

Chronic recurrent multifocal osteomyelitis: a first report from Saudi Arabia

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BACKGROUND AND OBJECTIVES: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, systemic, aseptic, inflammatory disorder that involves different sites. Pathogenesis of chronic recurrent multifocal osteomyelitis is currently unknown. To our knowledge, there are no reports of CRMO from Saudi Arabia. We describe the clinical and laboratory features and treatment of a cohort of children with CRMO.

DESIGN AND SETTING: Retrospective, patients referred to pediatric rheumatology clinic at a tertiary care center in Riyadh, Saudi Arabia.

PATIENTS AND METHODS: The diagnosis of CRMO was based on evidence of recurrent osteomyelitis with radiographic evidence of chronic osteomyelitis involving at least two sites in the absence of infectious cause in a child less than 14 years old.

RESULTS: Ten patients (9 female, 1 male) with CRMO; 2 patients presented in infancy. The referral diagnosis was inaccurate in all patients. All of them presented with pain and 8 of them had associated swelling and were found to have multifocal lesions. Imaging studies showed findings consistent with chronic osteomyelitis. Histopathological and microbiological examination confirmed the diagnosis in 9 patients. Cyclic pamidronate infusions induced good improvement in 6 patients.

CONCLUSION: This report indicates that CRMO may be overlooked in our community. Early diagnosis and treatment are required to avoid potential complications.

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare systemic autoinflammatory disorder. It is an osteopathy characterized by multifocal recurrent noninfectious lytic lesions, predominantly in the metaphyses of the long bones.^{1,2} The disease is characterized by bone pain and soft tissue swelling with or without fever. The disease has an episodic course with periods of exacerbations and remissions. It might be associated with other inflammatory conditions such as pustulosis palmoplantaris, Sweet syndrome, psoriasis and pyoderma gangrenosum and inflammatory bowel disease.³⁻⁵ Like other autoinflammatory disorders, the etiology is largely unknown; it results from complex interactions between a number of predisposing factors in genetically predisposed individuals. As in other rare disorders, there is no standardized therapy for CRMO patients. The disease has worldwide distribution. To our knowledge, there are no reports of CRMO from Saudi Arabia. In this study, we describe the clinical and laboratory features

and treatment of a cohort of children with CRMO seen at King Faisal Specialist Hospital and Research Centre (KFSHRC) in Riyadh, Saudi Arabia.

PATIENTS AND METHODS

Medical records of all children with CRMO seen between 1990 and 2010 at KFSHRC, Riyadh were reviewed. The diagnosis of CRMO was made on the basis of the following criteria: evidence of recurrent clinical signs of osteomyelitis (localized pain, swelling, and impairment of limb motion) with radiographic evidence of chronic osteomyelitis (osteomyelitis with sclerosis) involving at least two sites in the absence of an infectious cause in a child less than 14 years old. All patients were reviewed retrospectively for demographic characteristics, age at disease onset, disease duration, follow-up duration, referral diagnosis, musculoskeletal findings and extra-osseous manifestations that could be seen in association with CRMO, including dermatologic manifestations and other systemic diseases such as synovitis.

Laboratory data including histological and radiological findings as well as the treatment and outcomes were reviewed. Active disease was defined by patient reporting of ongoing or deteriorating musculoskeletal findings, increase in the erythrocyte sedimentation rate (ESR) and/ or C-reactive protein (CRP), and radiological evidence of disease progression. In contrast, improvement was defined by pain and swelling relief and improvement in the inflammatory markers and radiological findings.

RESULTS

Ten children (9 female, 1 male) were diagnosed with CRMO during the study period. The age of onset ranged from 2 to 144 months with mean of 55.5 months; 2 patients had their disease onset before 6 months of age while the age of diagnosis ranged from 5 to 147 months with mean of 87.6 months. There was a mean delay of 18 months (ranged 3-87 months) before referral to our hospital and diagnosis after the first symptoms had appeared. All patients were referred to our clinic with an inaccurate diagnosis. All patients had bony pain, 7 patients had associated low grade fever. The associated bony/soft tissue swelling was seen in 8 patients. All patients had multifocal lesions with relapses. A total of 31 individual bones were affected with an average of 3 bones affected in each patient. The femur

was the most affected bone followed by the tibia and clavicle. Two patients had vertebral bone involvement, but no associated compression fractures and one had unilateral sacroilitis at the time of diagnosis. Among the 10 patients, one patient had sternum and another patient had mandible involvement. Five patients had associated arthritis. Only two patients had cutaneous manifestation, one had psoriasis and one had vitiligo.

Three patients had a low total white cell count that ranged from $3.2-4.0 \times 10^9$ ($5-15 \times 10^9/L$) with a normal differential cell count; one also had anemia with a transient positive direct Coombs test and a weakly positive antinuclear antibody with a titer of 1:160 ($<1:40$). However, the extractable nuclear antigens and complement levels were normal. None of the patients had a low platelet count or abnormal cells in the peripheral smear. Eight patients (80%) had elevated ESR with mean of 73 that ranged from 21-123 mm/h (0-5 mm/h); in contrast, only 3 patients had elevated CRP. Unfortunately, HLA-B27 was not done for the patient with sacroiliac joint involvement. All other laboratory markers were unremarkable.

Table 1 summarizes the demographic features, lesion distribution and treatment. All patients had a plain x-ray and technetium bone scan which confirmed the bony lesions in all patients but one, who had an inconclusive bone scan study. The plain x-ray studies showed

Table 1. summarized the demographic features, lesions distribution and treatment.

Patient	Age at onset (Months)	Age at diagnosis (Months)	Referral diagnosis	Associated symptoms	Location of lesions	Treatment	Outcome
1	60	68	Osteomyelitis/ bone tumor	Bone pain, fever	L femur, L tibia, L navicular	NSAID	Partially improved
2	84	96	Chronic osteomyelitis	Bone pain, swelling, fever	R humerus, R iliac bone	NSAID	Partially improved
3	48	68	Histocytosis	Bone pain, swelling	Both femurs	NSAID, Bisphosphonates	Improved
4	2	5	Chronic osteomyelitis	Bone pain, swelling	R radius, L radius, R tibia, fibula	NSAID, Steroids, MTX	progressive course (lost follow up)
5	26	74	Undiagnosed	Bone pain, fever	R sacroiliac Joint, S1, R clavicle	NSAID, Steroids	Partially improved
6	50	65	Undiagnosed	Bone pain, swelling, fever	Body of sternum, L clavicle, R navicular	NSAID, Steroids Bisphosphonates	Improved
7	78	131	Arthritis of R hip	Bone pain, swelling, fever	Bilateral iliac, R 2nd tarsal, L5	NSAID, Bisphosphonates	Improved
8	3	90	Caffey disease	Bone pains welling, fever	R femur, R tibia, both maxillae, R mandible	NSAID, Steroids Bisphosphonates	Improved
9	144	147	Immunodeficiency	Bone pain, swelling, fever	R femur, L tibia, R clavicle	NSAID, Steroids Bisphosphonates	Improved
10	120	132	Chronic osteomyelitis	Bone pain, swelling	R femur, R clavicle, R 4th rib	NSAID, Steroids Bisphosphonates	Improved

combinations of lytic and sclerotic lesions and periosteal reactions in more than one site. All but one patient had a bone biopsy prior to diagnosis of CRMO to exclude other diagnoses of malignancy or infectious osteomyelitis. Histopathology examination showed a chronic inflammatory reaction with a predominance of granulocytic/lymphocytic infiltrate in 5 patients while 4 patients had fibrosis with minimal chronic reaction. Cultures and special stains of bone biopsy specimens for bacteria, fungi and mycobacteria were negative.

All patients were treated with broad spectrum antibiotics without improvement. None of our patients had spontaneous remission. All of our patients received nonsteroidal anti-inflammatory drugs (NSAID). However, NSAIDs alone were sufficient to achieve remission in only two patients. Systemic corticosteroids were used in eight patients and methotrexate was added in one patient. In six patients with frequent relapses, cyclic pamidronate infusion was used. All treated patients received one-day intravenous pamidronate treatment (1 mg/kg/day, with maximum dose of 60 mg/day) once every 3 months. Pamidronate treatment was well tolerated and induced significant improvement in the clinical symptoms and radiological findings. **Figure 1** shows the effects of pamidronate in one of our patients. None of our patients required treatment with biological agents.

DISCUSSION

CRMO is a rare systemic autoinflammatory disorder that primarily affects the skeletal system, though it may also be associated with other autoimmune disorders.^{3,4} CRMO usually affects children and was regarded as the pediatric subset of SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome. Recently, however, children with SAPHO syndrome have been described.² It is classified as the most severe form of chronic non-bacterial osteomyelitis. The diagnosis is often difficult because the clinical findings and course of disease vary significantly. The diagnosis is usually made by exclusion of other serious entities, namely malignancy and infectious osteomyelitis. The diagnosis is also supported by the presence of multifocal bone lesions and failure of antibiotics and progression of the disease.²

The etiopathogenesis of CRMO is unknown. However, several observations suggest the contribution of genetic factors to the etiology of CRMO; mutations in Lpin1-related mouse genes 2 (LPIN2) cause a syndromic form of chronic recurrent multifocal osteomyelitis known as Majeed syndrome.⁶⁻⁸

CRMO is described throughout the world. There are several reports from Jordan.^{8,9} Unfortunately, no epidemiological data on CRMO from Arab countries

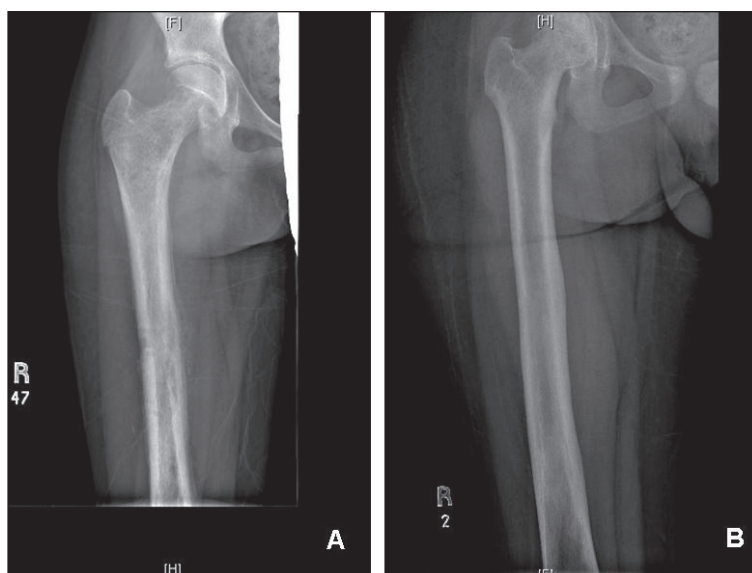


Figure 1. A) Lytic lesions with wide zone of transition involving the neck and shaft of the right femur with interrupted periosteal reaction. B) Improvement of the overall bone density as compared to the previous film. These findings are suggestive of an interval healing process.

exist. To the best of our knowledge this is the first report of CRMO from Saudi Arabia. All our patients had an inaccurate referral diagnosis. All of them were symptomatic with clinical findings involving different bones. Apart from two patients, there was a delay in making the diagnosis. Accordingly, recognizing CRMO might obviate the need for unnecessary investigations or prolonged uses of antibiotics if an infectious etiology is considered.

The clinical presentation of our patients is consistent with previous reports. Bone pain was the most frequent clinical presentation (100%). Most of the patients had bony/soft tissue swelling (80%) and fever (70%). All patients had multifocal lesions. The most affected bone was the femur; only three patients had axial skeletal involvement. Associated autoimmune manifestations were not frequent in our cohort; only psoriasis and vitiligo developed in two patients during the follow-up period. One patient had transient hemolytic anemia with a weakly positive antinuclear antibody; the follow-up assessment did not find any findings supporting the diagnosis of systemic lupus erythematosus.

To date there is no uniformly effective treatment for CRMO. Therapy depends on the disease severity; experts in the field have tried several medications. We used a bisphosphonate (pamidronate) that showed encouraging results in patients with CRMO and recently biological agents such as anti-TNF- α therapy have

been considered for severe cases refractory to bisphosphonate.^{10,11} We observed significant improvement in the symptoms as well as in the imaging studies in six patients treated with cyclic intravenous pamidronate. We did not use pamidronate for other patients because three patients had been already transferred to the adult service before the availability of pamidronate and the fourth patient was lost to follow up. However, we did not attempt to assess the efficacy of treatment in this cohort because of the study limitations and design. None of our patients needed treatment with biological agents.

CRMO needs to be considered in the differential diagnosis of patients presenting as chronic osteomy-

elitis whose culture results are negative or when response to antibiotics is not optimal. The outcome of CRMO is usually good, but some patients can have a severe and protracted disease course despite intensive treatments. Few studies have proposed risk factors for persistent disease and probably poor outcome, early onset and number of bony lesions considered to be predictive of poorer outcome.^{1,12,13}

All patients in our study were surviving and in stable condition at the time of writing without disability, but one patient was lost follow up. This report indicates that CRMO may be overlooked. Early diagnosis and treatment are required to avoid potential complications.

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