Chronic Recurrent Multifocal Osteomyelitis

A Concise Review and Genetic Update

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Chronic recurrent multifocal osteomyelitis is an autoinflammatory disease characterized by bone pain and fever, a course of exacerbations and remissions, and a frequent association with other inflammatory conditions. Because its etiology is largely unknown, the diagnosis is still based on clinical criteria; treatment is empiric and not always successful. The diagnosis is supported by the presence of osteolytic lesions with surrounding sclerosis apparent on radiographs, and silent asymptomatic lesions frequently appear on nuclear scans. The histologic findings in bone biopsies are nonspecific, showing inflammatory changes with granulocytic infiltration. Several observations suggest the contribution of genetic factors to the etiology of chronic recurrent multifocal osteomyelitis. Indeed, mutations in LPIN2 cause a syndromic form of chronic recurrent multifocal osteomyelitis known as Majeed syndrome, while mutations in pstpip2 cause a murine form of the disorder. The roles played by LPIN2 and the human homolog of pstpip2, PSTPIP2, in the etiology of chronic recurrent multifocal osteomyelitis are uncertain but are currently being investigated. We emphasize the need to validate diagnostic clinical criteria and develop new pathogenesis-based targeted therapy.

Level of Evidence: Level IV, therapeutic and prognostic study. See the Guidelines for Authors for a complete description of levels of evidence.

Autoinflammatory diseases are a group of disorders characterized by seemingly unprovoked inflammation in the absence of high-titer autoantibodies or antigen-specific T cells. They include the hereditary periodic fever syndromes and are believed the pediatric presentation of the latter is believed the pediatric presentation of the former.

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tified genes that play a role in its etiology. Although a genetic contribution to the etiology of CRMO has been suggested, we here present an overview of the two recently identified genes that are responsible for a syndromic human form of CRMO and for a murine form. We also discuss and speculate on the role of these two genes in bone inflammation.

Search Strategy
We performed a PubMed search of the MEDLINE biomedical literature, using the terms chronic recurrent multifocal osteomyelitis (141 references), LPIN2 (10 references), PSTPIP1 or PSTPIP2 (30 references), SAPHO syndrome (29 references), chronic sclerosing osteomyelitis (94 references), and pustulotic arthroosteitis (15 references). Our searches of articles published in the English language revealed considerable overlap in articles identified under the different search terms, and we reviewed the articles for pertinence to our review article. We also searched articles in French or German languages. We reviewed the abstracts of the articles published in these languages and obtained and utilized the articles that added any information to this review.

Due to the rarity of these conditions, we elected to include all studies in our analysis, however, when information overlapped we referenced the most recent articles built on conclusions or reports of previous articles. We also extracted information and views from the abstract book, presentations, posters, and discussions from the fourth international meeting on autoinflammatory disorders, “FMF and Beyond,” held in Bethesda, MD, USA, on November 6–10, 2005.

Clinical Picture
The classic clinical picture of chronic recurrent multifocal osteomyelitis is dominated by periodic bone pain and fever. There is a slight female predominance. The age at onset of symptoms ranges from infancy to 55 years with a median age of 10 years.12 The onset is almost always insidious with pain and tenderness, whereas the swelling and fever are not always present.20,23 At any one time, the number of osteomyelitis lesions is variable, ranging from two to 18.71,97 The course of disease is characterized by periodic waxing and waning of symptoms over a duration of 1 to 20 years.20,23,25,27 The inflammatory lesions are localized in a distribution that is similar to the hematogenous osteomyelitis of childhood usually in the metaphyses of long bones and the clavicle.12 The involvement of other bone sites, such as the vertebrae,6,23 the mandible,23 and the frontal and sphenoid bones99 is less frequently reported. Many individuals develop a very similar clinical picture but with monofocal inflammatory lesions or multifocal nonrecurring lesions. A clinical classification was proposed in a recent study that included a sizable cohort with sterile osteomyelitis.50 Patients were grouped as: (1) acute nonbacterial osteomyelitis (symptoms for less than 6 months with one or more bone lesions); (2) chronic nonbacterial osteomyelitis (symptoms for more than 6 months without remissions with one or more bone lesions); or (3) CRMO (multiple bone lesions or one bone lesion with PPP and recurrence).

The most consistent laboratory abnormality is the elevation of the erythrocyte sedimentation rate.12,88,97 The white blood cell count may or may not be elevated.88 TNF-α was elevated (> 25 pg/mL) in 66% of patients with CRMO.50 All cultures of blood, bone biopsies, and pus-tules were negative for fungal and bacterial growth, including mycobacterium, mycoplasma, and anaerobes.88 There have been suggestions of a viral etiology91 which is supported by the response to interferon treatment in a few patients.3,33 However, there is otherwise little or no data supporting a role of viruses in the disease process or the successful treatment with interferon.

Radiographs usually show irregular osteolytic lesions (radiolucency) with surrounding sclerosis (Fig 1).11–13,25,29,34,35,37,41,42,63,64,77,79,84,89,90,100 There is increased uptake on nuclear scans using Tc-99, and silent asymptomatic lesions may appear as well (Fig 2).25–29,34,37,32,64,77,79,84,89,90,100 A computed tomography scan or an MRI scan may be required to confirm the diagnosis.37,42,54,63,67,85,89 MRI can be helpful in determining disease activity and extent of disease, and can be used to help guide the bone biopsy procedure.53

A bone biopsy taken from an active lesion usually shows nonspecific inflammatory changes with granulocytic infiltration (Fig 3)13,24,25,29,34,35,37,41,42,63,64,77,79,84,89,90,100 Examination of biopsies at different stages showed CRMO begins as an acute inflammatory process with a predominance of polymorphonuclear (PMN) leukocytes plus evidence of osteoclastic bone resorption with or without multinucleated giant cells.12 At a later stage, the inflammatory infiltrate shows predominance of lymphocytes, plasma cells, histiocytes, and PMN leukocytes.12 New bone formation is evidenced by fibrosis around foci of inflammation, irregular bone narrow space, and increased osteoblast activity.63 Progressive sclerosis and hyperostosis occur mostly in the clavicle and occasionally in the tibia, femur, metatarsal, jaw, and ischiopubic bones.25,61 Sometimes biopsies show acute, subacute, and chronic nonspecific osteomyelitis mixed in the same lesion.22,76,89 Histologic changes correlated poorly with clinical features but relatively well with radiographic findings.22 Skin biopsy from pustular lesions showed intraepidermal collection of neutrophils with mild hyperkeratosis.79

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In general, CRMO has a self-limited course causing major symptoms but leaving most affected individuals with no permanent long-term skeletal abnormalities. However, sequelae are reported in some cases in the form of residual joint changes, ankylosis of the sacroiliac joints, growth disturbance, thoracic outlet syndrome, disuse atrophy of the muscles, and evolution into a spondyloarthropathy with unusual features such as unilateral sacroiliitis in the absence of the HLA-B27 association. Several reports suggested the sequelae of CRMO are not as benign as previously thought, and in one followup study, a considerable proportion of patients were at risk for physical and psychological complications resulting from the prolonged course despite the apparently good physical outcome.

After its original description, it became recognized that CRMO can be associated with other disorders, mostly of an inflammatory nature, including PPP; generalized pustulosis involving the trunk, groin, thighs, and buttocks; Sweet syndrome; psoriasis; pyoderma gangrenosum with or without inflammatory bowel disease; SAPHO syndrome; recurrent sterile subcutaneous abscesses; and inflammatory bowel disease.

**Diagnosis**
For the diagnosis of classic CRMO, all of the following criteria should be met: (1) multifocal bone lesions; (2)
prolonged clinical course over several years with remissions and exacerbations; (3) lack of response to antimicrobial therapy; and (4) radiographic examination showing multiple foci of osteolysis surrounded by sclerosis. Based on clinical observations, a suggestion for a new classification of nonbacterial osteitis, and review of the available literature, a panel of major and minor diagnostic criteria was proposed (Table 1). The study suggests the general diagnosis of nonbacterial osteitis is reached if two major criteria or one major criterion plus three minor criteria are found. Applying the proposed diagnostic criteria, the authors found the fewer the criteria that were met, the more likely the diagnosis of acute nonbacterial osteitis was reached. The more the criteria that were met, the more likely the diagnosis of CRMO was reached. However, this scheme of diagnosis has not been clinically validated and prospective studies examining the application of these criteria are needed to evaluate the usefulness of this diagnostic approach.

**Treatment**

The treatment of CRMO remains empiric due to the lack of controlled studies. Nonsteroidal antiinflammatory drugs (NSAIDs) are the first line of therapy resulting in clinical improvement in most treated patients. NSAIDs are often helpful in reducing the pain, swelling, and restricted mobility. However, many patients continue to have evidence of active disease despite improved pain and need additional antiinflammatory agents. Steroids have been used with reported benefit. There are two reports of clinical improvement using interferon α or interferon γ. Tumor necrosis factor-α blocking agents such as infliximab have been reported to provide clinical improvement in the treatment of CRMO. Bisphosphonates have also been used for CRMO with reported success by several groups, however, no response to treatment with bisphosphonates has also been reported. In general, antibiotics do not have an effect on CRMO symptoms; however, a German study reported improvement in seven of 13 patients with CRMO treated with azithromycin. The improvement reported with this macrolide antibiotic is probably attributable to its antiinflammatory effects.

**Etiology**

The etiology of CRMO is currently unknown. Cultures are uniformly negative, and there is typically no response to antibiotic therapy, making an infectious etiology highly unlikely. In addition, there is no evidence for immune deficiency or autoimmunity. An early report did not

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**TABLE 1. Proposed Major and Minor Diagnostic Criteria for Nonbacterial Osteitis**

<table>
<thead>
<tr>
<th>Major Diagnostic Criteria</th>
<th>Minor Diagnostic Criteria</th>
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<tbody>
<tr>
<td>Radiologically proven osteolytic/sclerotic bone lesion</td>
<td>Normal blood cell count and good general state of health</td>
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<tr>
<td>Multifocal bone lesions</td>
<td>CRP and ESR mildly to moderately elevated</td>
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<tr>
<td>PPP or psoriasis</td>
<td>Course is longer than 6 months</td>
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<tr>
<td>Sterile bone biopsy with signs of inflammation and sclerosis</td>
<td>Hyperostosis</td>
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<tr>
<td>Association with other autoimmune diseases other than PPP or psoriasis</td>
<td>Grade I or II relatives with autoimmune or autoinflammatory disorders or with NBO</td>
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PPP = pustulosis palmoplantaris; NBO = nonbacterial osteitis
support hereditary or autoimmune etiologic factors. However, there are currently several observations that point to the genetic etiology of CRMO. First, there are at least three reports of affected siblings with normal parents, thus suggesting autosomal-recessive inheritance. Second, a published study reports one monozygotic twin pair concordant for CRMO and another monozygotic twin pair in which CRMO was diagnosed in one and PPP was diagnosed in the other, both pairs with normal parents. In the same paper, the authors mention they have seen a child with CRMO whose father developed chronic noninfectious osteomyelitis of the sternum as an adult. In another report, there was more than one member affected with sterile osteomyelitis in 6% of the families that comprised their cohort. These family relationships were: father and son, monozygotic twin sisters, two pairs of sisters, and two sisters and their father. Multiple affected family members were also observed. Third, it has been recently shown, through an association study, there is a susceptibility locus on chromosome 18q21.3-22. Fourth, the autosomal-recessive Majeed syndrome, in which CRMO is the main component, is the result of mutations in LPIN2.

The role of genetic factors in the etiology of CRMO is potentiated by the presence of a spontaneously occurring mouse model (cmo) with clear autosomal-recessive inheritance. These mice develop tail kinks by 6 to 8 weeks of age and hind foot deformities by 3 months of age (Fig 4). Males and females are equally affected. The caudal and spinal vertebrae in these mice are partially or completely destroyed by an inflammatory infiltrate composed of macrophage and PMN cells by 3 to 4 weeks of age. Subsequently, there is resorption of both cancellous and cortical bone by osteoclasts followed by reactive new bone formation with associated fibrosis; these findings are very similar to those seen in human CRMO. The gene responsible for the murine cmo phenotype has been identified to be pstpip2.

Majeed syndrome is an autosomal-recessive disorder characterized by CRMO and congenital dyserythropoietic anemia, which has been clearly described in three families with seven affected individuals. Homozygosity mapping, parametric linkage analysis, and various mutation detection techniques led to the identification of LPIN2 as the gene responsible for the Majeed syndrome phenotype. Little is known about the function of LPIN2. It shares a lipin domain with the human ortholog of murine lipin1, which plays a role in fat metabolism. Studies of the fission yeast (Schizosaccharomyces pombe) Ned1 gene, which belongs to an evolutionary conserved gene family that includes the mammalian LPIN genes, revealed mutations have a high incidence of chromosome missegregation, aberrantly shaped nuclei, overdeveloped endoplasmic reticulum-like membranes, and increased sensitivity to microtubule destabilizing agents. The role of human lipin2 in fat metabolism is not clear, because LPIN1 mutations have not been reported in patients with lipodystrophy. Based on suggested mechanism for pyrin, the protein implicated in the archetypal autoinflammatory disorders, familial Mediterranean fever, we hypothesize lipin2 plays a role in the regulation of the innate immune system, and the defect in the protein would lead to increased production of proinflammatory signals. One way this could occur would be if lipin2 plays a role in promoting apoptosis in polymorphonuclear leukocytes and its normal function were to curtail the inflammatory milieu. Mutations in LPIN2 would then lead to a disturbed function and persistence of inflammation. An alternative hypothesis is based on the observation that LPIN2 expression is upregulated in response to oxidative stress in lung macrophages. Mutations in LPIN2 would disturb its protective function against oxidative stress, and the oxidative stress would lead to inflammation secondary to tissue damage. Both hypotheses assume there is tissue-specific redundancy in the role played by lipin2 and its related pathway in the downregulation of inflammation with a lower level of redundancy in skin and bone.

Mutations in pstpip2 have been identified in two mutant mouse lines, which have chronic osteomyelitis as the main phenotype. The first mouse model is a spontaneous mutant model described in 1991 and named the cmo (chronic multifocal osteomyelitis) mouse.
multifocal osteomyelitis) mouse.\textsuperscript{17} The gene locus was mapped by RFLP analysis to a 21 cM location on murine chromosome 18.\textsuperscript{17} The gene was subsequently identified using a backcross breeding strategy followed by direct sequencing of candidate genes in the refined region. A missense mutation (L98P) in \textit{pstpip2} was detected, which was predicted to be deleterious by protein modeling and the leucine in the ninety-eighth amino acid position is highly conserved across species.\textsuperscript{30} Independent confirmation that mutations in \textit{pstpip2} caused the phenotype came shortly thereafter when Grosse et al\textsuperscript{40} reported an ENU mutant mouse (Lupo mouse) with an overlapping phenotype that also had homozygous missense mutation in \textit{pstpip2}. The Lupo mouse showed inflammation in a similar tissue distribution as the cmo mouse but with variable severity. This difference in severity may be explained by the different mutations in Pstpip2 domains or other factors relating to the different genetic backgrounds of the mice.

The human \textit{PSTPIP2} is located on 18q21.1, in the vicinity of the region identified by the association study.\textsuperscript{39} Its role in human CRMO has been examined in a limited number of patients\textsuperscript{45} but is currently under study in our laboratory in a larger number of patients.

\textit{Pstpip2} is a proline-serine-threonine phosphatase interacting protein (also called \textit{MAYP}—macrophage actin-associated tyrosine phosphorylated protein) that belongs to the Pombe \textit{CDC15} homology family of proteins that are important in actin-based cellular functions.\textsuperscript{66} \textit{Pstpip2/MAYP} is highly expressed in macrophages.\textsuperscript{40} As predicted, under- or overexpression of \textit{pstpip2/MAYP} in mouse macrophages (in vitro) affects the ability to rearrange the cytoskeleton to form filopodia and membrane ruffles and also affects cell motility.\textsuperscript{21} The level of \textit{pstpip2/MAYP} in wild-type mouse macrophages increases with LPS stimulation, but this response to LPS is dampened in the Lupo mouse in which \textit{MAYP} expression is threefold lower than wild type.\textsuperscript{40} The exact mechanism has not been elucidated, but it appears mutations in \textit{pstpip2} lead to an inflammatory phenotype by disrupting normal macrophage function; thus, wild-type \textit{pstpip2/MAYP} appears to play an anti-inflammatory role in normal immunologic function of the monocytic cell lineage. Both \textit{LPIN2} and \textit{PSTPIP2} are expressed in macrophages\textsuperscript{95} and the Lupo mouse is a macrophage-mediated autoinflammatory disorder\textsuperscript{40} suggesting a common pathway for down-regulation of bone and skin inflammation.

\section*{DISCUSSION}

CRMO is an autoinflammatory disorder of bone that is often associated with other inflammatory conditions. Although its etiology is currently unknown, evidence for causative genetic factors is emerging. Several observations such as affected siblings, a syndromic monogenic disorder with CRMO as a prominent phenotypic feature, and a spontaneously occurring mouse model led to the identification of two genes that play a role in the etiology of CRMO. The role of mutations in \textit{LPIN2} has been proven to cause the syndromic form of CRMO called Majeed syndrome, and mutations in \textit{pstpip2} cause a murine form of the disorder, cmo. There are currently ongoing studies to delineate the contribution of common or rare variations in \textit{LPIN2} and \textit{PSTPIP2} to the etiology of CRMO and its associated inflammatory conditions. The goals of these studies are to better understand the pathophysiology of CRMO and to guide the treatment modalities, based on the understanding of the bone inflammatory process. Identifying the pathway involved in bone inflammation will aid in identifying other genes that play a role in the etiology of CRMO, which is clearly a heterogeneous and multifactorial condition.

The diagnosis of CRMO has been hampered by the lack of a specific diagnostic test and the reliance on clinical criteria and recurrence of the disease to reach a firm diagnostic conclusion. Algorithms for the clinical diagnosis have been proposed but remain to be validated for extended clinical use. As mentioned above, the current treatment modalities are empiric with varying degrees of success. There is an obvious need for appropriately designed drug trials that are supported by deeper understanding of the pathophysiology of CRMO. Identifying all genes contributing to the etiology of CRMO will undoubtedly provide the framework for studies of the pathophysiology and the interaction of those genes with the environment to produce the phenotype. It may also lead to individualization of treatment modalities based on an etiology-based classification.

In this review, we provided an outline for the clinical presentation and the management aspects of CRMO and discussed the genetic factors contributing to its etiology. We outlined the need for validation of clinical schemes for the diagnosis of this disorder and the deeper understanding for its underlying pathophysiology. This in turn can provide the basis for treatment trials that have a high rate of success, or individualization of the treatment based on an etiologic classification of the disorder.

\section*{Acknowledgment}

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\section*{References}


