Bisphosphonate Treatment for Chronic Recurrent Multifocal Osteomyelitis in an Adolescent

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Chronic Recurrent Multifocal Osteomyelitis (CRMO) is a non-bacterial inflammatory disorder of unknown cause occurring in children and adolescents. It is characterized by the insidious onset of pain and swelling to multifocal involved bones, recurring over months to years. Non-steroid anti-inflammatory drugs (NSAIDs) and steroids are the first choice for the initial and relapse treatment. However, multifocal and frequent relapses might require more intensive anti-inflammatory treatment. Here, we report that an adolescent with CRMO refractory to antibiotics, NSAIDs and steroids over a two-year responded well to bisphosphonate. To our knowledge, this is the first case using bisphosphonate in adolescent refractory CRMO in Korea. (J Rheum Dis 2016;23:271-275)

Key Words. Chronic recurrent multifocal osteomyelitis, Bisphosphonates, Adolescent

INTRODUCTION

Chronic recurrent multifocal osteomyelitis (CRMO) is a relapsing inflammatory disease affecting a variety of bones, which was first described by Giedion et al. [1] in 1972 as “an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis.” In the past, it has been called as subacute symmetric osteomyelitis (OM), chronic symmetric OM, chronic multifocal symmetric OM. However inflammatory lesions are not symmetric and new lesion sometimes occurs in the recovered region so, it is named CRMO [2].

The disease is rare and mostly affects young girls, with a male to female ratio of 1 : 2.1 [3,4]. CRMO is primarily a disease of childhood, with the mean age at presentation around 10 years [5]. The youngest age at CRMO has been reported to be 6 months, and the oldest 55 years [3]. Although most of the initial reports of CRMO comes from Europe, cases have been reported worldwide and shows no racial predilection [6]. Pathogenesis of CRMO continues to be poorly understood. Environmental, genetic, and immunological factors have been postulated as causative factors with varying evidence. Negative findings on culture are the rule, and no improvement is noted with antimicrobial therapy. Non-steroid anti-inflammatory drugs (NSAIDs) are now the first-line therapy and corticosteroid, bisphosphonate have been used when pain is not responsive to NSAIDs. Although generally a self-limiting disease, it can have prolonged course and result in significant morbidity.

This article describes clinical presentation, radiographic appearance and histology of a case of CRMO involving femur and humerus in a 14-year-old boy, who showed good response to bisphosphonate after refractory course of disease over 2 years despite treatment with antibiotics, NSAIDs and steroids.

CASE REPORT

A previously healthy, 14-year-old boy presented with
3-month history of pain and swelling affecting right side femur and left side humerus. Plain radiography of the right femur and left humerus showed osteolytic lesion with periosteal reaction, and he was referred to clinic for bone biopsy on the impression of osteomyelitis and osteosarcoma.

At admission, the initial vital sign was normal and might be summarized as follows: body temperature, 36.5°C; pulse rate, 86 beats/min; blood pressure, 126/70 mmHg; and respiratory rate, 20 breaths/min. He looked acute ill appearance and mental status was alert. His height was 169 cm and weight was 73 kg. Clinical examination showed pain with swelling on right side femur and left side humerus. There was no focal heatness or redness on the lesion but he refused to jump or run because of severe pain and showed limited range of motion. There are no family or personal history of psoriasis, skeletal disease or inflammatory bowel disease. The peripheral blood test showed following values: White blood cell, 8,500/mL (polymorphous, 69%); erythrocyte sedimentation rate (ESR), 11 mm/hr; C-reactive protein (CRP), 4.8 mg/L (reference range, < 8 mg/L); and the alkaline phosphatase (ALP), 318 IU/L (reference range, 75~379 IU/L). Bone biopsy revealed subacute or chronic inflammation with leukocytic or mixed cell infiltrate, some fibrosis and no demonstrable organism. Cultures of blood and bone biopsy were negative (Figure 1).

Plain radiographs of right side femur and left side humerus showed osteolytic lesion and erosion located adjacent to the metaphysis with lamellar-nodular periosteal reaction (Figure 2). Magnetic resonance imaging (MRI) revealed edematous marrow changes of right proximal fe-

![Figure 1](image1.png)

**Figure 1.** (A) Bony tissue of left arm shows marrow fibrosis with chronic nonspecific inflammation. (B) Cortical bone and periosteum of right arm reveals osteocartilaginous tissue without histologic abnormality (A, B: H&E, ×40)

![Figure 2](image2.png)

**Figure 2.** (A) Plain radiography of the right femur shows osteolytic lesion and periosteal reaction in midshaft of right femur with overlying soft-tissue swelling, (B) plain radiography of the left humerus shows small lytic lesion in the mid humerus with mild associated periosteal reaction, after 13 months of bisphosphonate treatment, plain radiography of the right femur (C) and left humerus (D) shows improvement in inflammation and osteolytic lesion.
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mur, including T1 hypointensity and hyperintensity on T2 sequences. There was a diffuse enhancement along the periosteum with soft-tissue inflammation. There was no abscess, sequestra formation or sinus tract, which are often identified in pyogenic osteomyelitis (Figure 3). Technetium 99m bone scan showed multifocal increase in intensity of radiotracer uptake in the right femur shaft and left proximal humerus (Figure 4). Although culture of bone aspiration and biopsy yielded negative results, a presumptive diagnosis of osteomyelitis was made, and the patient was treated with intravenous antibiotics (2nd cephalosporin) and Naxen-F (1,500 mg/d). The symptoms subsided, but 1 month later, the patient deteriorated with recurrence of pain in the same area. His ESR was 35 mm/h, and his CRP level was 48 mg/L. Result of MRI and bone scan showed no interval change in the signal intensities, suggestive of osteomyelitis. He was started with the same antibiotics with NSAIDs treatment. However, his pain was not improved, and CRP level remained elevated at 58 to 75 mg/L. Blood culture was negative. Additional tests were performed, including serologies for rheumatoid factor, anti-nucleated antibody, anti-streptolysin O (ASO) and candida, which were normal. Tuberculin skin test was negative. Antibiotics then was switched to intravenous glycopeptides (teicoplanin). He improved symptomatically, his ESR fell to 2.7 mm/h, and CRP fell to 14 mg/L. After 3 months later, there was an accident of falling off a bicycle, patient developed similar pain and tenderness in the right femur, and had a difficulty in walking. MRI of the right femur revealed newly developed distal inflammatory lesion except fracture. His ESR was 29 mm/hr, CRP level was 17.3 mg/L, and cultures once again yielded negative results. The combination of atypical clinical course, which is no response to antibiotics and radiographic appearance and MRI implied that CRMO was the likely cause. The presence of another new lesion in the right distal femur supported the provisional diagnosis of CRMO. He was started with oral prednisolone (20 mg/d) treatment and had dramatic response in both pain reduction and bone scan findings. The patient was given maintenance treatment of prednisolone, after 3 months, his symptoms returned, with pain now spreading proximal tibia. His ESR was 31 mm/h, CRP was 17 mg/L and ALP level was 367 IU/L. Osteocalcin was normal at 47.3 ng/mL (reference range, 24 ~ 70 ng/mL) and C-terminal telopeptide of collagen type I (β-CTX), which is bone resorption marker, was elevated at 1.01 ng/mL (reference range, <0.584 ng/mL). He was decided to start with a further course of alendronate (1 mg/kg/week) and, within 1 month, he was reported no pain and additional radiographs and bone scan showed improvement of the femur lesions (Figures 2 and 4). Patient remained asymptomatic 15 months later.

Figure 3. Coronal T2-weighted magnetic resonance image shows newly developed fracture on the right supracondylar femur and increased extent of bone marrow edema on right distal femur with diffuse periosteal reaction.

Figure 4. (A) Technetium 99m bone scan shows diffusely increased multifocal radiotracer uptake in the right femur shaft and left proximal humerus. After 13 months of bisphosphonate treatment, Technetium 99m bone scan (B) reveals further decrease in intensity of radiotracer uptake in the right femur shaft and left proximal humerus, probably associated with healing state of osteomyelitis.
CRMO is a rare relapsing inflammatory disease affecting bones. Patient typically presents with insidious onset of localized bone pain, associated with bone and soft tissue swelling [1]. The disease course involves intermittent periods of exacerbation and improvement in different locations over several months to years. It can also be accompanied with fever and skin lesions. The most commonly affected sites involve the long bones and clavicle, but lesions have been described throughout the skeleton. The etiology of CRMO is unknown, but widely thought to be in the spectrum of autoimmune and autoinflammatory disease. This is supported by high rate of multiple autoimmune disease, including arthritis, psoriasis and inflammatory bowel disease in patients. The role of tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) in the pathology have been speculated recently, and provide targeting therapeutic strategy in CRMO. In laboratory test, white blood cells, ESR and CRP may be normal or minimally elevated. Cultures of blood, urine, synovial fluid are negative and sometimes ASO and rheumatic factor turn to positive, and ALP is elevated [2,7].

Radiographs shows osteolytic destruction within the metaphysis adjacent to the physis in the early stages. Periosteal reactions can occur at any stage, and hyperostosis and sclerosis may be seen subsequently [8]. MRI is useful and safe method for evaluation the extent of disease, because it often shows greater marrow involvement than suspected on radiography. In MRI, active lesion reveals edematous marrow changes, including T1 hypointensity and hyperintensity on both T2 and short tau inversion recovery sequences. There was no abscess, sequestra formation or sinus tract, which are often identified in infectious osteomyelitis [9]. The typical bone scan finding is increased uptake of the radiopharmaceutical at affected sites consistent with osteomyelitis. Because of similarity of radiographic appearance of CRMO with bone infection or malignancy, bone biopsy on all suspected cases is recommended. Histology of early lesions reveals noncharacteristic features of acute and chronic inflammation, with predominant polymorphonuclear cells. Later lesions show principally infiltration with lymphocyte and plasma cells, with areas of necrosis and new bone formation [3,10,11].

CRMO is diagnosed by a peculiar pattern of clinical, radiological, and histopathological findings. For the diagnosis CRMO, all of the following criteria should be met: (1) the presence of one or more clinically or radiographically diagnosed bone lesions; (2) a prolonged course of at least 6 months with characteristic exacerbations and remissions; (3) typical radiographic lytic lesions surrounded by sclerosis with increased uptake on bone scan; (4) a lack of response to parenteral antibiotic therapy of at least 1 month’s duration to cover clinically suspected organisms; and (5) a lack of an identifiable etiology [10].

In our case, at initial presentation the patient was treated with antibiotics and anti-inflammatory drugs for the working diagnosis of suspicious infectious osteomyelitis. However, the symptoms seemed unaffected by antimicrobial therapy and the patient suffered a long period of pain with frequent relapse for 16 months. The bacterial culture study was negative, MRI revealed additional inflammatory focus of lesion that present concurrently or sequentially compared to previous result. So the diagnosis of CRMO has been made, and the targeted treatment with NSAID and steroids started, which resulted to a progressive resolution of the lesion in few months. However, the recurrence of bone pain episodes observed during the follow-up of patient. It led us to use the second-line drug, and the bisphosphonate was chosen to reduce the progression of the disease according to the most recent indications of the literature. The pain was improved significantly, within 1 months of bisphosphonate, he remained asymptomatic 15 months later.

NSAIDs is the first choice for the treatment of initial CRMO episodes and relapses [12]. When pain is unresponsive to NSAIDs, corticosteroids, anti-TNF agents and bisphosphonates have been used [13]. There have been case reports of response to IFN-α, IFN-γ, sulfasalazine, and infliximab, but varied mechanism of action of these drugs suggest unpredictable response at most [12]. Bisphosphonates are anti-osteoclastic agents and their beneficial effect in CRMO is postulated to their ability to inhibit bone resorption, to have pain modifying effect, and to suppress proinflammatory cytokines [14]. They are usually recommended with NSAIDs as bridging treatment with oral corticosteroids, and additional drug are not successful.

CRMO has a relapsing and remitting course with variable prognosis. In majority of cases, a good outcome can be expected, with remission in late childhood, but in some cases, prolonged course occurs. Premature epiphyseal fusion can occur and lead to inequality in leg lengths and consequent disability [15].
Although NSAIDs with steroid treatment remains the first choice, bisphosphonate and biologic drugs such as TNF-α, IL-1 inhibitors should be considered as the alternative therapy for CRMO treatment. This case illustrates the refractory nature of CRMO despite treatment with extended regimen of steroid and anti-inflammatory medication. This patient shows a good response to bisphosphonate, however, due to lack of long-term study for using second-line drugs in pediatrics, further studies are needed.

**SUMMARY**

CRMO is a rare and underdiagnosed disease. Knowledge of this condition and prompt diagnosis of CRMO allow patient to avoid the lengthy use of antibiotic therapy and repetition of unnecessary study. And it is essential to provide the proper treatment, which can avoid a long-term complication.

Here, we report an adolescent CRMO which showed good response to bisphosphonate after refractory nature of disease over 2 years despite treatment with antibiotics and steroids. To our knowledge, this is the first case using bisphosphonate in adolescent refractory CRMO in Korea.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**REFERENCES**