

CASE REPORT

Chronic Recurrent Multifocal Osteomyelitis in a 9-year-old Boy

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Abstract

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare aseptic, auto-inflammatory bone disorder. CRMO presents with bone pain with or without fever. The diagnosis of CRMO is a diagnosis of exclusion and should be included in the differential diagnosis of chronic inflammatory bone lesions in children. Cultures of the bone are typically sterile, antibiotic therapy does not result in clinical improvement whereas anti-inflammatory drugs improve the condition. Furthermore, biopsy should be considered in chronic and relapsing bone pain and swelling unresponsive to treatment. Herein, we present a nine-year-old boy complaining of recurrent pain in his upper and lower extremities. On examination he had mild fever and cervical lymphadenopathy. He also had experienced bone pain and weight loss in the recent month. Based on biopsy and bone scan he was finally diagnosed with CRMO. Naproxen and Pamidronate was prescribed and he was getting better and returned to normal life and activity without need to corticosteroids.

Keywords: Bone pain, Children, Chronic Multifocal Osteomyelitis (CRMO)

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare aseptic, auto-inflammatory bone disorder (1-3). It represents with recurrent episodes of osseous pain over several years due to sterile inflammation of the bone (3-5). CRMO primarily affects children and adolescents, predominantly girls (3, 4, 6). The lesions are usually located at the metaphyseal region of long bones, but can occur at any site in the skeleton. The prevalence of CRMO is estimated to be less than 1/1,000,000 and is the final diagnoses in 2-5% of all osteomyelitis cases (4-7); however it is still thought to be under reported or misdiagnosed. The onset is usually around the age of 10 years with a range between 4-14 years (4, 5).

The clinical presentation of CRMO is variable. Pain, local swelling, and warmth in the absence or presence of fever are the main manifestations (5). Bone pain was reported in all 40 patients by Catalano-Pons *et al*, (4) whereas fever was detected in only nine cases. CRMO is not easy

to diagnose as its lesions often appear ill defined with no pathognomonic features in various imaging studies (1).

The clinical course is unpredictable, with remarkable variation depending on the lesions' location and the disease's severity stage (5, 7). CRMO is considered a self-limiting disease with episodes of remission and relapse in which the affected bones eventually remodel and normalize prior to skeletal maturity, yet sequelae may occasionally occur (4-7).

Laboratory findings are of little diagnostic value because they typically reveal nonspecific evidence of inflammation, such as elevated ESR and CRP and alkaline phosphatase levels detected in around two-third of patients (5, 8). The essential factors leading to the diagnosis of CRMO include patient demographics, clinical course, and lesion localization.

Herein, we report a case of CRMO which highlights the importance of considering this diagnosis for chronic recurrent lower extremity bone pain in adolescents.

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Case Report

A nine-year-old boy presented to our clinic with recurrent pain and discomfort in his lower extremities since six months before.

He had initially presented to his family physician with the chief complaint of pain in the temporal area. Blood pressure was normal and eye examination revealed a normal optic disk, so a brain MRI was recommended to rule out intracranial lesions. His MRI had also been reported as normal. Following supportive treatment his headache resolved, but after several weeks he started to experience pain and discomfort in his upper and mainly lower extremities, therefore he was referred to the pediatric infectious diseases clinic.

He was born of nonconsanguineous parents with no known diseases. He was fully vaccinated, did not recall a precipitating event and had no history of lower extremity injuries. His physical and neurological developmental stages were normal and he had a normal height and weight for his age.

On physical examination mild fever and right-sided cervical lymphadenopathy was detected. However, his joints were not involved and no gait disorders were diagnosed. The patient had no remarkable chest or abdominal findings, or other abnormalities such as a rash. He had experienced around two to three kg weight loss in the recent month; his pain persisted at rest and even sometimes woke him during the night.

Regarding prolonged fever, lower extremities pain and cervical lymphadenopathy, laboratory tests for brucellosis were requested which were all negative.

Complete blood count was also normal indicating no neutropenia, a normal hemoglobin level and platelet count; coagulation tests also came out as normal. Acute phase reactants were elevated while liver enzymes were in the normal range. Table 1 demonstrates the patient's laboratory test results at presentation. Bone marrow aspiration revealed active marrow, blood culture and marrow culture was negative in BACTEC blood culture system.

Accordingly, further lab tests were requested giving the following results: high Anti-streptolysin O (ASO) titer and negative anti-nuclear antibody (ANA) and rheumatoid factor (RF). Echocardiography study was also unremarkable. Eventually, acetaminophen tablets

were prescribed as needed and he was recommended to come to the clinic every two weeks.

On the first follow-up visit he complained of exacerbated pain in his lower extremities. He then expressed that the nature of his pain is recurrent with 8-10 day duration and a two-week interval. On physical examination he had no noticeable swelling, bruising or deformity of the lower extremities. Acute phase reactants were still high, so a peripheral blood smear (PBS) was requested, reported as normal along with normal LDH and uric acid test results. Eventually pediatric hematologic consult was requested and bone marrow aspiration (BMA) reported active marrow with no evidence of malignancy.

Plain x-rays showed multifocal areas of mixed lytic and sclerotic lesions in carpal bones accompanied by a fine periosteal reaction along radius and ulna [Figure 1]. In the next step a whole body bone scan was performed; its findings were more in favor of an active inflammatory process in the involved regions including the mandible, distal of humeri, bilateral ulna and tibia and mid and distal portion of the femur [Figure 2]. For final diagnosis needle biopsy and bone curetting of the right proximal tibia was conducted; pathologic examination reported osteosclerotic lesions with mild chronic nonspecific inflammation. Microbiological exam was negative in specimens.

According to final diagnosis, Naproxen 15mg/kg/day plus intravenous Pamidronate as 1mg/kg for three days, was prescribed.

Subsequent to four weeks of therapy, the patient resumed his normal activities with considerable relief of symptoms.

He was discharged with Naproxen 500mg/q12h and was advised to come back every three months for Pamidronate therapy. After two courses of Pamidronate, the child went to remission with no fever and pain while the acute phase reactants returned to normal levels. The patient gained weight and returned to normal daily activities.

Table1. Patient's laboratory test results at presentation			
Complete blood count		Biochemistry	
WBC	μl 103× 6.3	AST	U/l 23
Neutrophils	60.3%	ALT	U/l 27
Lymphocytes	28.1%	ALP	511U/l
RBC	μl 106× 5.11	Calcium	9.3mg/dl
Hb	12.2gr/dl	Phosphor	mg/dl 4.2
Hct	37.5%	CRP	mg/l 54.8
Plt	μl 103×361	ESR	105



Figure1. Plain radiography showed multifocal areas of mixed lytic and sclerotic lesions in carpal bones accompanied by a fine periosteal reaction along radius and ulna.

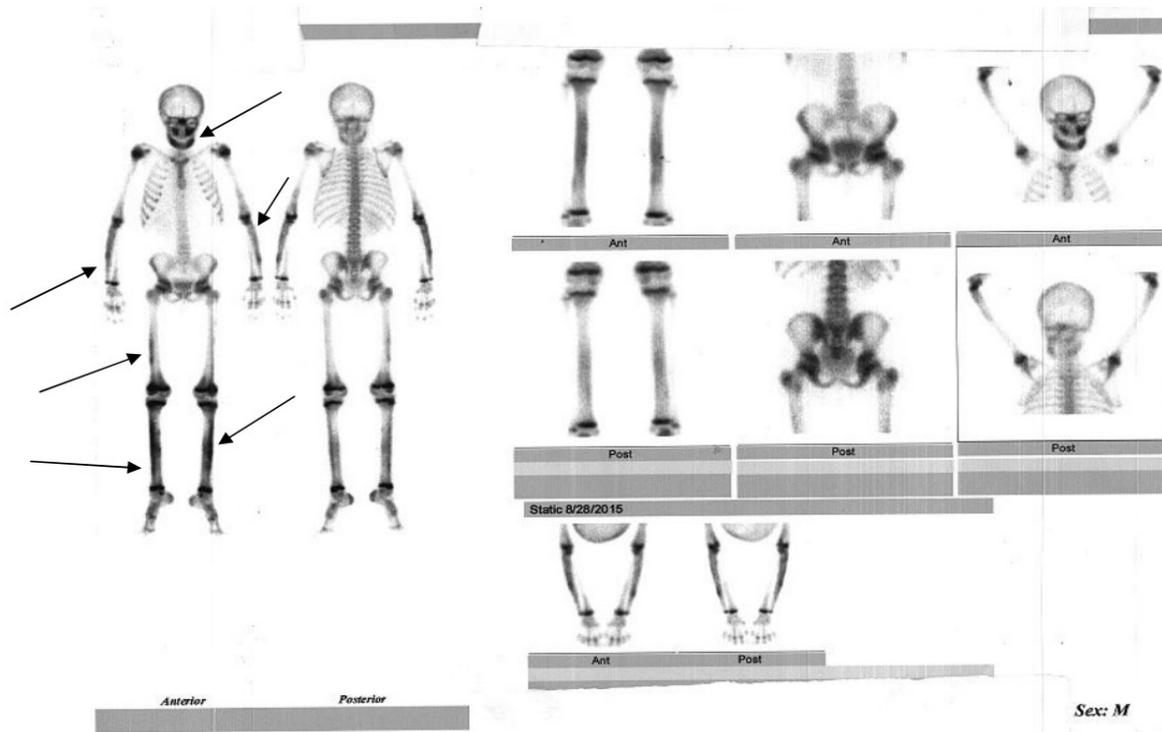


Figure 2. Whole body radionuclide scan revealed increased uptake in the involved regions including the mandible, distal of humeri, bilateral ulna and tibia and mid and distal portion of the femur.

Discussion

CRMO is an idiopathic, aseptic, auto-inflammatory disease with no uniformly effective treatment (8). It was first described by Giedon *et al.* in 1972 as “an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis” (4, 7). CRMO has a worldwide distribution affecting multiple races and ethnicities (9). Other organs such as the skin, gastrointestinal tract, lungs and the eyes may also be affected that complicate the clinical picture (6). We experienced none of these complications in our patient.

In most cases CRMO presents as lytic destruction with sclerotic borders within the metaphysis, resembling an infectious or neoplastic process. Common locations for CRMO include the tibia, pelvis and femur, however several reports of the calcaneus, spine, clavicle, mandible and sternum involvement are available in the literature (7). In the present case, multifocal bony lesions in the long bones of the upper and lower extremities along with the mandible were diagnosed.

CRMO has a predominancy in girls at the age of four to 14 years; but our case was a nine-year old boy, similar to Aelami *et al.* reported case with bilateral involvement (10). The predisposing factor causing the disease is unknown in our patient; his bone pain woke him up during the night while he had no history of trauma or sign of any infection. Fever accompanies bone pain in 17-33% of individuals at presentation (11, 12). Our case

also initially presented with bone-pain and mild fever.

The clinical course of CRMO is prolonged and recurrent while its prognosis is not predictable but is thought to resolve spontaneously despite lasting from months to as long as 20 years in some cases, regardless of intervention (7).

Symptoms may recur repeatedly in one location, or new areas can be affected with subsequent flare ups. Flare up episodes occur insidiously and pain is often worse at night (7).

As no evidence of immune deficiency has been found in the vast majority of children, CRMO does not seem to have an immunologic basis (9). In a German cohort positive ANA was detected in one third of the cases. Moreover, modest elevation of ESR and CRP is seen in the majority of affected subjects. Our patient had a negative test result for ANA but with mild elevation of the later mentioned factors (12).

Radioisotope bone scan can assist in establishing the diagnosis and in identifying lesions that are initially silent (11, 13). We also performed a ^{99m}Tc-methylendiphosphonate (MDP) whole body bone scan in which the involvement of the mandible, distal of humeri, bilateral ulna and tibia along with the mid and distal portion of the femur was reported. However, definite diagnosis relies on histopathology confirmation by bone biopsy to rule out both chronic bacterial osteomyelitis and malignancy (4, 6). Osteosclerotic lesions with mild

inflammation were reported in the biopsy of tibia. As the patient exhibited multiple bone lesions with a recurrent course, had a biopsy indicative of chronic inflammation and a negative blood culture for bacteria, the diagnosis of CRMO was confirmed. Worth noting, MRI is a better choice than CT scan in the imaging of suspected young patients because of high sensitivity for early subclinical bone marrow lesions and no risk of radiation (7).

CRMO is widely believed to be a pediatric variant of SAPHO syndrome in adults, an inflammatory bone disorder which is characterized by synovitis, acne, pustulosis, hyperostosis and osteitis that commonly presents with skin manifestations (4, 5, 14). In fact, current estimates suggest that up to 25% of CRMO patients have some sort of accompanying inflammatory disorder (15). Other autoinflammatory bone disorders include deficiency of IL1 receptor antagonist (DIRA), Majeed syndrome, pyogenic artheritis, pyoderma gangrenosum and acne (PAPA) syndrome (14).

Since no specific diagnostic biomarkers are available, the diagnosis of the sporadic CRMO is based on the exclusion of other etiologies. In this respect, treatment is done aimed at inducing remission along with providing normal function and growth of the bone (4). Due to participation of prostaglandins in osteoclast activation and bone remodeling, non-steroidal anti-inflammatory drugs such as naproxen are usually recommended as first line (14, 8) providing some degrees of symptomatic relief in up to 80% of cases (12). The second line treatment includes corticosteroids (CSs), sulfasalazine, methotrexate, anti- TNF agents, and bisphosphonates (4, 5, 9). The use of CS despite a response rate up to 95% is limited due to many side effects (9).

In the study by Miettunen *et al.* Pamidronate resulted in resolution of pain and MRI documented inflammation in all nine patients with CRMO at 6 months (8). So far over 50 individuals treated with various biphosphonates resulting in a positive response have been reported (9). Our patient also responded well to this treatment and

went to remission with no fever and pain following two courses of Pamidronate therapy. His acute phase reactants also returned to normal.

The diagnosis of CRMO is a diagnosis of exclusion and should be considered in the differential diagnosis of chronic inflammatory bone lesions in children. This condition might commonly go undetected, misdiagnosed or mistreated, so biopsy should be considered in chronic and relapsing bone pain and swelling unresponsive to treatment.

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