CASE REPORT

Chronic recurrent multifocal osteomyelitis: a rare skeletal disorder

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SUMMARY

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare non-infectious inflammatory bone disease of unknown aetiology. CRMO mainly affects the metaphyses of long bones and spine in children and young adolescents. It presents with recurrent episodes of bone pain and fever, resembling bacterial osteomyelitis, but cultures of lesions are sterile and it is unresponsive to antibiotic therapy. We report a case of a 3-year-old boy diagnosed with CRMO, who was initially treated for bacterial osteomyelitis, and received prolonged antibiotic therapy for chronic pain, and swelling of mandible and ulna. CRMO should be kept in mind in the differential diagnosis of chronic bone pain and osteomyelitis unresponsive to antibiotic treatment.

BACKGROUND

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare auto-inflammatory, non-infectious disorder of the bone; it presents with recurrent episodes of pain due to sterile inflammation of the bone. The disease was first reported in 1972 by Giedon and colleagues, as subacute and chronic 'symmetrical' osteomyelitis. CRMO mainly affects children and adolescents; the onset is usually around the age of 10 years with a range between the ages of 4–14 years, with female predominance. The most common affected sites are the metaphyses of long bones, pelvis, clavicle and mandible.¹ However, lesions can appear at any site in the skeleton. Radiography of bone lesions shows similarities to bacterial osteomyelitis, with osteolytic and sclerotic lesions, but culture of the affected sites is sterile and there is no response to antibiotics.² Because of the atypical clinical trial of the disease, biopsy should be considered in the diagnosis of CRMO to rule out both chronic bacterial osteomyelitis and malignancy. This will change the treatment modality and follow-up of the patient.

CASE PRESENTATION

A 3-year-old boy was admitted to the paediatric infectious disease division with pain and swelling of the mandible for 8 months. He was earlier given oral antibiotics and non-steroid anti-inflammatory drugs, but the symptoms did not improve so he was referred to our clinic. He was born of non-consanguineous parents with no known diseases. His physical and neurological developmental stages were normal. His height and weight were in the normal range. He was fully vaccinated; he had no history of disease or trauma. On physical

examination, he was afebrile and appeared generally well. There was a fixed, tender palpable mass in the left submandibular region, 3×2 cm in diameter. Physical examination of the chest, abdomen, and neurological and cardiovascular system was normal. A complete blood count revealed a total leucocyte count of 15 400/mm³, haemoglobin 10.5 g/dL and platelet count of 526 000/mm³. Erythrocyte sedimentation rate (ESR) was 85 mm/h and C reactive protein level was 6.5 mg/dL. Laboratory analysis of electrolytes, and liver and renal function, was normal. Serum immunoglobulin levels were normal. Blood culture did not yield any microorganisms. Panoramic radiography of the mandible was suggestive of osteomyelitis. Ultrasonography displayed soft tissue swelling *with periosteal thickening in the left half of the mandibular corpus*, which was confirmed with X-ray and MRI (figure 1A, B). Taking into account the clinical symptoms, increased inflammatory markers and radiological findings, the patient was diagnosed with osteomyelitis. Empirically, he was given intravenous cephalosporin and amikacin. The swelling of the mandible improved but did not completely resolve. During the second week of treatment, the infection markers had not changed, and, in addition, a new lesion was noted at the distal region of the right ulna. X-ray of the ulna revealed lytic lesions with periosteal reaction, suggesting malignancy (figure 2). Because of the atypical clinical course and unresponsiveness to antibiotic treatment, a biopsy was performed on the mandible, to rule out malignancy and the other causes. The haemoculture, aspirate material culture and acid-fast bacilli (AFB) culture, were sterile. Cytology did not reveal malignancy. The histopathological evaluation of the sample pointed to CRMO.

DIFFERENTIAL DIAGNOSIS

Malignancy and bacterial osteomyelitis must be considered in the differential diagnosis of CRMO.

TREATMENT

The patient was given tumour necrosis factor (TNF) α blocker (etanercept) treatment.

OUTCOME AND FOLLOW-UP

The patient had a dramatic clinical response to the TNF blocker: at 4 months follow-up he had relief of symptoms, the swelling of the mandible and ulna disappeared, and the infection markers were in the normal range. He is still followed by our rheumatology department and has remained asymptomatic.

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Figure 1 (A) and (B) Soft tissue swelling with periosteal thickening on X-ray and MRI.

DISCUSSION

CRMO is an uncommon type of osteomyelitis, presenting in 2–5% of all diagnoses. It is characterised by focal, chronic and multiple non-infectious inflammation of the bone, with recurrent periods of exacerbation and remission.

The aetiology of CRMO is unknown. Microorganisms including *Propionibacterium acnes*, anaerobic streptococci, coagulase-negative staphylococci, atypical mycobacteria and autoimmune processes have been suggested as, but have not demonstrated to be, the cause.

Figure 2 Lytic lesions with periosteal reaction, suggesting malignancy.

The clinical presentation of CRMO is variable. Bone pain is usually the initial symptom, and was reported in all 40 patients in a paper by Catalano-Pons *et al.*³ but fever was reported in only nine patients. The main symptom of our patient was recurrent episodes of pain and swelling, without fever. Inflammatory markers can be increased in up to two-thirds of cases, as was reported by Brown and Wilkinson⁴ in 65% of their 11 patients. This finding also leads the physician to suspect bacterial osteomyelitis, as in our case.

The lesions are commonly symmetrical and multifocal, appearing as a lytic lesion at the metaphysis, and can progress to sclerosis or hyperostosis. Our patient had two foci, with lytic lesions of the ulna and mandible. A bone biopsy is required to confirm the diagnosis and to rule out malignancy. The histopathological features are usually non-specific, but biopsy findings can demonstrate inflammation with lymphocyte infiltration and can show fibrosis and lack of an organism.

CRMO can be associated with various other inflammatory diseases, such as SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis), psoriasis, inflammatory bowel disease and peripheral arthritis. Majeed syndrome, characterised by CRMO and congenital dyserythropoietic anaemia, and Sweet syndrome (acute febrile neutrophilic dermatosis), are other accompanying disorders reported with CRMO.⁵ Our patient did not have these components of the disease.

Premature closure of the epiphysal plate, bone deformities and ankylosis are reported as complications of CRMO. Healing of epiphysal destruction with sclerosis and hypertrophy can be responsible for permanent bone deformities. Hip subluxation in an 11-year-old boy diagnosed with CRMO was reported by Sirisha *et al* in 2014.⁶ We did not experience any such complication in our case.

Autoinflammatory pathogenetic mechanisms are also considered as causes of CRMO. One hypothesis is the instability between proinflammatory and anti-inflammatory cytokines.⁷ Also, increased IL-1 β secretion by peripheral mononuclear cells of patients with CRMO during active disease has been shown by Scianaro *et al*.⁸ The aim of treatment is both to induce remission of the disease and to provide normal function and growth of the bone. Non-steroidal anti-inflammatory drugs are usually recommended as first choice. Corticosteroids, bisphosphonates, methotrexate, sulfasalazine and colchicine have been used for treatment of CRMO, but there is no consensus on the appropriate treatment protocol.

Since IL-1 and TNF- α are important in the pathogenesis of the disease, IL-1 blocking agents and TNF- α inhibitors can be used in treatment. Their efficacy has been reported in recent reports.⁹ However, IL-1 blocking therapy seems to be less effective due to its multifactorial mechanism of action.¹⁰ Also, local production of TNF- α in lesions has been demonstrated, so

TNF-blocking agents can be considered in treatment of CRMO.³

We started a TNF- α inhibitor (etanercept) at a dose of 0.8 mg/kg once weekly by subcutaneous injection in our patient, as his symptoms did not improve on non-steroidal anti-inflammatory drugs and steroids. He has, to date, remained asymptomatic and has not displayed any adverse effects of TNF- α inhibition, such as tuberculosis.

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Contributors DA, KB, YC and OK participated in the management of the patient, obtained clinical data, reviewed the literature and drafted the manuscript. OK was the principal clinician involved in the clinical management of the case, helped to draft the manuscript, and critically revised the final manuscript. All the authors have read and given final approval to the manuscript submitted.

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Learning points

- CRMO must be suspected in the differential diagnosis of chronic and recurrent bone pain.
- Biopsy should be considered in chronic and relapsing bone pain and swelling unresponsive to treatment.
- Early diagnosis will prevent unnecessary and prolonged antibiotic usage.

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