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Review

Chronic recurrent multifocal osteomyelitis in children and adults: current understanding and areas for development

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Abstract

Since the first descriptions of chronic recurrent multifocal osteomyelitis in the 1970s, there have been numerous case reports in the literature; both unusual case reports and case series from all over the world. Our understanding of the pathogenesis has significantly changed, with it now being regarded as an autoinflammatory condition. Treatment options have also expanded, but little progress has been made in developing the evidence for treatments. Advancing gene studies have provided a mouse model, but the quest for a single gene to match the phenotype has been elusive. Early cohorts of patients have grown up into adults, allowing prospective data to inform the expected outcomes.

Key words: chronic recurrent multifocal osteomyelitis, chronic non-bacterial osteitis, autoinflammation

Rheumatology key messages

- Chronic recurrent multifocal osteomyelitis is believed to arise from the innate immune system causing autoinflammation.
- Whole-body MRI has shown spinal involvement to be common in chronic recurrent multifocal osteomyelitis.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory bone disease characterized by sterile bone lesions. It was first described in 1972 by Giedion *et al.* [1] as an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis. As CRMO is not always multifocal or recurrent, it has also been called chronic non-bacterial osteomyelitis or non-bacterial osteitis; but the term CRMO (first used in 1978 by Probst *et al.* [2]) is the most common in the literature and therefore, to avoid confusion, it would be helpful if it were universally adopted for this condition. This is likely to be the same disease process seen in SAPHO syndrome, which is predominantly described in adults [3].

As a little-known disease, it is likely to be significantly underdiagnosed, although there are more than 500 cases of CRMO in both children and adults described in the literature as individual cases and case series from all continents of the world.

Definition and diagnoses

The typical constellation of history, examination, radiology and pathological findings will be described below, although it remains a diagnosis of exclusion, with the association of positive and negative findings. A good response to NSAIDs without antibiotics is a helpful indication of the underlying diagnosis [4].

Clinical features

Pain is a consistent feature of CRMO, usually with an insidious onset, and is associated with swelling and tenderness over the affected bones. The classical picture is a swollen clavicle; the metaphyses and epiphyses of the femur, tibia or humerus are more frequently affected. Lesions may occur in any bone, including vertebrae [5–14].

In the initial descriptions of CRMO, vertebral involvement was thought to be rare [15]; however, when the spine is imaged (often after the diagnosis of CRMO) spinal involvement is commonly found [5, 10, 16].

Skin involvement includes palmoplantar pustulosis, acneiform lesions or psoriasis. In early case series,

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palmoplantar pustulosis was reported in ~20% of patients, although more recent series have not found it so commonly [3, 4, 17–19]. This may be because of the preferential diagnosis of CRMO in patients with palmar involvement in earlier decades when the condition was very rarely recognized.

IBD, particularly with Crohn's-like lesions, has been described in CRMO and may represent 'enteropathic CRMO' [20–24].

The female preponderance has been reported by all the case series, with twice as many girls affected, and a median age of onset of ~10 years [14, 25–29].

Inflammatory markers, such as ESR, CRP concentration, leucocytes and fibrinogen, are commonly elevated. The increases are usually moderate and return to normal during quiescent periods. If these markers are very significantly elevated there is a higher likelihood of infection, and therefore further investigations (such as biopsy) may be necessary to ensure the correct diagnosis is made. Fevers may be a feature during episodes of disease flare but are not usually prominent [6, 26, 30–32].

Differential diagnoses include bacterial infection, leukaemia, bone tumours and histiocytosis, all of which may present insidiously. These should be considered carefully and ruled out before a diagnosis of CRMO.

Radiological features

In the early phase of the disease process, plain X-rays may be normal. As the disease progresses, features identical to bacterial osteomyelitis develop, including osteolysis, sclerosis and new bone formation. Some lesions have periosteal reactions or soft tissue swelling; others have lytic areas and they may mimic bone tumours [33]. A combination of these features, particularly in multiple sites, may help to distinguish the condition from other diseases [26].

Radionuclide bone scans have been used to identify silent lesions in other bones (as foci of increased uptake) and to monitor the response to therapy. Where available, whole-body MRI (WB-MRI), using short tau inversion recovery sequences, permits identification of the characteristic features of areas of bone marrow oedema (hyperintensity on short tau inversion recovery images) with a metaphyseal predilection. It is also more sensitive than radiographs or bone scans to identify silent lesions without radiation [34]. In many cases, this will help to identify multifocal lesions where only one has been noticed clinically and make the diagnosis more obvious [35–38].

WB-MRI is also helpful for monitoring response to treatment. Pain may be attributable to mechanical problems rather than active CRMO, and conversely, symptoms arising from active lesions may wax and wane, making it difficult to assess the efficacy of treatment. WB-MRI provides a more objective measure of disease activity without any radiation [35, 36, 39].

Where the clinical history, examination and radiology are typical, the diagnosis can often be made without the need for a biopsy, although in some cases, particularly in isolated lesions, biopsy may be necessary to exclude malignancy, infection, histiocytosis or other diagnoses [40]. As MRI is a very sensitive way of clearly identifying lesions, it can also be used to ensure accurate location for biopsy [41].

Histopathology

Bone biopsies from affected lesions show non-specific inflammatory changes. Early lesions demonstrate acute inflammation, with PMNs accumulating in the marrow. Osteoclastic bone resorption and necrosis may be present. Subsequently, lymphocytes and plasma cells become more common in the inflammatory infiltrate, and some cases display granulomatous foci. In the later stages, fibrosis becomes more prominent, and osteoblasts may be seen with signs of reactive new bone forming around the inflammation. This parallels findings that are seen radiologically as osteosclerosis [2, 42]. Despite there being a 'typical picture' on biopsy, none of these changes is specific to CRMO and therefore histological examination alone, whilst being suggestive, cannot differentiate CRMO from bacterial infection [5, 43–45]. However, as malignancy is a differential diagnosis, particularly for solitary lesions, biopsy may be essential to exclude a more sinister condition [46, 47].

Genetics and pathogenesis

The specific genetics of non-syndromic CRMO and SAPHO have been elusive, unlike the similar autoinflammatory conditions of Majeed syndrome [48, 49] and deficiency of the IL-1 receptor antagonist. Majeed syndrome is caused by mutations in *LPIN2* and usually presents within the first 2 years of life with non-infectious osteomyelitis, skin lesions and dyserythropoietic anaemia. Deficiency of the IL-1 receptor antagonist is caused by mutations in *IL1RN* and presents in the first weeks of life with destructive sterile osteitis and periostitis, skin pustulosis and joint swelling [50, 51]. The shared features of non-infectious bone and skin inflammation suggest a similar genetic and immunological pathogenesis to CRMO. Although affected family members and monozygotic twins are not uncommon within CRMO case series, no single gene has been identified [4, 5, 52]. A study of 60 patients found that only one had a heterozygous missense variant in *IL1RN*, suggesting that mutations in this gene are not an important cause in non-syndromic CRMO [53]. A significant association of CRMO with a rare allele of marker D18S60 microsatellite polymorphism pointed towards the existence of a susceptibility gene on chromosome 18, potentially contributing to the aetiology of CRMO [52]. In the mouse model of CRMO, a missense mutation in *pstpip2* produces very similar abnormalities to human CRMO [54, 55]; however, when 10 patients with CRMO were screened for mutations in the genes *PSTPIP1* and *PSTPIP2*, no mutations were found [5].

The underlying pathogenesis of CRMO, and the adult counterpart SAPHO, is thought to be dysregulation of the innate immune system [56, 57]. There appears to be an imbalance between pro-inflammatory cytokines, such as

IL-6 and TNF-α, and anti-inflammatory cytokines, such as IL-10 [58]. Assays of serum from untreated CRMO patients have shown elevated IL-6 and TNF-α and undetectable levels of IL-10 [59]. *In vitro* stimulation of peripheral blood mononuclear cells (PBMCs) from CRMO patients with innate immune system activators, such as lipopolysaccharide, generated significantly less IL-10 than PBMCs from control subjects. In another study, the inflammasome response in PBMCs from CRMO patients showed a significant increase in IL-1β release when stimulated compared with healthy control cells, indicating that there is dysregulation in this pathway [60], while increased concentrations of monocyte chemotactic protein 1, IL-12 and soluble IL-2 receptor were correlated with incomplete remission in CRMO patients compared with patients with Crohn's disease and healthy controls [61].

Two mouse models of CRMO exist, both caused by homozygous mutations in *pstpip2*; the chronic multifocal osteomyelitis (cmo) mouse with spontaneous mutations and the lupo mouse generated by mutagenesis [55, 62]. Studies on the cmo mouse have shown the importance of IL-1β in pathogenesis of osteomyelitis [63–65]. It appears to be neutrophils rather than bone marrow macrophages that are the main source of this cytokine, and production is independent of the inflammasome [65, 66]. Dietary manipulation, via its effect on the microbiome, may have an effect on pathogenesis and disease progression. In one study, cmo mice fed a normal low-fat diet had relative enrichment of inflammation-associated intestinal bacteria compared with those on a high-fat diet [67]. The latter mice seemed to be protected from development of osteomyelitis. The mechanisms of this apparent effect and whether results can be translated to human disease await further investigation.

Therapeutic options

Some patients experience spontaneous resolution of symptoms, whereas others have persistent severe disease. As the disease is not well recognized by many clinicians, symptoms have usually been present for many months before a diagnosis is made [29]; therefore, only those with fairly persistent disease will be diagnosed, selecting out the milder forms of the condition from being included in many case series [11].

Active disease causes bone pain, which may be severe, resulting in disruption of normal activities and, potentially, permanent bony deformities [68–70].

When treating CRMO, the dual aims are to minimize pain and maintain normal bone growth (in childhood), allowing normal function of adjacent joints [71]. There are currently no randomized controlled trials of treatment in CRMO to guide the most effective therapy.

NSAIDs

NSAIDs are usually considered first-line treatment and may be very effective, producing a clinical and radiological improvement in many patients [72–74]. It is postulated that NSAIDs act by inhibition of the cyclooxygenase pathway, thereby inhibiting prostaglandin synthesis [33]. A review compiling case reports found that overall 79% of patients had a good response to a variety of NSAIDs [17]. Indomethacin and naproxen have been described as effective both in primary lesions and for relapses [13, 33, 75, 76]. If there is a failure to respond to one NSAID, it is worth trying others because the response may vary between patients [5, 27, 31, 32].

In the absence of randomized controlled trials, case series where NSAIDs have been used may be compared with the duration of symptoms seen in the early case series (as historical controls). As Girschick *et al.* [13] point out, in the cohort of Björkstén *et al.* [3] the mean duration of symptoms was 6.3 years, compared with 19 months in the treated cohort Girschick *et al.* [13], although the cohorts may not be directly comparable because the cohort of Björkstén *et al.* [3] included adults and children, whereas the patients of Girschick *et al.* [13] were entirely paediatric, and the outcome measures used were not easily comparable.

CS therapy

For those patients who fail to respond to NSAIDs, steroid therapy has been used with good effect: i.v. methylprednisolone, oral prednisolone or hydrocortisone. Despite initial benefit, the resolution of pain may be transient, with symptoms recurring once steroids are stopped [5, 33, 77, 78].

DMARDs

MTX and AZA are generally considered to be ineffective as single-agent therapy [5], although there are individuals within case series where benefit has been found, usually when added as adjunctive therapy [29, 79]. SSZ has also been used sporadically, with some cases appearing to respond well, although there is little consistency in response to treatment [8, 29, 32].

Bisphosphonates

The data on bisphosphonates (mainly pamidronate) in CRMO continue to grow, with increasing evidence of efficacy where NSAIDs have failed to control symptoms. It has been widely recognized to reduce pain, sometimes dramatically, and improve function. The use of MRI to demonstrate resolution (or reduction) of active lesions has contributed to the evidence for benefit in the absence of randomized controlled trials and allowed a more objective measure of disease activity where symptomatology can wax and wane [10, 39, 70, 80–86]. MR scanning, after pamidronate, has also demonstrated improvement in vertebral modelling and height, causing some authors to suggest its early use, particularly in children with spinal lesions [10, 86].

Pamidronate was the first bisphosphonate to be used in CRMO because there was already experience of using it in a paediatric population in osteogenesis imperfecta [87]. Therefore, the same 3-day paediatric protocols were used. The dose used in our own cohort was 1 mg/kg/day (maximum 60 mg/day) for 3 consecutive days every 3 months for 1 year, after which assessment was made as to whether remission had been achieved [39]. Neridronate

(an aminobisphosphonate) has also been used in CRMO and appears to have similar effects to pamidronate [88].

It is not clear exactly what the mechanism of action is in CRMO; bisphosphonates are known to inhibit osteoclasts [89] and may reduce lesion expansion by an action on these cells. The anti-inflammatory effects were brought to light when they were used as an adjuvant therapy in RA [90]. They have been found to be effective in AS and spondyloarthropathies, ameliorating clinical symptoms [91].

Other agents

Early treatments of CRMO included interferon, with case reports of good results in a teenager and an adult [92, 93]. Others reported incomplete resolution of disease [94]. The development of biological therapies directed toward the elevated cytokines have superseded this as treatment for CRMO resistant to NSAIDs.

Biological therapies

In the last decade, the use of biological agents has increased dramatically for a variety of diseases, and particularly for autoinflammatory conditions. In the majority of published CRMO case series, the patients who are treated with these agents represent a subset of patients with disease resistant to the use of multiple agents, usually NSAIDs, pamidronate and steroids.

Infliximab has been used on a handful of patients in varying doses, with mostly positive results [84, 95, 96]. In 2005, a child was treated with infliximab (5 mg/kg) every 4 weeks for 12 months and then at 8-weekly intervals. Remission of symptoms allowed cessation of both steroids and NSAIDs [97]. A large (89 patients) retrospective cohort study found that two patients had required and been treated successfully with infliximab [5]. In another child with CRMO, who also developed Crohn's disease, there was resolution of pain, and bony lesions reduced in size following infliximab therapy [21]. Using a lower dose at similar intervals, there was resolution of pain continuing for 2 years of follow-up, and bone scans demonstrated radiological improvement [94]. Not all cases had complete success, with one child (after initial improvement) requiring long-term treatment with a shortened interval and requiring the addition of AZA before symptoms were fully controlled. The second child in the report had a relapse after infliximab was stopped because of fungal infection [94].

Etanercept (a recombinant, humanized TNF receptor that antagonizes soluble TNF) has also been used in treatment-resistant CRMO. In combination with MTX, it achieved clinical remission in two cases [80].

The apparent effectiveness of TNF blockade in controlling CRMO suggests that TNF plays a part in the progression of CRMO. Surprisingly, TNF has not been implicated in the mouse model of CRMO [98].

Anakinra (recombinant IL-1 receptor α) was used in one patient with CRMO having first demonstrated marked elevation of IL-1. Using a daily dose of 2 mg/kg, there was a good response initially, which persisted for 17 months before further symptoms developed and, after 3 years, necessitated switching therapy to adalimumab (humanized IgG1 anti-TNF-α mAb) [94].

In SAPHO syndrome, predominantly in adults and in a few cases in children, an increase in TNF-α has been well documented, and there are significant numbers of reports of good results, including reduction in swelling and pain, when using anti-TNF agents in this relative of CRMO [19, 99–104].

Disease activity monitoring

International consensus guidelines on monitoring of 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 [74]: ESR, number of radiological lesions, severity of disease estimated by physician, severity of disease estimated by patient/parent and childhood HAQ (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 $>30\%$.

Patients with CRMO may develop chronic non-inflammatory pain, and correlation of symptoms with radiological findings is important before modifying treatment [56]. We have previously reported the use of WB-MRI to monitor bony lesions before and after a course of pamidronate [39]. Reliable serum biomarkers of disease activity have not yet been fully evaluated. However, a prospective study of patients with CRMO treated with naproxen showed significant positive correlation of several potential biomarkers, such as ESR, CRP, IL-12 and monocyte chemotactic protein 1 with disease activity in those patients who achieved full clinical remission [61].

Long-term outcomes

The course of the disease is very variable, with relapsing and remitting symptoms. This variability led the authors of initial reports to believe that resolution was spontaneous, with remission occurring by puberty. Longer-term follow-up has shown that many patients continue to have impairments in adult life. Bony deformity, disability and chronic pain are commonly reported long term, although many of the studies were before bisphosphonates or biological therapies were routinely used for resistant symptoms [3, 35, 69, 86]. In some patients, there is an evolution into an atypical spondyloarthopathy, although numbers are small [19]. A follow-up study using clinical parameters and WB-MRI showed that longer-term clinical symptoms are not well correlated with radiological lesions. Many significant radiological lesions were not causing symptoms at the time of the follow-up. This is particularly concerning where spinal lesions are involved, and authors suggest that long-term follow-up with WB-MRI (where possible) would be advisable [36].

Future developments

The recent work using biomarkers to distinguish between patients with active lesions and those who are in remission may play a role in the future in helping to decide whether further treatment is warranted [61]. Increasing understanding of the biomarkers and the overlap between autoinflammatory disorders may also help with determining which biological agent is most likely to be effective in each patient.

Randomized trials of treatment are necessary but are often thought to be infeasible. Work into using novel trial designs for rare conditions in order to generate useful data may be the way to answer some of the questions that remain for these patients [105, 106].

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