Case Report

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Chronic Recurrent Multifocal Osteomyelitis: A Case Report

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Abstract

Introduction: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare idiopathic auto-inflammatory bone disease of unknown aetiology that typically affects children and adolescents. It presents as recurrent episodes of bone pain and fever, resembling bacterial osteomyelitis, but cultures from lesions are sterile. It is unresponsive to antibiotic therapy. CRMO is a diagnosis of exclusion since no single clinical feature is pathognomonic. Radiological tests are often required and a bone biopsy may be needed in unclear cases.

Case report: We report a case of an 8-year-old girl, with pain over both ankles and upper chest; history and radiological evaluation suggested osteomyelitis, but no adequate response to antibiotic treatment was observed. A bone biopsy was done to rule out malignancy. Whole body imaging revealed multiple bony lesions; based on which a diagnosis of chronic recurrent multifocal osteomyelitis was made. Patient was started on specific anti-inflammatory treatment with resolution of symptoms.

Conclusion: Chronic recurrent multifocal osteomyelitis should be suspected in a child with recurrent, multiple bone pain, modest increase of inflammatory indices, and lytic or sclerotic bone lesion on radiographs. Typical locations are the metaphyses of long bones, pelvis, clavicle, vertebral column, sternum, but any bone can be involved. We want to increase the awareness of this entity and as a differential diagnosis of recurrent, multifocal bone pain in an adolescent, thereby avoiding unnecessary antibiotic administration and bone biopsies.

Keywords: Chronic recurrent multifocal osteomyelitis, Bone pain, Non-steroidal anti-inflammatory drugs

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an auto-inflammatory bone disease of unknown origin, that mostly affects children and adolescents, causing multiple focal bony lytic lesions characterised by periodic exacerbations and remissions [1]. The entity was first described by Giedion et al. [2] in 1972 as "an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis." The term CRMO (first used in 1978 by Probst et al) [3] is the most common in the literature. Approximately 400 cases of CRMO have been described in the literature.

The female: male ratio is 5:1 with adolescent girls being at greatest risk. It is most common between the ages of 4 and 14 years [4]. The consistent feature of CRMO is the insidious onset of pain with swelling and tenderness localised over the affected bones with periodic remissions and exacerbations. Skeletal manifestations are unifocal or multifocal, bilateral and symmetrical. Typical localizations are metaphyses of the long bones (74%), pelvis (38%), vertebral column (46%), clavicle (25%), jaw (18%), sternum (8%), ribs (8%) [5]. The involvement of the clavicle, sternum or jaw makes CRMO more probable [6]. Skin involvement includes palmoplantar pustulosis (PPP), acneiform lesions or psoriasis.

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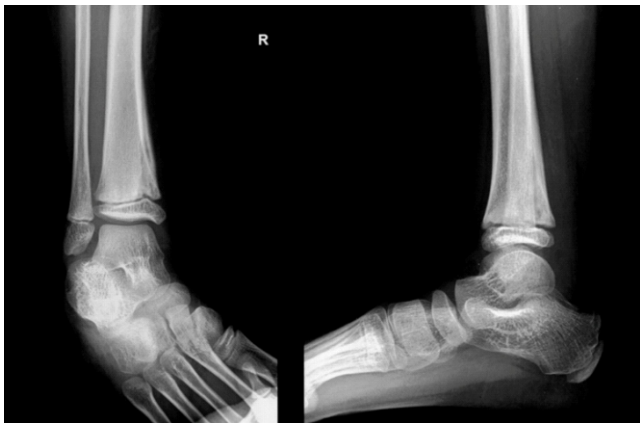

Figure 1: Plain radiograph right ankle. Antero-posterior (AP), Lateral (LAT)

The pathogenesis of CRMO is unclear. It has been suggested that an imbalance between pro-inflammatory cytokines (interleukins 1, 6, tumour necrosis factor alpha) and anti-inflammatory cytokine (IL-10) could be responsible. These cytokines are involved in bone resorption and remodelling through the activation of osteoblasts and osteoclasts.

CRMO is commonly misdiagnosed as bacterial osteomyelitis resulting in delays in referral. This may lead to prolonged courses of antibiotics, unnecessary radiation exposure from multiple plain radiographs or bone scans and repeated bone biopsies. The diagnosis of CRMO is made by exclusion of other diseases, and commonly requires a bone biopsy in order to exclude infection, neoplasia or Langerhan cell histiocytosis (LCH).

Case report

An 8-year-old girl, presented to us with occasional pain over both legs of 2 months duration. She developed pain initially over the right ankle followed by the Left side, for which she was evaluated at a local hospital. Complete blood count (CBC) was

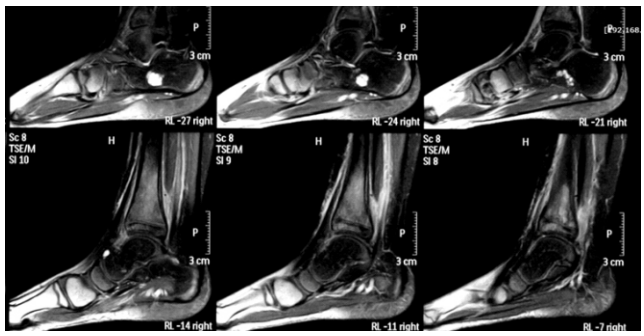

Figure 2: Magnetic Resonance Imaging right ankle, sagittal image

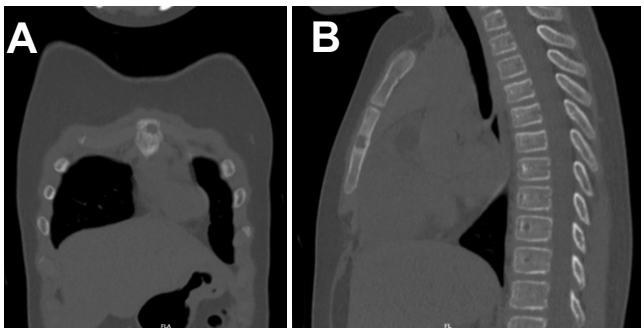

Figure 3: Computed Tomography Thorax, coronal image (A), sagittal image (B)

normal. Erythrocyte sedimentation rate (ESR) was 53 mm/hour and C-reactive protein (CRP) was 16 mg/l. Plain radiographs (Fig. 1) showed a well-defined, eccentric, lytic lesion with marginal sclerosis, narrow zone of transition and periosteal elevation over the right distal tibial metaphysis. Magnetic resonance imaging (MRI) of the right ankle (Fig. 2) showed diffuse hyperintensity over right distal tibia and calcaneum, suggesting infective or neoplastic pathology. She was started on oral non-steroidal anti-inflammatory drug (NSAID) and cefuroxime.

There was no precipitating event, local trauma, fever, or weakness. There was a family history of psoriasis in a second-

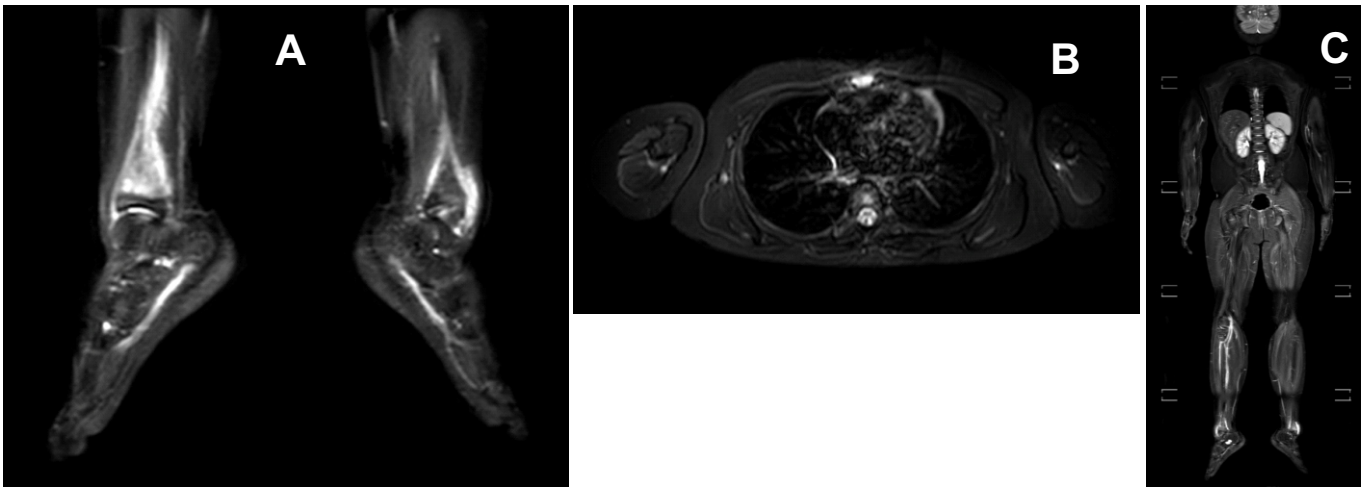

Figure 4: Whole Body Magnetic Resonance STIR Imaging, whole body coronal image (A), both ankles sagittal image (B), thorax axial image (C)

degree relative. The pain was low grade, intermittent, dull aching type, more on the right ankle, aggravated on activity, without any diurnal variation. On clinical examination, there was mild swelling, tenderness and local rise of temperature over the medial aspect of right distal tibia with painful restriction of terminal ankle movements. The left ankle and systemic examination were normal. Inflammatory blood markers were within the normal range. A core needle biopsy from the right distal tibia was performed to rule out malignancy. The biopsy showed chronic inflammatory cells without any evidence of granuloma, infection or neoplasm. She was advised NSAID and protected weight bearing on the Right leg.

The ankle symptoms resolved over the subsequent two weeks. However, the child developed pain over the upper chest with sleep disturbance. Computed Tomography (CT) of the thorax (Fig. 3) showed a small osteolytic lesion with cortical thinning over the sternum. Multiple bony lesions, with biopsy negative for bacterial culture and neoplasm raised the suspicion of CRMO.

Whole body MRI (WB-MRI) was then performed (Fig. 4) showing STIR hyperintensity over right distal tibia, left distal fibula, right calcaneum and sternum. Thus, diagnosis of CRMO was made. Oral naproxen (250 mg) twice daily and weekly 1 ml methotrexate (15mg/ml) were commenced. At 2 months follow-up, there was significant clinical improvement, relief of pain and normal blood inflammation markers. Presently, at 6 months follow-up, she is asymptomatic with normal blood inflammatory markers, resolution of lytic lesions on follow-up WB-MRI. No new osteolytic foci were observed.

Table 1. Diagnostic Criteria Proposed by Jansson et al.

Major	Minor
1. Radiologically proven osteolytic/−sclerotic bone lesion	1. Normal blood count and good general state of health
2. Multifocal bone lesions	2. CRP and ESR mildly-to-moderately elevated
3. PPP or psoriasis	3. Observation time more than 6 months
4. Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis	4. Hyperostosis
	5. Associated with other auto-immune diseases other than PPP or psoriasis
	6. Grade I or II relatives with autoimmune or autoinflammatory disease, or with CRMO
CRMO is confirmed by two major criteria or one major and three minor criteria.	

Table 2. Diagnostic Criteria Proposed by Roderick et al. (Bristol diagnostic criteria)

1. The presence of typical clinical findings: Bone pain +/−localized swelling without significant local or systemic features of inflammation or infection.
2. The presence of typical radiological findings: X-ray showing combination of lytic areas, sclerosis and new bone formation, or STIR MRI showing bone marrow oedema +/− bone expansion, lytic areas and periosteal reaction.
Associated with
1. More than one bone (or clavicle alone) without significantly raised CRP (CRP < 30 g/L)
or
2. Unifocal disease (other than clavicle), or CRP > 30 g/L, with bone biopsy showing inflammatory changes (plasma cells, osteoclasts, fibrosis or sclerosis) with no bacterial growth whilst not on antibiotic therapy

Discussion

Chronic recurrent multifocal osteomyelitis (CRMO) is an auto-inflammatory bone disease of unknown origin, that mostly affects children and adolescents [7]. Symptoms of CRMO might be varied from asymptomatic single-bone involvement to chronic, recurrent, multifocal inflammation with systemic symptoms such as weakness, fever, and weight loss [1]. It usually involves the metaphysis of long bones; it is often symmetrical and bilateral. It may present with lytic lesions or sclerosis with varying degrees in radiology. It is followed by exacerbation and recovery attacks [8].

The diagnosis of CRMO can be complicated by conflicting clinical and imaging findings [9]. It often remains a diagnosis of exclusion between tumours and infectious arthritis [10]. Laboratory tests are not specific, though an increase of inflammatory markers may be seen, in association with leukocytosis [6]. The initial approach in a child with bone pain is a conventional X-ray that may be normal in the early stages of the disease. The first radiological findings are changes in the metaphyseal regions of long bones, while osteolytic and sclerotic lesions usually appear in the late stages of the disease [11]. WB-MRI STIR sequence is useful to identify multiple bone lesions and tissue oedema and it is more accurate than bone scintigraphy. Though there are no specific histologic features, bone biopsy is important to exclude other causes of bone pain such as infectious osteomyelitis, malignant bone tumour or LCH.

Some authors have suggested diagnostic criteria and a clinical score to facilitate diagnosis and reduce the numbers of bone

Table 3. Diagnostic Score Proposed by Jansson et al.

Normal blood cell count	13
Symmetric Lesions	10
Lesions with marginal sclerosis	10
Normal body temperature	9
Vertebral, clavicular, sternal lesions	8
Radiologically proven lesions	7
CRP 1 mg/dl	6
Total Clinical Score	63
0 to 28: probably not CRMO, 29 to 38: uncertain diagnosis, 39 and above: probably CRMO	

Table 4. Treatment Protocol for CRMO

First line treatment– NSAIDs:
Ibuprofen 30–40 mg/kg/day in 3–4 divided doses for 1–3 months
Naproxen 10-15 mg/kg/day in 2 divided doses for 1–3 months
Second line treatment– Corticosteroids:
Prednisolone 1–2 mg/kg/day in 1 dose for 5–10 days up to clinical improvement, NSAIDs as the continuation of the therapy; In severe cases prednisolone treatment may be prolonged up to 4–6 weeks
Third line treatment– DMARDs
Sulfasalazine
Methotrexate
Bisphosphonates (Pamidronate)
TNFα-inhibitors

biopsies (Table 1, 2, 3) [5, 6, 12]. Manson et al proposed remission and exacerbation of signs and symptoms for at least 6 months, lack of an identifiable cause, lack of response to antibiotics for at least one month and chronic, non-specific inflammation consisting of lymphocytes, plasma cells and histiocytes at histopathologic examination [13]. Beretta-Piccoli et al advised that CRMO can be diagnosed if the disease course lasts at least 3 months with histological evidence of chronic bone inflammation, exclusion of other diseases, and negative microbiology [14].

CRMO was diagnosed in the present case according to the criteria of Jansson et al (3 major, 3 minor) and Roderick et al (Bristol diagnostic criteria for CRMO) with a score of 57 out of 63, with negative cultures and biopsy.

NSAIDs are the first choice of treatment for pain management and to prevent bone damage [1]. Corticosteroids, methotrexate, bisphosphonates including pamidronate, sulfasalazine, anti-tumour necrosis factor α (TNF-α) drugs have been used with good results (Table 4) [15,16,17].

International consensus guidelines on monitoring disease activity in CRMO are currently lacking but will be important for future prospective trials of treatments. Response to treatment is usually assessed by a combination of patient reporting of symptoms (particularly pain), physician examination, measurement of inflammatory markers (ESR and CRP) and WB-MRI. A prospective study of naproxen in CRMO defined a core set of five outcome variables [18]: ESR, number of radiological lesions, severity of disease estimated by physician, severity of disease estimated by patient/parent, and childhood health assessment questionnaire (CHAQ). Using these, one measure of improvement was the PedCNO30 score, defined as at least 30% improvement in at least three of the five core set variables, with no more than one of the remaining variables worsening by >30%.

Conclusion

The diagnosis of CRMO continues to be missed with an average delay in diagnosis of up to 12 months. In a child with recurrent bone pain, modest increase of inflammatory indices, lytic or sclerotic lesion on radiographs, bone marrow oedema on STIR MRI, CRMO should be suspected. Early diagnosis is important in terms of prevention of unnecessary investigations, prompt treatment and prevention of complications.

Treatment is based on experience from case series and expert consensus treatment plans, and includes anti-inflammatory agents (NSAIDs, corticosteroids, DMARDs) and bisphosphonates.

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Declaration of patient consent : The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given the consent for his/ her images and other clinical information to be reported in the journal. The patient understands that his/ her names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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