


# Chronic recurrent multifocal osteomyelitis: Report of three cases and literature review

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## ABSTRACT

Chronic recurrent multifocal osteomyelitis (CRMO) is a sterile inflammatory disorder in limbs. It affects mainly children simulating infectious osteomyelitis. It can be associated with other cutaneous and intestinal inflammatory disorders. The levels of acute phase reactants are normal or slightly increased. X-rays show osteolytic lesions surrounded by sclerosis, but at the beginning of the condition they can be normal. Identifying the characteristics inherent in this condition and ruling out infectious etiology makes it possible to establish opportune diagnosis and provide the patient with adequate management.

We present three cases of CRMO: A 24 year-old male with an eight-year history of persistent and recurrent inflammatory signs in his right ankle. An 11 year-old girl who consults repeatedly due to pain in her right hemithorax and clavicle plus her left ankle. And a 12 year-old girl with multiple brief episodes of inflammatory signs in both ankles. The three cases, with no increase in WBC counts and acute phase reactants only slightly increased or normal, meet Jasson major and minor criteria to diagnose CRMO. The patients improved with non-steroidal anti-inflammatory drugs.

It is important to recognize this rare entity as a diagnostic possibility, because opportune diagnosis prevents the patient from receiving unnecessary antibiotic treatment, and it is possible to treat the patient with non-steroidal anti-inflammatory drugs with no need for surgical procedures which increase comorbidities.

**Key words:** Chronic osteomyelitis; recurrence; multifocal; sterile osteomyelitis; non-steroidal anti-inflammatory drugs

**Level of evidence:** V

## OSTEOMIELITIS CRÓNICA RECURRENTE MULTIFOCAL. REPORTE DE TRES CASOS Y REVISIÓN BIBLIOGRÁFICA

### RESUMEN

La osteomielitis crónica recurrente multifocal es un trastorno inflamatorio estéril en las extremidades. Afecta principalmente a niños simulando una osteomielitis infecciosa. Puede estar asociada a trastornos inflamatorios cutáneos y del tracto intestinal. Los niveles de reactantes de fase aguda están normales o levemente altos. Las radiografías muestran lesiones osteolíticas rodeadas por esclerosis, pero pueden ser normales al inicio de la enfermedad. Identificar las características propias de la enfermedad y descartar una etiología infecciosa permiten establecer un diagnóstico oportuno y ofrecer el manejo adecuado.

Conflict of interests: The authors have reported none.

Se presentan tres casos de esta patología. Un hombre de 24 años con síntomas inflamatorios persistentes y recidivantes en el tobillo derecho, de 8 años de evolución. Una niña de 11 años que acude reiterativamente por dolor en hemitórax, clavícula derecha y tobillo izquierdo, y una niña de 12 años con múltiples episodios breves de síntomas inflamatorios en ambos tobillos. Los tres casos, sin leucocitosis, reactantes de fase aguda levemente aumentados o negativos, con criterios mayores y menores de Jasson para diagnóstico de esta patología. Los cuadros mejoraron con antiinflamatorios no esteroides. Es importante conocer esta rara entidad como posibilidad diagnóstica, pues un diagnóstico oportuno evita el uso innecesario de antibióticos y la resolución del cuadro se logra con antiinflamatorios no esteroides, sin necesidad de procedimientos quirúrgicos que aumentan las comorbilidades.

**Palabras clave:** Osteomielitis crónica; recurrente; multifocal; osteomielitis estéril; antiinflamatorios no esteroides.

**Nivel de Evidencia:** V

## Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an inflammatory disorder characterized by episodes of recurrence and remission of osteoarticular symptoms, which affects children who are 10 years old, on average; however, 10% of the patients are older than 20 years of age.<sup>1</sup> Its prevalence is at least 1 case per million of patients. Approximately 50% of the CRMO patients' first- or second-degree relatives has one of these conditions;<sup>2</sup> therefore, there must be a genetic component associated.

It was described by Giedon in 1972 for the first time as "an unusual form of symmetric subacute or chronic multifocal bone lesions of osteomyelitis".<sup>3,4</sup> It is also known as sterile osteomyelitis, non-bacterial chronic osteomyelitis, non-bacterial osteitis, among other terms, and it is considered a chronic disease of aseptic bone-lesion foci with courses of symptoms lasting from 2 to 20 years.

In fact, this clinic profile can represent a juvenile form of seronegative spondyloarthropathy. At least 50% of the patients show bone pain which worsens at night, along with edema and heat in the compromised area. It mainly involves the metaphysis of long bones, clavicles, and vertebral bones, although it has also been described in other areas such as mandible, pelvis, carpal bones and feet.<sup>5-7</sup>

Imaging studies such as X-rays show osteolytic lesions with surrounding sclerosis in the metaphysis of long bones, with neither periosteal reaction nor bone sequestra. Apart from determining the extension of the disease, bone gammagraphy helps diagnose asymptomatic presentations. The most sensitive study to detect CRMO is MRI which, in the active way of the condition, shows bone marrow changes such as T1 hypointensity and T2 and STIR hyper-intensity. Lab studies show CBC, ESR and RCP slightly increased or normal. In general blood and secretion cultures show no results. If germs such as *Staphylococcus epidermidis* and *Propionibacterium acnes* are found, samples might have been contaminated.<sup>6,8</sup>

Time until diagnosis is approximately 18 months, although sometimes it takes longer due to lack of awareness about the condition. This disease is diagnosed by the Jasson criteria (Table): two major criteria or one major plus three minor criteria.

Treatment is empiric for the most part—non-steroidal anti-inflammatory drugs represent the first-choice treatment for the disease, and 80 of the cases respond favorably.<sup>9</sup> Tumor necrosis factor and bisphosphonates have also been acknowledged to treat CRMO.

The aim of this study is to create awareness about CRMO's essential characteristics and clinic presentation.

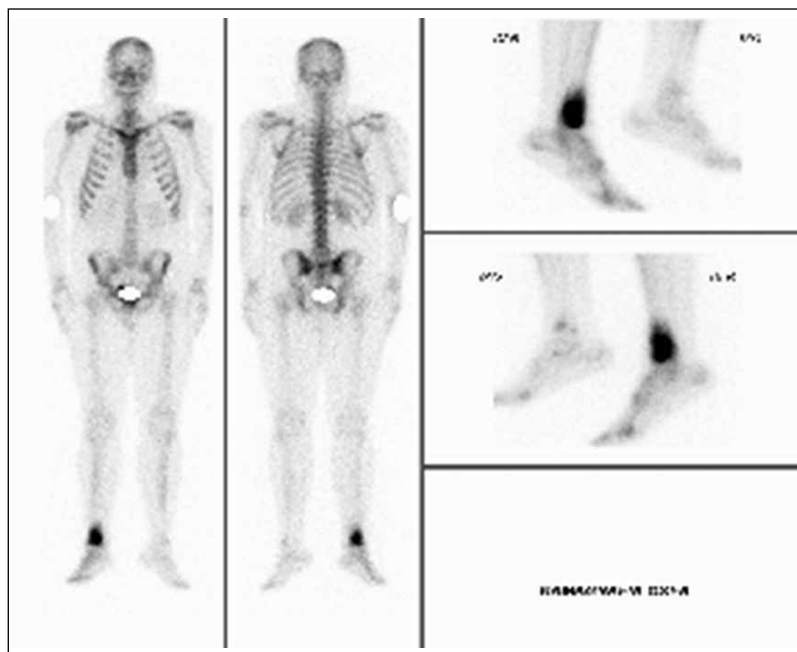
**Table.** Jasson criteria for aseptic bone inflammation

| Major criteria  | Minor criteria            |
|---|---------------------------|
| Multifocal profile  | >6-month history          |
| Psoriasis or palmoplantar pustulosis                          | Autoimmune diseases       |
| Osteolytic and sclerotic lesions                              | (-) Acute phase reactants |
| Bone marrow biopsy: inflammation, fibrosis or sclerosis signs | Hyperostosis              |
|   | Good general condition    |

### Case 1

It is the case of a twenty-four year-old male with no remarkable history, a non-smoker who consults due to an eight-year-history disorder whose onset was pain in his right ankle in association with edema, while practicing sports. Four years later and given the fact that symptoms have not receded, we get X-rays that show cortex thickening in distal tibial bone. Three-phase bone gammagraphy shows severe increase in osteogenic activity and relative vascularity in the distal metaphysis of the patient's right tibial bone (Figure 1). We take CT scan-guided sample, with normal results.

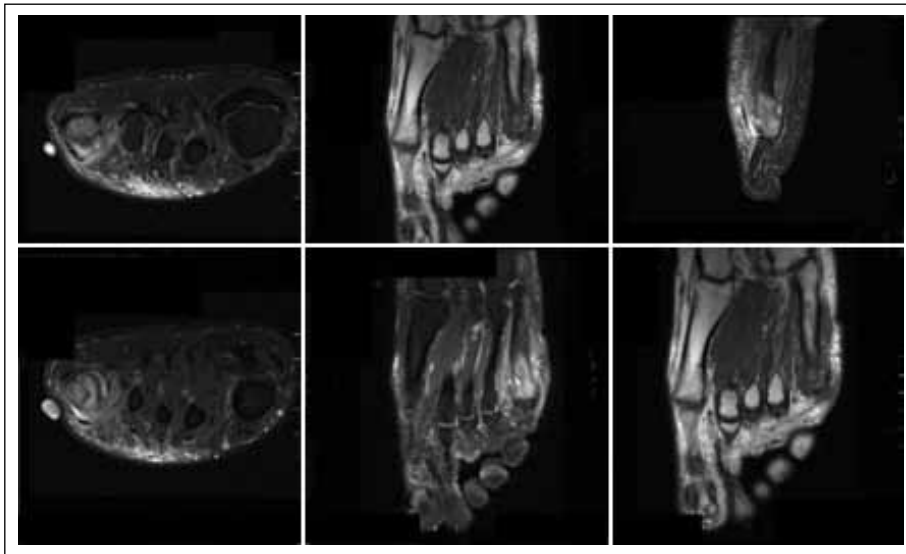
One year later, he consults due to persistence of symptoms, onset of pain and edema in ipsilateral second and third metatarsal bones. He is admitted and he is subject to multiple surgical toilets with bone curettage in his lesions. He is given antibiotics: initially, 2-g oxacillin every 4 hours during 7 days, and then 2-g cefazolin every 8 hours until completing six weeks. The patient has partial recovery. Three years later he consults with a new episode of pain and edema in his contralateral foot while bearing weight. We carry out simple X-rays and MRI in his left foot (Figures 2 and 3). On the other hand, symptoms in his right ankle are back, and we carry out MRI (Figure 4).



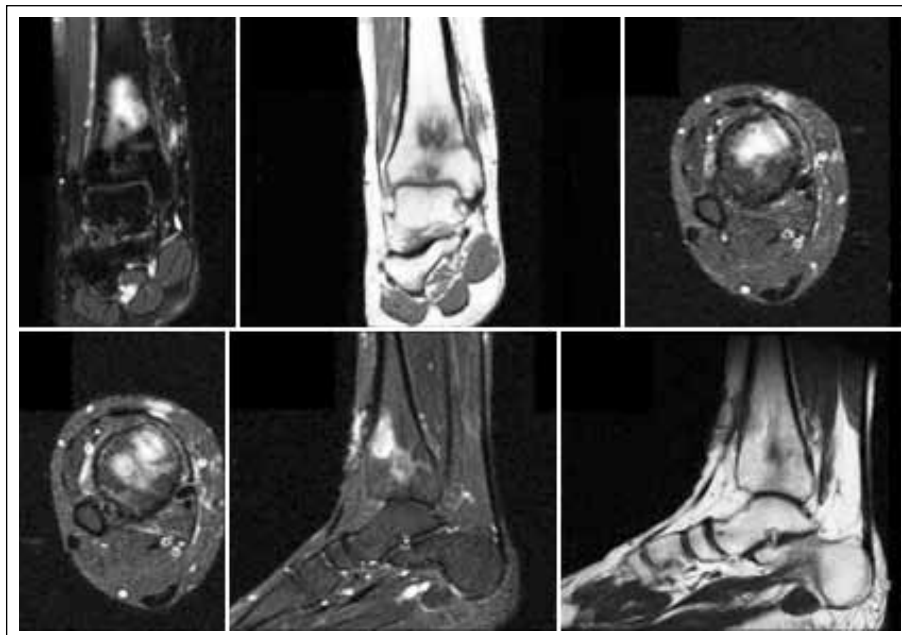
▲ **Figure 1.** Three-phase bone gammagraphy. Severe increase in osteogenic activity and relative vascularity in the distal metaphysis of the right distal tibial bone which rules out infectious processes.



▲ **Figure 2.** Left foot X-ray. Edema and increase in density in periarticular soft tissues around the fifth toe- metarasophalangeal joint.



▲ **Figure 3.** MRI of left feet. Bone marrow edema in the distal end of the fifth metatarsal bone plus edema in surrounding soft tissues.



▲ **Figure 4.** MRI of right ankle. Bone marrow edema in the distal anterior metaphysis of the tibial bone with inflammatory compromise of soft tissues.

The patient is subject to bone resection and bone curettage in his fifth metatarsal bone. Histological analysis shows synovial tissues with chronic inflammation, fragments of osteocartilaginous tissues, and proliferation of fibroconnective tissue of the reparative type.

Throughout, RCP was slightly increased or plainly normal, and ESR was negative without WBC count increase. Due to the lack of improvement and persistent symptoms in the patient's right ankle, we carry out new imaging stud-

ies with identical results. We diagnose CRMO because the patient meets three mayor Jasson criteria (multifoci, osteolytic/sclerotic lesions, sample with signs of inflammation and fibrosis) and three minor criteria (>6month-history, negative RCP and ESR and good general condition).

We initiate treatment with i.m. 4 mg-zolendronic acid in unique dose and 250 mg-naproxen every 8 hours during 10 days, with complete improvement of symptoms during follow-up.

## Case 2

It is the case of an eleven year-old girl with one-year history of right clavicle and hemi-thorax pain, and no other remarkable history or traumatism. She consults the ER repeatedly due to pain in her left ankle while bearing weight, in association with a six-month history of edema, local heat

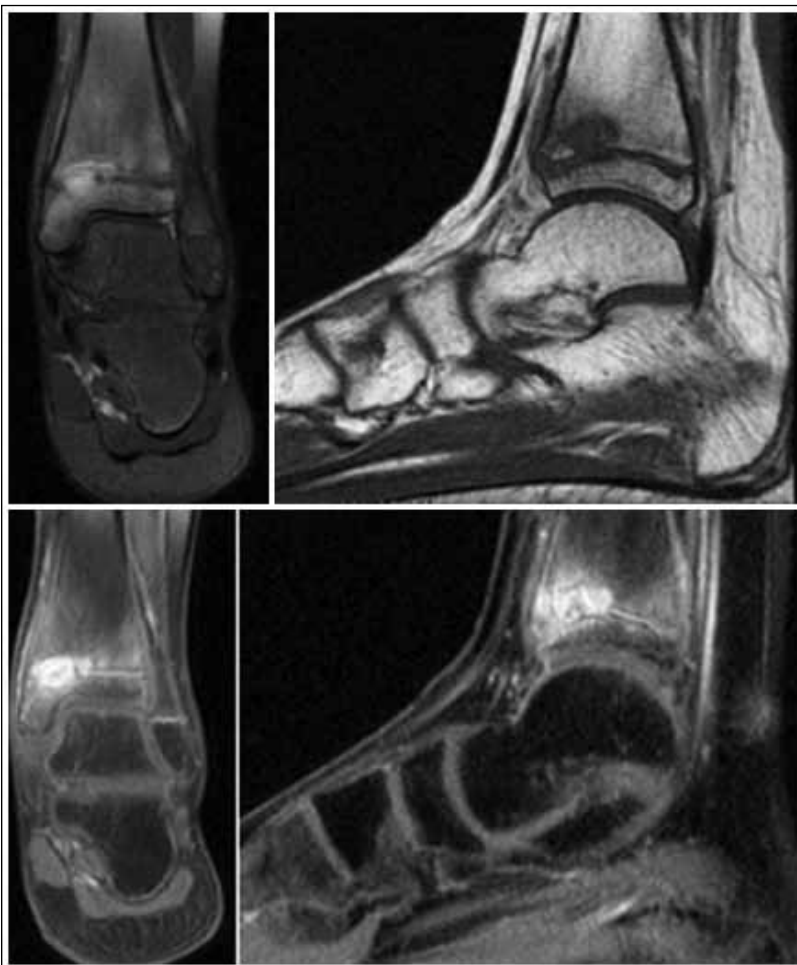
and fever. Ankle X-rays show a lytic lesion in her distal tibial bone (Figure 5).

MRI with contrast in the affected area shows an antero-medial 28x25x9 mm-focal injury in tibial metaphysis, with minimal compromise of growth plate in T1 sequence, high compromise in T2 sequence, and capsular enhancement with contrast (Figure 6).

**Figure 5.** Left ankle X-ray. Radiolucent focal bone lesion which compromises the anterior aspect of the tibial metaphysis, with definite contour and no signs of aggressive periosteal reaction.



**Figure 6.** MRI of ankle with contrast. Distal AM metaphyseal lytic lesion in the tibial bone, extensive to the growth plate with irregularity and bone marrow edema, and a little 8-mm physeal collection within the bone.

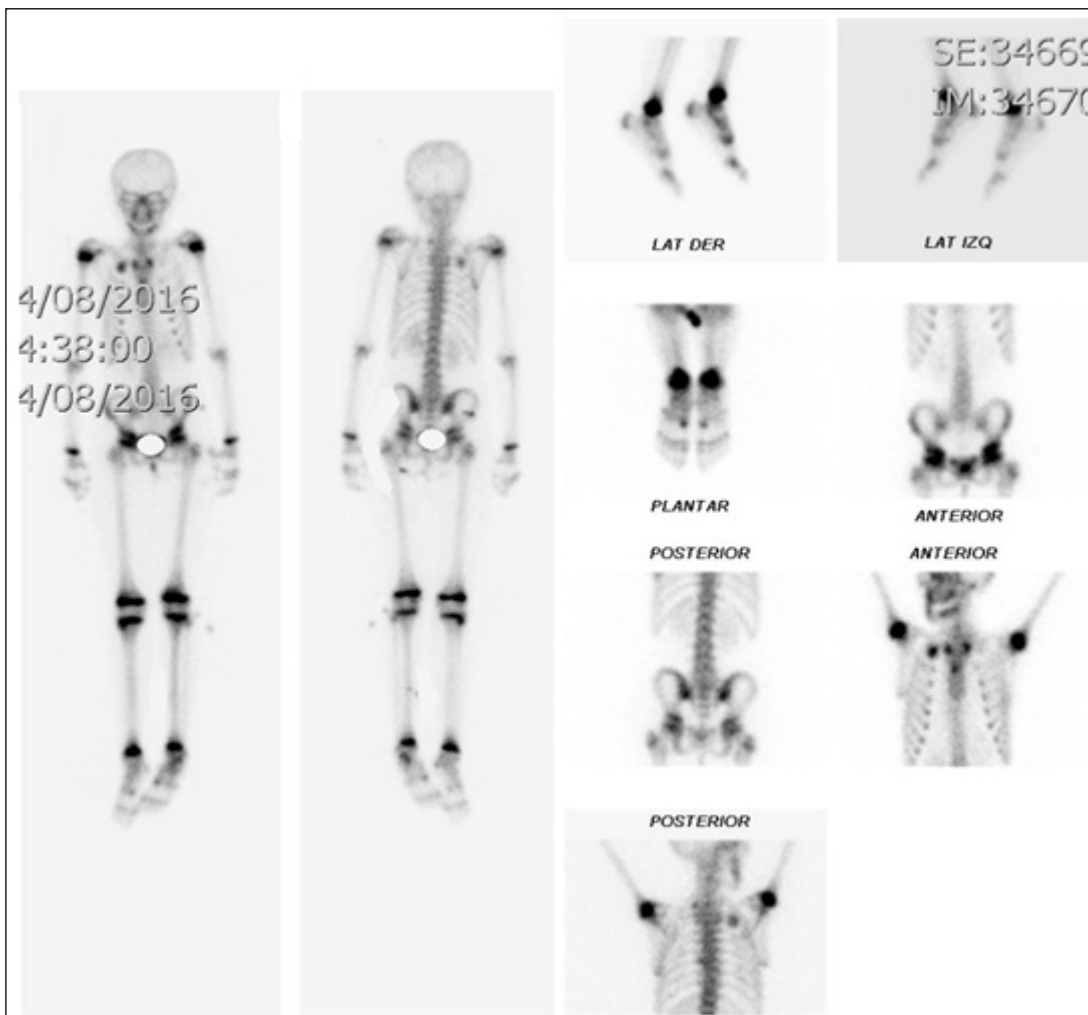


Bone gammagraphy shows enhancement in her first right costal arch near costochondral junction, and also in T8 costovertebral junction (Figure 7).

We rule out a neoplastic condition by biopsy in the patient's left distal tibial bone, which shows fibrous tissues with granulomatous process, and reaction of the foreign body type and suppurative reaction. We prescribe ambulatory treatment with non-steroidal anti-inflammatory drugs, which results in partial improvement. One month later, she consults again due to persistence in ankle pain, with no changes in physical examination. The patient is admitted to treat pain and rule out an atypical infection.

We carry out bone curettage and resection of sequestra in distal tibial bone, and take a new sample for histological analysis, which reports mature bone trabeculae with changes due to bone resorption and unspecific mild chronic inflammation, with no tumor. Cultures for mycobacteria, anaerobic and aerobic microorganisms are negative.

Throughout, acute phase reactants (RCP and ESR) were negative. The patient meets three major and three minor Jasson criteria; therefore, she is diagnosed CRMO and prescribed ambulatory treatment with naproxen. During follow-up, she shows symptoms no more.



▲ **Figure 7.** Three-phase bone gammagraphy. The late image of bone metabolism gives evidence of the satisfactory fixation of the radiomarker phosphate in bone structures in relationship with the patient's age. CT scan shows abnormal focal enhancement involving the right first costal arch near the costochondral junction. Slight enhancement in T3 vertebral body-costovertebral joint towards its left aspect.



### Case 3

It is the case of a twelve-year old girl who initially consults due to one-week history of pain in her left ankle which increases with physical activity, with neither edema nor history of traumatism. She is prescribed analgesic treatment, and symptoms improve. Nine months later, she suffers a new episode with edema in her right ankle in association with pain on her ankle lateral aspect which does not improve with paracetamol. In physical examination she does not show heat or redness. WBC count, ESR and RCP are normal; therefore, she is administered a short cycle of non-steroidal anti-inflammatory drugs, with partial improvement in symptoms. Four months later, she consults again due to pain and edema in her right ankle. MRI shows a 12 mm well defined injury in the distal metaphysis of her fibular bone, adjacent to her growth plate, what suggests ruling out infectious processes (Figure 8). We carry out bone gammagraphy (Figure 9) and diagnose osteomyelitis in her right fibular bone; therefore, we carry out surgical toilet plus bone curettage in her right fibular bone, with negative cultures. We prescribe antibiotic treatment during eight days.

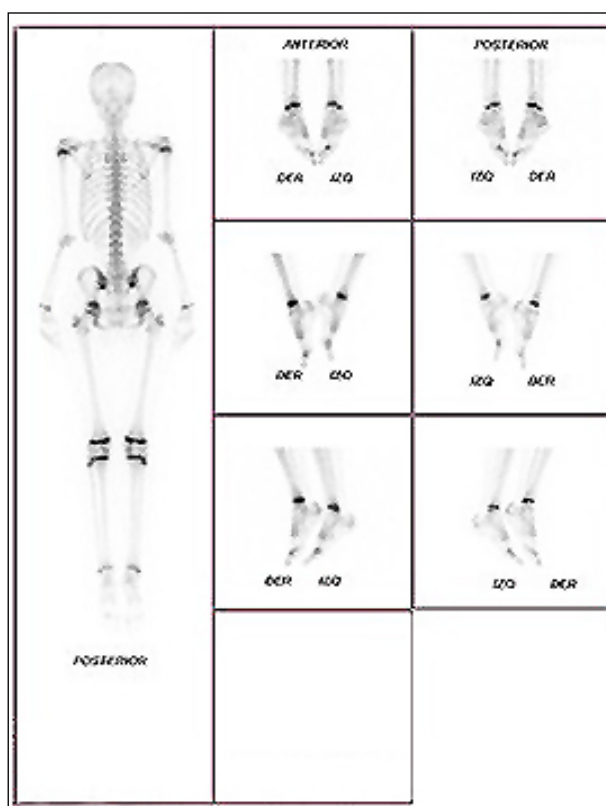
Two months later, she consults due to a five-day history of pain, edema and functional limitation in her right knee and left ankle. The Rheumatology Department prescribes treatment with sulfasalazine, prednisolone, naproxen and Vitamin D. Due to lack of response to sulfasalazine, this treatment is interrupted and the patient is prescribed methotrexate. WBC count, ESR and RCP are negative. One year later, the patient suffers another episode of pain in her left acromial bone and reactivation of pain in her left leg in association with local edema. She is treated with 20 mg-methylprednisolone per day; lab results rule out leukemia, and corticosteroids are interrupted. The patient shows no more symptoms until her latest check-up.

### Discussion

CRMO is a condition with an unusual and recurrent presentation. Its onset is insidious, and it is characterized by pain in joints, bone protuberances and edema in soft tissues. It has intermittent periods of exacerbation and improvement which can last from months until several years, which are the characteristics shown in the three reported cases in this study. It can be associated with fever and cutaneous lesions. The most frequently compromised areas are long bones and clavicle, but there are reports on cases differently distributed,<sup>5-7</sup> such as presentation in costal arches (Case 2). Its ethology is unknown, but it is believed to be an autoimmune and inflammatory condition. In the reported cases, we got diagnosis by ruling out infection. Lab results such as RCP and ESR were normal or slightly increased, as they are in reports in specialized literature.<sup>5,6,10</sup>



▲ **Figure 8.** MRI of left foot-ankle with contrast. Well-defined 12-mm injury in the distal metaphysis of the fibular bone adjacent to the growth plate, what suggest ruling out infectious processes.



▲ **Figure 9.** Three-phase bone gammagraphy. Osteomyelitis in left distal fibular bone.

With respect to radiologic images, findings are the typical ones in osteomyelitis, with osteolytic destruction involving areas adjacent to metaphyses and growth plates in the early stages of the condition, findings which were more frequent in our three patients' ankles. MRI is the imaging study most frequently used to evaluate the extension of the condition and rule out other processes such as infection or

malign neoplasms; however, once CRMO is suspected, it is recommended to take sample for histological analysis, which simultaneously helps rule out malign conditions, as we show in one of the cases we present.

In our patients, clinical onset did not vary; at the beginning, the management was aimed at infectious processes implementing antibiotics, prolonged hospital stay and surgical procedures, as the case usually is with this entity. However, the unusual progression of the cases, their multifocal profile, and results in cultures and imaging studies eventually led us to suspect and diagnose CRMO. In view of such new clinic scenario, we initiated treatment with non-steroidal anti-inflammatory drugs, with improvement in patients' symptoms, what reinforces diagnoses, as it is sustained by specialized literature. As the case usually is when it comes to CRMO, patients underwent recurrence, what made us administer biphosphonates to the patients, at least in one of the cases; all in all, the administration of non-steroidal anti-inflammatory drugs resulted in good outcomes. In follow-up, the three patients show no symptoms after a two-month treatment. The response to first-line drugs such as non-steroidal anti-inflammatory drugs is favorable in up to 80% of the cases;<sup>9</sup> in this context, we had to administer biphosphonates to just one patient, and that is why we believe that only symptoms persistence or recurrence may suggest that non-steroidal anti-inflammatory drugs are not enough to treat the patient, and it is necessary to resort to biphosphonates or biological drugs.

The documented response to inhibitors of the tumor necrosis factor is clinic improvement (65%) or no improvement at all (35%). However, safety with blockers of the tumor necrosis factor (malign neoplasm and infection) and biphosphonates (mandible osteonecrosis, atypical femoral fracture, and other uncertain risks and long-term secondary effects) is still a matter of debate; therefore, it is necessary to carry out more studies to determine their safety in the treatment of CROM.<sup>11</sup>

## Conclusions

It is important to create awareness about this rare entity as a diagnostic possibility in the scenario of the cases we have just described, since bearing CROM in mind may allow us to timely diagnose it and thus decrease prolonged administration of antibiotics and avoid unnecessary surgical procedures which increase morbidity, hospital stay and health costs. Diagnosis is based on clinical, imaging and histological findings and also in objective evaluation of the Jasson criteria. Since it is an exclusion-diagnosis disorder, it is necessary to carry out a thorough analysis of patients' symptoms, images and lab analyses, because in children it pretends to be whichever other disorder which requires aggressive management, such as infectious osteomyelitis, which may end up in disease or even death if not timely diagnosed.

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