

Review Article

Chronic recurrent multifocal osteomyelitis

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Introduction

Chronic Recurrent Multifocal Osteomyelitis (CRMO), also known as Chronic Non-bacterial Osteomyelitis (CNO), is characterised by sterile inflammation involving the bones in children. If unrecognised, it will cause permanent severe bone destruction^{1,2}. It is a very rare disease with only a few hundred cases reported worldwide³. This may be due to lack of awareness about this entity among physicians. This is attributed mainly to the absence of validated diagnostic criteria⁴. Although it can occur at any age, CRMO occurs mainly between the ages of 7 and 12 years with a slight female preponderance^{5,6}. When the disease occurs at a younger age, autoinflammatory conditions like Majeed syndrome or deficiency of interleukin-1 (IL-1) receptor antagonist should be suspected⁷.

Genetics

The exact molecular cause of CRMO remains a mystery. However, association with the Human Leucocyte Antigen (HLA) B27 was more common in children affected with CRMO than in the general population^{8,9}.

Pathogenesis

The pathophysiology of this sterile bone inflammation is intriguing. Available evidence points to the interplay of genetic, environmental and immunological factors. Alteration in the gut microbiome and imbalance between the pro-inflammatory and anti-inflammatory cytokines are often suspected to result in CRMO¹⁰. In CRMO, there is upregulation in the production of pro-inflammatory mediators like IL-6, tumour necrosis

factor alpha (TNF alpha) and IL-20, and there is a lack of production of anti-inflammatory cytokines like IL-10 and IL-19^{11,12}. It has been hypothesised that decrease in the production of IL-10 causes activation of NLR family pyrin domain containing 3 (NLRP3) inflammasome. This results in the activation of bone destruction by kappa-B ligand (RANKL) pathway¹².

Clinical features

The presenting features of CRMO include non-specific bone pain, which is insidious in onset. Child may sustain fracture of the involved bone following trivial trauma. The metaphysis of long bones of the lower limbs are commonly affected, followed by pelvis, vertebrae and long bones of the upper extremity. CRMO may be unifocal or multifocal.

Investigations

These are done mainly to rule out the mimics of CRMO. Complete blood count (CBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are essentially normal^{6,13}. Serum uric acid and serum lactate dehydrogenase are done to rule out leukaemia; blood cultures are taken to rule out infectious osteomyelitis.

Imaging

Computed Tomography (CT) scan shows lytic lesions, hyperostosis, sclerosis and cortical irregularity. Magnetic Resonance Imaging (MRI) shows increased intensity of Short-T1 Inversion Recovery (STIR) signal within the marrow and bony expansion. Bone scintigraphy and Positron Emission Tomography (PET) CT show increased uptake.

Bone biopsy

This is mainly indicated to rule out malignancy and infectious osteomyelitis. Common findings in CRMO in bone biopsy include destruction of normal bone structure with infiltration of neutrophils, monocytes, lymphocytes and plasma cells in the early phase with fibrosis during the later phases¹⁴.

Diagnostic criteria

There are two sets of criteria to diagnose CRMO, Jansson criteria and Bristol criteria¹⁵. They are shown in Tables 1 and 2.

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Table 1: Jansson criteria to diagnose chronic recurrent multifocal osteomyelitis (CRMO)

| Major criteria | Minor criteria |
|---|---|
| <ul style="list-style-type: none"> • Radiologically proven osteolytic or sclerotic bone lesion • Multifocal bone lesions | <ul style="list-style-type: none"> • Normal blood count and good general state of health • Erythrocyte sedimentation rate, C-reactive protein mild to moderately elevated |
| <ul style="list-style-type: none"> • Palmar-plantar pustulosis (PPP) or psoriasis • Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis | <ul style="list-style-type: none"> • Lesions present for more than 6 months • Hyperostosis |
| | <ul style="list-style-type: none"> • Associated with other autoimmune diseases apart from PPP or psoriasis |
| | <ul style="list-style-type: none"> • Grade I or II relatives with autoimmune or autoinflammatory disease |

Threshold for diagnosis ≥ 2 major or 1 major and three minor criteria

Table 2: Bristol criteria to diagnose chronic recurrent multifocal osteomyelitis (CRMO)

| Major criteria | Minor criteria |
|---|--|
| <ul style="list-style-type: none"> • Presence of bone pain without significant local or systemic features of inflammation • Magnetic resonance imaging showing lytic areas, sclerosis and periosteal reaction | <ul style="list-style-type: none"> • More than one bone involvement without increased C-reactive protein (CRP) • CRP > 30g/dl with bone biopsy showing inflammation |

Threshold for diagnosis: Both major and either one of the minor criteria

Differential diagnosis

- *Acute lymphoblastic leukaemia*: Age of incidence 2 to 5 years. Fever, hepatosplenomegaly, pallor, lymphadenopathy and bone pain will be present. CBC, with differential count and bone marrow biopsy confirm the diagnosis.
- *Hodgkin lymphoma*: Age of occurrence is between 15 to 19 years. Constitutional symptoms like fever and weight loss are common. Lymph node biopsy is diagnostic¹⁶.
- *Langerhans cell histiocytosis*: Age of occurrence is between 5 to 10 years. Pain is restricted in localised area of bone. X ray shows punched out lesions. CD1a staining on bone biopsy confirms the diagnosis.
- *Chronic infectious osteomyelitis*: Often presents with fever, localised bone pain and constitutional symptoms. CRP and ESR are elevated. Blood and bone cultures are positive. MRI shows subperiosteal collections of pus.

Management

Initial therapy: Use of non-steroidal anti-inflammatory drugs (NSAIDs) is the cornerstone of initial therapy^{17,18}. Half of the patients achieve remission in the first year. However, relapses are common requiring re-treatment with NSAIDs. The duration of treatment is very arbitrary. Clinicians tend to taper and stop NSAIDs if the child is symptom-free and MRI shows no disease activity.

Refractory disease: Children who continue to have active symptoms and abnormal MRI findings even after 4 to 6 weeks treatment with NSAIDs are started on TNF alpha inhibitors, bisphosphonates and Disease-Modifying Anti-Rheumatic Drugs (DMARDs)^{19,20}.

Supportive care: Regular appropriate physical and occupational therapy is required with meticulous monitoring of medication toxicity.

Prognosis

The disease severity may range from mild to very severe with uncontrolled inflammation, bone deformities, arthritis, growth failure and psychosocial dysfunction, resulting in a poor quality of life^{13,21}. Factors associated with poor prognosis include bone pain that is multifocal, high ESR and CRP, male sex and severe extraosseous manifestations like inflammatory bowel disease and psoriasis.

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