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. It is a very rare disease with only a few hundred cases reported worldwide. This may be due to lack of awareness about this entity among physicians. This is attributed mainly to the absence of validated diagnostic criteria. Although it can occur at any age, CRMO occurs mainly between the ages of 7 and 12 years with a slight female preponderance. When the disease occurs at a younger age, autoinflammatory conditions like Majeed syndrome or deficiency of interleukin-1 (IL-1) receptor antagonist should be suspected.

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.

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 CRMO. 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. 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) pathway.

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. 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 phases.

Diagnostic criteria
There are two sets of criteria to diagnose CRMO, Jansson criteria and Bristol criteria. They are shown in Tables 1 and 2.
Table 1: Jansson criteria to diagnose chronic recurrent multifocal osteomyelitis (CRMO)

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>• Radiologically proven osteolytic or sclerotic bone lesion</td>
<td>• Normal blood count and good general state of health</td>
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<tr>
<td>• Multifocal bone lesions</td>
<td>• Erythrocyte sedimentation rate, C-reactive protein mild to moderately elevated</td>
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<tr>
<td>• Palmar-plantar pustulosis (PPP) or psoriasis</td>
<td>• Lesions present for more than 6 months</td>
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<tr>
<td>• Sterile bone biopsy with signs of inflammation and/or fibrosis, sclerosis</td>
<td>• Hyperostosis</td>
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<tr>
<td>• Associated with other autoimmune diseases apart from PPP or psoriasis</td>
<td>• Grade I or II relatives with autoimmune or autoinflammatory disease</td>
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Threshold for diagnosis ≥2 major or 1 major and three minor criteria

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

<table>
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<tr>
<th>Major criteria</th>
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<tr>
<td>• Presence of bone pain without significant local or systemic features of inflammation</td>
<td>• More than one bone involvement without increased C-reactive protein (CRP)</td>
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<tr>
<td>• Magnetic resonance imaging showing lytic areas, sclerosis and periosteal reaction</td>
<td>• CRP&gt;30g/dl with bone biopsy showing inflammation</td>
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