Chronic recurrent multifocal osteomyelitis

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Available online 26 March 2011

Abstract

Chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic nonbacterial osteomyelitis, is an orphan disease that manifests as recurrent flares of inflammatory bone pain with or without a fever. The pain is related to one or more foci of nonbacterial osteomyelitis. To distinguish unifocal CRMO from a tumor or an infection, a bone biopsy is required in nearly all patients and a trial of antibiotic therapy in many. CRMO is now considered the pediatric equivalent of SAPHO syndrome, and recent data suggest that CRMO should be classified among the autoinflammatory diseases. The treatment of CRMO is not standardized. Although no randomized placebo-controlled trials are available, there is general agreement that nonsteroidal antiinflammatory drugs constitute the best first-line treatment and that bisphosphonates and biotherapies such as TNFα antagonists are effective in the most severe forms. Although CRMO is considered a benign disease, recent data suggest an up to 50% rate of residual impairments despite optimal management.

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1. Introduction

Chronic recurrent multifocal osteomyelitis (CRMO), also known as chronic nonbacterial osteomyelitis, is an orphan disease (OMIM#259680) whose prevalence is estimated at 1–2/106 (Orphanet.net) but may well be higher. CRMO was first described in 1972 by Giedon et al. [1]. The disease manifests as recurrent flares of inflammatory bone pain related to the presence of multiple foci of aspeptic osteomyelitis. CRMO is widely believed to constitute the pediatric equivalent of Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis (SAPHO) syndrome described in 1987 [2]. Initially, CRMO was thought to share similarities with the spondylarthropathies, based on the links between CRMO and SAPHO syndrome and on the presence in a substantial number of CRMO patients of psoriasis or chronic inflammatory bowel disease (Crohn’s disease or ulcerative colitis). However, recent genetic data from mice with chronic multifocal osteomyelitis (cmo) and humans with Majeed syndrome (CRMO with dyserythropoietic anemia) suggest that CRMO may belong to the vast family of autoinflammatory diseases. Here, we discuss recent data on the clinical features, outcomes, imaging study findings, nosology, and management of CRMO.

2. Diagnosing chronic recurrent multifocal osteomyelitis

The diagnosis of CRMO rests on a convergence of positive and negative findings. A number of features suggest CRMO (chiefly the occurrence of attacks of multifocal bone pain), and investigations must then be performed to rule out the main differential diagnoses (mainly infectious osteomyelitis, bone tumor, and Langerhans cell histiocytosis).

2.1. Clinical features

The mean age at CRMO onset is 10 years [3–5] and girls are affected more often than boys [3–7]. The mean time from symptom onset to the diagnosis of CRMO is 18 months, with a range of few weeks to a few years [3,5].

The most suggestive feature is bone pain predominating in the metaphyses and epiphyses of the long bones. The main sites of involvement, in order of decreasing frequency, are the distal tibia, proximal tibia, pelvis, proximal femur, clavicle, and calcaneus [3–5,7,8]. The prevalence of vertebral involvement in retrospective studies ranged from 4 to 30% [3–5,7,9]. Involve ment of the sternum, clavicle, or mandible is particularly suggestive of CRMO. There may be a fever during the attacks of bone pain. Some patients have extraarticular manifestations such as psoriasis [4,10], palmarplantar pustulosis [3,6,7,10], Crohn’s disease [4,7,11–14], acne [15], or Sweet’s syndrome [16,17]. Although CRMO occurs at a young age, studies have shown that the disease remains active in 25 to 59% of cases after a median follow-up of more than 10 years [3,4,18]. CRMO was long believed to resolve without leaving any consequential residual impairments. Recent data suggest, however, that physical impairments may persist in up to 50% of patients [4]. They consist chiefly in chronic pain and bone deformities, sometimes with limb length abnormalities. These physical abnormalities
may have a major psychological impact, and visible deformities (clavicle, mandible) may require plastic surgery to improve the patient’s appearance [3,4]. Furthermore, there is evidence that CRMO may evolve into spondyloarthropathy with clinical and radiological sacroiliitis [6,10].

### 2.2. Laboratory tests

During the attacks of bone pain, about two-thirds of patients have laboratory evidence of systemic inflammation with elevations in the erythrocyte sedimentation rate, C-reactive protein (CRP) level, leukocytes, and fibrinogen [3]. However, the increases are usually moderate [3,19].

### 2.3. Radiological findings

Many studies are ongoing to evaluate the role for imaging studies in CRMO. The recent introduction of whole-body magnetic resonance imaging (MRI) warrants a reappraisal of the relative roles for each imaging technique.

Radiography is the first-line imaging study in pediatric patients with a limp or pain possibly originating in the bone. The radiographs are often normal initially in CRMO. The first changes are usually seen in the metaphyses, near the growth plates. Later on, osteolytic, sclerotic, or mixed lesions develop, generally with no periosteal reaction [19]. However, the radiological findings vary widely, with some patients having breached cortices and/or periosteal appositions [5] suggesting a tumor, particularly if the lesion is unifocal. The main differential diagnoses are osteomyelitis, primary bone tumors, lymphomas, and Langerhans cell histiocytosis. Diaphyseal lesions visible only as cortical thickening have been reported [19]. The prevalence of spinal involvement varies considerably, from 3 to 25%, depending on the study [3,20]. A literature review suggests that the vertebral lesions may predominantly affect the thoracic spine, followed by the lumbar spine then the cervical spine [21]. One or more vertebral bodies are involved, while the disks are intact [21]. Vertebral plana and crush fractures may develop [7,8], and the main differential diagnosis is Langerhans cell histiocytosis.

The presence of multiple bone lesions and involvement of the metaphyses strongly suggest CRMO, obviating the need for a bone biopsy. Multiple lesions that are not visible on radiographs can be detected using either radionuclide bone scanning or whole-body MRI (Fig. 1). Radionuclide bone scanning may show multiple asymptomatic foci of increased uptake [22]. A map of the lesions at the time of the diagnosis can be obtained (Fig. 2), and the number of lesions may reflect the risk of persistent symptoms [3]. Early radionuclide uptake suggests inflammation and late uptake bone sclerosis. The main limitations of radionuclide bone scanning are the normally high uptake in the growth plates and patient exposure to radiation.

Whole-body MRI is more sensitive than radionuclide bone scanning. However, the long acquisition time and high cost limit the use of this investigation. MRI delineates the anatomy of the bone lesions (Fig. 3) and soft tissues. Inflammatory CRMO lesions generate low signal on T1 images and high signal on T2 images. A recent study showed that metaphyseal lesions were accompanied with epiphyseal lesions in 67% of cases [8,23]. The identification of patients with epiphyseal involvement may be helpful, as these patients may be at increased risk for growth disturbances [24]. Another advantage of MRI is detection of synovial involvement near the bone lesions [7,8,23].

### 2.4. Histological features

Children with a solitary bone lesion whose clinical and radiological features raise concern or lack specificity should undergo a surgical or imagery-guided bone biopsy to rule out an infection (via cultures) or tumor. This invasive investigation is usually unnecessary in patients with multiple lesions.

Bone biopsies from CRMO lesions [7,25] show nonspecific osteitis. Initially, there is an infiltrate composed of neutrophils and giant cells, as well as areas of osteolysis. Subsequently, histology shows reactive bone formation, sclerosis, and a predominantly lymphocytic infiltrate [25]. In some studies, these two stages could not be separated, as acute, subacute, and chronic changes coexisted within the same specimens [26,27].

### 2.5. Diagnostic score

Jansson et al. recently developed a score to assist in the diagnosis of CRMO while diminishing the number of unnecessary bone
biopsies [28]. They used a retrospective cohort of 224 patients, of whom 102 had CRMO and 122 had other diseases including benign and malignant bone tumors and bacterial osteomyelitis. The clinical score is based on weighted variables and can range from 0 to 63. When used in a diagnostic algorithm based on the presence of pain, abnormalities on standard radiographs, and/or one or more abnormalities on a whole-body imaging study, the score helps to diagnose CRMO and to avoid an unnecessary bone biopsy [28]. A prospective study in a larger cohort is needed to validate this algorithm.

3. Pathophysiology of chronic recurrent multifocal osteomyelitis

The pathophysiology of CRMO is unclear, and consequently the nosology of the disease remains ill defined. Until recently, CRMO was classified among the enthesitis-related forms of juvenile idiopathic arthritis or juvenile spondyloarthropathy, according to the Edmonton classification scheme [29]. A number of arguments suggest that CRMO may belong to the spondyloarthropathy spectrum: associations have been reported with psoriasis [4,10], sacroiliitis [6], and Crohn’s disease [4,7,11–14]; CRMO can evolve into spondyloarthropathy [10], and enthesitis may be the starting point for the bone lesions. However, there are a number of discordant facts, such as the absence of an association with HLA B27 [5,7]. Furthermore, some of the clinical features of CRMO suggest a link with a highly distinctive form of spondyloarthropathy known as SAPHO syndrome. It has been suggested that CRMO may constitute a pediatric form of SAPHO syndrome. These two entities share many features such as aseptic osteomyelitis and palmoplantar skin lesions.

Recent evidence indicates that CRMO is probably one of the autoinflammatory diseases. First, spondyloarthropathies may share similarities with autoinflammatory diseases. In 2006, McGonagle et al. [30] suggested a continuum from pure autoimmune disease to pure autoinflammatory disease. Disorders located
toward the middle of this continuum exhibit both autoimmune and autoinflammatory features; they consist chiefly of spondyloarthopathies and associated diseases such as psoriasis and uveitis. Second, associations have been reported between CRMO and both Sweet’s syndrome [16,17,31,32] and Crohn’s disease [4,7,11–14], two multifactorial autoinflammatory diseases [30]. However, no associations were found between the NOD2/CARD15 gene polymorphisms implicated in Crohn’s disease and CRMO [33].

Third, although most cases of CRMO are sporadic, several facts suggest a genetic component. In several families, two affected children were born to unaffected parents [34,35], suggesting autosomal recessive inheritance. Affected monozygous twins born to unaffected parents have been reported [36], as well as a case in a child whose father had aseptic osteomyelitis confined to the sternum [36]. The histological findings in CRMO suggest a link with autoinflammatory disease: the inflammatory infiltrates usually seen early in the disease are composed chiefly of neutrophils, the key cells in autoinflammatory diseases such as PAPA syndrome, together with giant cells and foci of osteolysis [7,25].

Studies of murine models of CRMO led to the identification of a region of interest and subsequently of one of the causative genes. There are two murine models, cmo mice [37–39] and Lupo mice [40]. A study in cmo mice identified a 21cM region of interest on chromosome 18 [37]. The same group subsequently showed that the cmo phenotype was due to a mutation in the pstpip2 gene coding for proline-serine-threonine phosphatase-interacting protein 2, located on chromosome 18 [39]. Although the exact role for the pstpip2 protein remains unknown, a study in the Lupo model showed that the causative mutation induced abnormalities in innate immunity [40] and that the pstpip2 protein was expressed in the monocyte cell line, which is the key cell line involved in innate immunity. These data are supported by the results of studies in humans. Mutations in the PSTPIP1 gene for a protein involved in regulating pyrin are responsible for the autoinflammatory disease known as PAPA syndrome (OMIM#604416). This disease manifests as progressively destructive aseptic arthritis with neutrophil infiltrates and skin lesions such as cystic acne, aseptic dermal abscesses, and/or pyoderma gangrosum [41]. PSTPIP1 binds to pyrin, a regulator that inhibits the NALP3 inflammasome. The two mutations described as causing PAPA syndrome may prevent PSTPIP1 from binding to the inhibitory phosphatases PSP-PEST and PTP-HSCF. Loss of this negative feedback effect mediated by dephosphorylation may lead to excessive binding of PSTPIP1 to pyrin, and therefore, to activation of the downstream NALP3 inflammasome pathway (Fig. 4) [42].

Recent genetic studies further support the classification of CRMO among the autoinflammatory diseases. In 2002, a study that used the family trio design (n = 27) demonstrated an association between an allele (166pb) of the D18S60 microsatellite polymorphism and CRMO [36]. This polymorphism is located in the region of the human chromosome 18 that is homologous to the region associated with the murine cmo phenotype [36–38]. A copy of the rare allele was identified in a single control compared to 11 of 27 patients with CRMO. In addition, the 166pb allele was preferentially transmitted to children with CRMO (P = 0.003). In 2005, Ferguson et al. identified the gene responsible for Majeed syndrome (OMIM#609628), a recessive autosomal disease manifesting as severe CRMO with closely spaced attacks of florid osteomyelitis and dyserythropoietic anemia [43]. Majeed syndrome is caused by a mutation in the LPIN2 gene at 18p11.31. The functional role for LPIN2 in Majeed syndrome remains unknown.

Multifocal inflammatory bone disease is a manifestation shared by CRMO and two autosomal dominant Mendelian diseases, cherubism (OMIM#118400) and deficiency of the IL-1 receptor antagonist (DIRA) (OMIM#612852). A greater degree of osteolysis in cherubism is the main difference with CRMO. Histology in cherubism shows an abundance of connective tissue and osteoclast-type cells. Two genes have been implicated in cherubism, SH3BP2 [44] and PTPN11 [45]. Although the role for these genes remains unclear, a murine model for cherubism is characterized by abnormal activation of cells involved in innate immunity (macrophages) with an excess of osteoclasts [46]. DIRA is a more recently described Mendelian autoinflammatory disease characterized by multifocal aseptic foci of osteolysis, periostitis, and pustulosis. Symptom onset occurs at a younger age than in CRMO, and the phenotype is more severe, with a fatal outcome in three of nine patients. DIRA is characterized by expansile lesions of the ribs, a feature not found in CRMO. Several mutations have been identified in the IL1RN gene encoding an IL-1 receptor antagonist protein [47].

Finally, susceptibility regions have been identified on chromosome 18 in two other diseases that share varying degrees of similarity with CRMO, familial expansile osteolysis and familial Paget’s disease of bone. In both diseases, the phenotype has been ascribed to mutations in the TNFRSF11A (RANK receptor activator of nuclear factor kappa B) gene at 18q22.1 [48,49].

4. Treatment

The treatment of CRMO is not standardized. Although no randomized controlled trials are available, there is general agreement about several points. NSAIDs are the accepted first-line medications for CRMO. NSAIDs are used either during the attacks or as maintenance therapy to prevent attacks. None has been proven superior over the others, but all are indisputably effective. In five patients given indomethacin to treat CRMO, the clinical and radiological response was excellent after 4 years of follow-up [50]. In patients with primary or secondary failure of NSAID therapy, one or two other NSAIDs should be tried as the susceptibility to NSAIDs varies across patients.

When NSAID therapy is inadequate, the main treatment options are bisphosphonates and TNFα antagonists. There is anecdotal
experience with other drugs such as azithromycin, interferon, sulfasalazine, methotrexate, intravenous immunoglobulins, and colchicine [3–8]. Oral glucocorticoid therapy is probably effective [51,52] but should be used only in limited dosages and durations, given the adverse effects of long-term glucocorticoid therapy on growth in these patients who are usually adolescents. Evidence that bisphosphonates might be effective was first reported in 2004 [53] and was confirmed by several subsequent publications [3–5,5,4,56–56]. In nine patients, the pain resolved almost completely within 48 hours of a pamidronate infusion [55]. However, many questions about the use of bisphosphonates in CRMO remain unanswered. The optimal pamidronate dosage and dosing interval remain to be determined. Studies are needed to assess potential adverse events, some of which may occur at a distance from the treatment. There is evidence that bisphosphonates are released into the urine for more than 8 years after treatment discontinuation [57]. At present, bisphosphonate therapy in patients with CRMO is given according to the schedule recommended for osteogenesis imperfecta [58]. No cases of jaw osteonecrosis have been reported in children given bisphosphonate therapy, for instance to treat osteogenesis imperfecta [58]. Jaw osteonecrosis seems to selectively affect older patients being treated for malignancies.

Finally, in a few patients with refractory CRMO, TNFα antagonists have been used, usually to good effect [3,19,5,60]. In four patients with CRMO treated with TNFα antagonists, including one previously given anakinra, sustained therapeutic effects were obtained [60]. However, one patient on infliximab therapy had an infection and another patient experienced escape phenomenon with anakinra. To our knowledge, this is the first patient given an IL-1 receptor antagonist for CRMO. In previous reports, infliximab or etanercept was described as effective in about 20 other patients with CRMO [60]. The authors concluded that TNFα antagonist therapy can be considered in patients with severe CRMO that fails to respond adequately to bisphosphonate therapy [60]. However, in patients with CRMO refractory to NSAID therapy, choosing between bisphosphonate therapy and TNFα antagonist therapy based on the manifestations may constitute a better approach. Thus, TNFα antagonist therapy may be the best choice in patients with marked inflammation (inflammatory pain, fever, CRP elevation, and early increased uptake during radionuclide bone scanning) and bisphosphonate therapy in those with predominant bone remodeling (involvement of the mandible, marked bone sclerosis, and increased uptake at the late phase of the radionuclide bone scan).

5. Conclusion

CRMO is a childhood-onset disease that can substantially impair quality of life by inducing persistent symptoms or sequelae. Although this chronic disease is not exceedingly rare, it remains poorly recognized by physicians and its prevalence is probably underestimated. As early as 2001, Cioide et al. pointed out that “national registries should be established to assist in the development of investigation and treatment protocols for CRMO”. With this goal in mind, a cohort of CRMO patients is being established in France, with the support of the SUREMIP, in order to collect all cases nationwide.1

Disclosure of interest

The authors have no conflicts of interest to declare.

References


1 Cases of CRMO can be reported to us by sending an email to julien.wipff@cch.aphp.fr. The objective is to obtain detailed clinical, laboratory, and imaging data and a follow-up of 5 years. A genetic study will look for CRMO susceptibility factors that may suggest new treatment options.