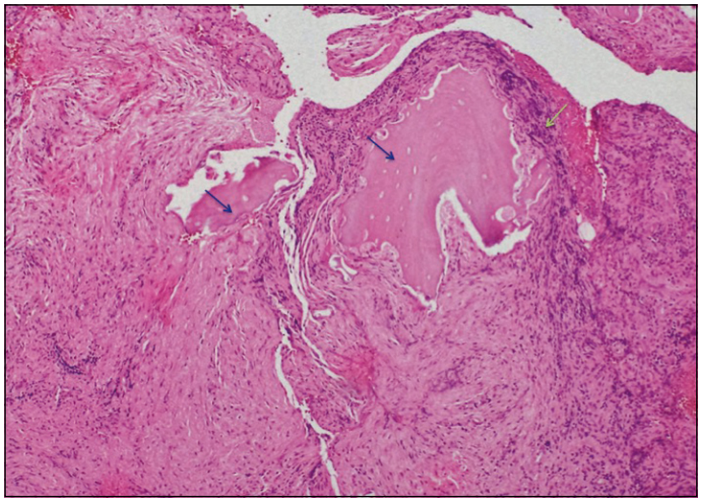

Figure 3. Whitin the fibroconective stroma, some small bone fragments were identified some of which showed necrotic appearance (blue arrows) with mixed inflammatory infiltrate (green arrow).

These findings led to the decision of taking the patient to the OR in order to rule out neoplastic etiology or histiocytosis. Biopsy tissue of right femur bone and left fibula were obtained. The histopathological study reported similar histological characteristics in both samples, but in the sample obtained from the fibula were far more acute. Multiple cross-sections showed clear evidence of the presence of dense fibroconective stroma with mixed inflammatory infiltrate, with a clear predominance of lymphoplasmocytic and neutrophil polymorphonuclear cells. Within the fibroconective stroma, small bone fragments were identified some of which showed necrotic appearance. In the fibula sample epithelioid histiocytes aggregates were seldom observed, with multiple foci of central necrosis (figure 3).

All these findings led to the conclusion that the patient's under an active chronic inflammatory process, morphologically compatible with osteomyelitis. Bone cultures and special stains for acid-fast bacilli, fungi, and aerobic bacteria, as well as the previous study for malignancy, all turned out negative. Langerhans-type multinucleated giant cells, S100 and CD1a markers were not identified in any of the samples, therefore ruling out Langerhans cell histiocytosis.

According to the onset and evolution of symptoms, along with the blood test, radiological and the histopathological findings, the diagnosis was CRMO. The proper treatment with naproxen was ordered and physical rehabilitation was started, with adequate clinical response follow up.

Discussion

CRMO is an aseptic inflammatory disease of the bones, with multiple exacerbations, as well as episodes of intermittent remission. It mainly affects to pediatric population, with more than 85% of cases presented in female patients. It occur usually between 5 and 10 years of age[5]. In Norway, from a certain cohort of children with CRMO, in which 28% of the patients included were Caucasians, 79% were of affected patients were female and the mean age of onset of the disease was 10.3 ± 2.2 years[6], a range that perfectly fits with the demographics of the patient in our study.

CRMO etiology is unknown, but the evidence supports that there is a strong genetic and immunological component. Recent clinical data have shown the role of IL-1 as an important pathway in the development of sterile bone inflammation, which has led the scientific community to believe that there is a marked imbalance between the pro-inflammatory cytokines (such as IL-6 and TNF-α) and the anti-inflammatory cytokines (in most cases IL-10)[7-9].

It mainly affects the metaphysis of long bones, being commonly found in the femur and the tibia, followed

by the clavicle and finally the vertebrae. It can sometimes compromise the jaw, and some calcaneus and less frequently lesions are detected in the ribs, sternum, pelvis and skull[10]. Barrani et al., reported a 12-year-old female patient who started recurrent episodes of left supraorbital headache, followed by periorbital dyschromia. He performed a brain and orbital MRI, which showed a subacute inflammatory process. Histological findings of the biopsy of the osteolytic lesions later found in the clavicle allowed him to establish a final diagnosis[11]. The CRMO could affect any bone in multifocal form and the symmetrical compromise is very commonly present[5,12,13]. Our case report patient had a compromise of the distal metaphysis of the right femur, left ankle, left distal fibula and right ulna, which are congruent with the commonest places of CRMO reported in the literature.

CRMO has an insidious onset of symptoms, with an average delay of diagnosis of up to 12 months in some reports. The patients firsts symptoms are in most cases local pain, functional impotence, erythema and cramps, which could be easily mistaken for bacterial osteomyelitis. Most of patients have more than one bone lesion at the time of diagnosis, with an average of around 5, and some of them may be asymptomatic as average. In a cohort of 178 pediatric patients with CRMO in France, 70% presented multifocal bone lesions, with an average of 2 to 9 lesions per patient at the time of diagnosis, and a 30% had a single bone lesion[14]. These Our patient also had an onset of inflammatory symptoms and signs in both knees and left ankle, however, the full body MRI reported multifocal, infiltrative bone changes in 4 joints.

Up to 25% of patients may present skin lesions, such as palmoplantar pustulosis, acne, psoriasis, pyoderma gangrenosum and SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis)[2,16] which is one of the most severe forms of sterile inflammation of the bones[17]. In addition, extra-osseous involvement has been reported, such as Crohn's disease, ulcerative colitis, Sweet's syndrome, anterior uveitis and respiratory system involvement[1,4,9,13,14].

The blood tests may show leukocytosis, an ESR increase and no microbiological isolation found in bone tissue cultures. From the immunological point of view, ANAS and rheumatoid factor are negative, although some patients may be positive for the HLA B27 antigen[2]. According to the previously mentioned cohort made in France, the laboratory tests showed an inflammatory response in a 67% of the patients, and the HLA-B27 antigen was detected in a 7%, and ANAS were positive in a 12% of the cohort[15].

The full body MRI should always be considered in order to detect hidden lesions, that were not previously found with physical examination. This procedure has a reported a sensitivity of 82-100% and a specificity of up to 96%. Furthermore, it has the advantage of being a ionizing radiation free study, that is very good at detecting lesions confined to the marrow and can also be used as a follow up study. Another option is the total Bone Scintigraphy, which has a sensitivity of 73-100% when performing 3 phases using 99mTc-MDP (methylene diphosphonate)[18]. In this clinical case presented, both exams showed multifocal infiltrative bone changes.

In this type of chronic diseases, blastic lesions can be found, and sclerosis associated with hyperostosis usually appears[2], although epiphyseal involvement is rare and the growth plate is generally not affected. Even though it is uncommon, our patient had compromise of the nucleus of growth and elevation of the periosteum of the right femur, and of the left distal tibia and fibula. In the acute phase, the histological study shows polymorphonuclear infiltration and bone resorption, indicating that there could be multinucleated giant cells. In the chronic phase, there is a predominance of lymphocytes and plasma cells with different degrees of fibrosis[8].

The differential diagnosis includes infectious osteomyelitis, fractures, arthritis related to enthesitis or psoriatic arthritis, benign tumoral bone lesions, malignancies, osteonecrosis, osteoporosis, langerhans cell histiocytosis, among others. Taking into account the clinical history, laboratory tests, radiological imaging and the histo-pathological study, the CRMO is a diagnosis of exclusion[13].

Tlougan, M.D et al.[1] proposed the following as the Major Criteria: osteolytic or sclerotic lesion in the X rays, multifocal osseous lesions, palmoplantar pustulosis or psoriasis and sterile bone biopsy with signs of inflammation and/or fibrosis. This along with the following Minor Criteria: normal blood count and overall good health condition, presenting an increased ESR or CRP, with a course greater than 6 months, hyperostosis, associated autoimmune diseases other than palmoplantar pustulosis or psoriasis, or family history with non-bacterial osteitis, autoimmune or autoinflammatory disorder. He also suggests establishing the diagnosis of CRMO with at least 2 major criteria or 1 major criterion and 3 minor criteria. The patient in this clinical case report had 2 major criteria and 2 minor criteria.

The first line of treatment is non-steroidal anti-inflammatory drugs, which shows response rates of up to 80%[12]. Other options described are corticoids, interferon, calcitonin, azithromycin, sulfasalazine and bisphosphonates. In severe cases, tumor necrosis factor (TNF) blockers may be used[3,17].

The prognosis of the disease is relatively benign, although most cases may be resolved spontaneously,

relapses may occur after months or even years, lasting for an average of 5 years, with asymptomatic intervals in between. Higher rates of remission have been seen in patients who have received an aggressive treatment at an early stage, improving the natural history in those in which it may become recurrent. It has been recently proposed that this condition may persist into adulthood, with possible long-term effects, in addition to complications such as infections, early epiphyseal fusion leading to height compromise, bone deformities, backbone kyphosis and persistence of bone sclerosis that have been reported in a minority of patients[1,2,3,14].

Conclusion

CRMO is a rare disease that remains difficult to diagnose. Early detection is often delayed because it can be confused with acute osteomyelitis infection. If patient presents a chronic joint signs and symptoms in several locations that does not respond adequately to proper antibiotic treatment, a high level of clinical suspicion is required. The lack of microbiological isolation, histo-pathological and imaging findings, together with an adequate response to NSAID therapy, should all be recognized as cornerstones and lead to proper diagnose of CRMO and to an early and better treatment.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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