Case Report

# Chronic Recurrent Osteomyelitis with Systemic Juvenile Idiopathic Arthritis

Naoya Arakawa[1], Takumi Takizawa[1], Yutaka Nishida[1], Hisako Yagi[1] and Hirokazu Arakawa[1]

1 Department of Pediatrics, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan

## Abstract

A 14-year-old-boy presented with pain and a lump on his left lower leg. Magnetic resonance imaging (MRI) revealed a medullary lesions on T1-weighted images and medullary enhancement after contrast injection. Bone marrow biopsy with curettage revealed an active marrow without evidence of malignancy or infection. The patient had acne on his face and legs. Accordingly, he was diagnosed with chronic recurrent multiple osteomyelitis (CRMO) syndrome. A few months later, the patient developed shoulder joint pain, remittent fever, and an erythematous rash accompanied by a high fever. Blood tests revealed elevated levels of CRP (10.2 mg/dL) and ferritin (557 ng/mL), and hypoalbuminemia (2.8 g/dL). A second bone marrow biopsy revealed hemophagocytosis, but no malignancies. Subsequently, a diagnosis of systemic juvenile idiopathic arthritis (s-JIA) was established.

*Article Information*

***Key words:***
autoinflammatory diseases,
chronic recurrent multiple osteomyelitis,
arthritis,
interleukin-6,
tumor necrosis factor-alpha

***Publication history:***
Received: May 8 , 2018
Accepted: May 24, 2018

***Corresponding author:***
Takumi Takizawa
Department of Pediatrics, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
Tel: +81−27−220−8205
E-mail: takizawt@gunma-u.ac.jp

## Introduction

Chronic recurrent multiple osteomyelitis (CRMO) syndrome, also known as nonbacterial osteomyelitis or chronic nonbacterial osteomyelitis (CNO), is a rare form of multifocal bone lesion with subacute and chronic symmetrical osteomyelitis. We recently encountered a case of an adolescent patient with CRMO who later developed systemic JIA.

## Case report

A 14-year-old-boy presented with a painful lump on his left lower leg. He was previously healthy, with no history of trauma. Plain radiography showed mixed lytic, sclerotic, and thickening lesions on the left tibia (Fig. 1a). Magnetic resonance imaging revealed medullary lesions on T1-weighted image and medullary enhancement after contrast injection (Fig. 1b). Three months later, bone marrow biopsy with curettage revealed an active marrow without evidence of malignancy or infection. The patient had acne on his face and legs. Accordingly, he was diagnosed with chronic recurrent multiple osteomyelitis (CRMO) syndrome and was administered non-steroidal anti-inflammatory drugs, prednisolone, and bisphosphonate, resulting in remission of the clinical symptoms. A few months later, the patient developed shoulder joint pain, remittent fever, and an erythematous rash accompanied by a high fever and diarrhea. Blood tests revealed elevated C-reactive protein (CRP) (10.2 mg/dL) and ferritin (557 ng/mL) levels, as well as hypoalbuminemia (2.8 g/dL). Culture tests for blood, feces, and pharyngeal swabs were negative. There were no indications of active viral or fungal infection (Table 1). Upper and lower gastrointestinal (GI), and capsule endoscopies revealed no obvious mucosal lesions in the GI tract. Computed tomography

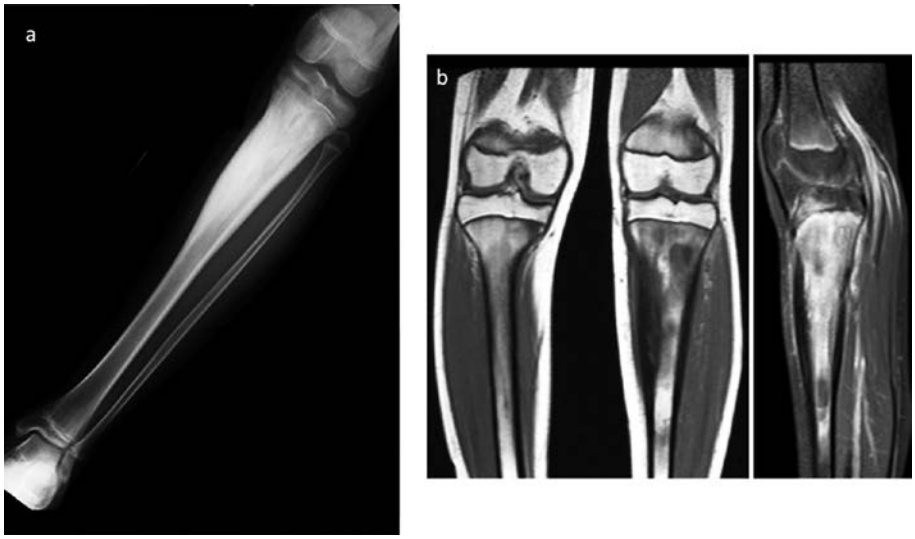


**Fig. 1** (a) Plain radiography shows mixed lytic and sclerotic lesions in the left tibia.
(b) Magnetic resonance imaging shows medullary lesions on coronal T1-weighted image and medullary enhancement on sagittal contrast-enhanced fat-suppressed T1-weighted image.

**Table 1** Laboratory findings

| | |
|---|---|
| WBC | 22,600 /PL |
| Neu | 90 % |
| Eos | 0 % |
| Hb | 11.9 g/dL |
| PLT | $17.7\times10^4$ /μL |
| Ferritin | 557.1 ng/ml |
| CRP | 10.26 mg/dL |
| sIL-2R | 2,028 U/mL |
| ESR 60min* | 54 mm |
| SAA † | 552 μg/mL |
| EBV VCA IgG | 174 |
| EBV VCA IgM | (−) |
| CMV IgG | ＜250 |
| CMV IgM | ＜41 |
| HBs antigen | (−) |
| HCV antibody | (−) |
| HIV antibody | (−) |
| QTF-3G †† | (−) |
| β -D-glucan | (−) |

*ESR: erythrocyte sedimentation rate, † SAA: serum amyloid A, ‡ EBV VCA: Epstein-Barr virus viral capsid antigen, § CMV: Cytomegalovirus, || HBs antigen: Hepatitis B virus surface antigen, ¶ HCV antigen: Hepatitis C virus surface antigen, **HIV:Human Immunodeficiency Virus, † † QTF-3G: Quanti FERON-3G

and PET showed only mediastinal lymph node enlargement. Therefore, inflammatory bowel diseases such as Crohn's disease were excluded from the list of probable diagnoses. A second bone marrow biopsy of the iliac crest revealed no specific findings, including malignancies. Subsequently, a diagnosis of systemic juvenile idiopathic arthritis (s-JIA) was established. The patient was treated with three courses of 3-day pulse methylprednisolone (1 g/day). Although his symptoms and clinical signs improved, he developed low-grade fever and showed elevated CRP levels a week later. Therefore, tocilizumab therapy (8 mg/kg/dose every two weeks) was initiated. Thereafter, his laboratory values and physical signs of s-JIA improved, but he continued to occasionally experience left tibial pain.

## Discussion

CRMO is also known as nonbacterial osteomyelitis or chronic nonbacterial osteomyelitis (CNO). It was first described by Giedon et al. in 1972 as an unusual form of multifocal bone lesion with subacute and chronic symmetrical osteomyelitis.[1] Its diagnosis is established by excluding other diseases that can cause inflammation in the bone, such as malignancies and bacterial infections. For this, not only a radiographic approach is required, but also a biopsy.[2] We performed bone marrow biopsy with the open bone approach, which showed no evidence of bacterial infection or tumor. CRMO is often complicated by other inflammatory diseases, such as autoinflammatory diseases, inflammatory bowel disease, and pustulosis palmoplantaris. However, there is no previous report of CRMO complicated with s-JIA. The present patient also developed diarrhea with fever, which indicated IBD; however, gastrointestinal endoscopy revealed no evidence of IBD. NSAIDs are the first-line treatment for CRMO. Various agents have been used as the second-line treatment owing to the lack of standardization of the treatment for CRMO. Our patient was initially administered NSAIDs alone; however, he failed to achieve remission and required further treatment, as previously mentioned.

s-JIA, currently classified as a subtype of JIA by the International League of Associations for Rheumatology (ILAR), is characterized by daily remittent fever, a salmon-colored macular rash, generalized lymph node enlargement, and hepatomegaly/splenomegaly.[3] The dysregulation in innate immunity and absence of autoan-

tibodies have led to the hypothesis that s-JIA is an auto-inflammatory syndrome. These pathogeneses, which distinguish s-JIA from other subtypes of JIA, have led to recent changes in s-JIA treatment. Biologics blocking IL-1 β and IL-6 rather than TNF- α -inhibiting agents have shown promising results in s-JIA treatment. Indeed, tocilizumab was effective for treatment of s-JIA in this patient. Although a case report of adult-onset Still's disease complicated with CRMO showed both symptoms and markers of inflammation that were controlled with tocilizumab,[4] in the current case, local tibial inflammation gradually subsided after starting tocilizumab. However, as the patient had also started increased doses of steroids at the same time, it is difficult to know whether tocilizumab was effective for CRMO. In general, TNF- α -inhibiting agents have been suggested to be effective for CRMO.[5] This suggests the possibility that TNF- α -inhibiting agents might be more effective for CRMO in the current case.

Some studies have reported synovitis as a complication of CRMO; hence, the shoulder pain of the patient might be one of the symptoms of CRMO. However, the patient presented remittent fever and erythematous rash, which are the pathognomonic symptoms of s-JIA; this made it difficult to judge whether the symptoms were complications of CRMO or s-JIA. As both CRMO and s-JIA have recently been classified in the family of auto-inflammatory diseases,[6] the symptoms observed in the current case may arise from the same auto-inflammatory disease spectrum.

## Disclosure

The authors declare no conflict of interest.

## Author contributions

N.A., T.T., Y. N., and H.Y. saw the patient and collected clinical data. H.A. and T.T. critically reviewed the manuscript and supervised the study. N.A. wrote the manuscript. All authors read and approved the final manuscript.

## References


1. Giedion A, Holthusen W, Masel LF, et al. Subacute and chronic "symmetrical" osteomyelitis. Ann Radiol (Paris) 1972; 15: 329-342.
2. Costa-Reis P, Sullivan KE. Chronic recurrent multifocal osteomyelitis. J Clin Immunol 2013; 33: 1043-1056.
3. Schneider R, Laxer RM. Systemic onset juvenile rheumatoid arthritis. Baillieres Clin Rheumatol 1998; 12: 245-271.
4. Sato H, Wada Y, Hasegawa E, et al. Adult-onset chronic recurrent multifocal osteomyelitis with high intensity of muscles detected by magnetic resonance imaging, successfully controlled with tocilizumab. Intern med 2017; 56: 2353-2360.
5. Marangoni RG, Halpern AS. Chronic recurrent multifocal osteomyelitis primarily affecting the spine treated with anti-TNF therapy. Spine (Phila Pa 1976) 2010; 35: E253-E256.
6. Hedrich CM, Hofmann SR, Pablik J, et al. Autoinflammatory bone disorders with special focus on chronic recurrent multifocal osteomyelitis (CRMO). Pediatr Rheumatol Online J 2013; 11: 47.