Chronic recurrent multifocal osteomyelitis (CRMO) is an autoinflammatory disorder of children and young adults that is characterized by nonbacterial osteomyelitis. Patients typically present with multifocal bone pain secondary to sterile osseous inflammation, and the disease has a relapsing and remitting course. The cause of CRMO remains unclear, although the results of several studies have suggested a genetic component. The typical imaging findings of CRMO include lytic and sclerotic lesions in the metaphyses of long bones and the medial clavicles. Other common sites of disease are the vertebral bodies, pelvis, ribs, and mandible. CRMO is often bilateral and multifocal at presentation. Owing to the lack of a diagnostic test, CRMO remains a diagnosis of exclusion. Although generally a self-limiting disease, CRMO can have a prolonged course and result in significant morbidity. Radiologists can be the first to suggest this diagnosis given its characteristic radiographic appearance and distribution of disease. Radiologists should be familiar with the typical imaging findings of CRMO to prevent unnecessary multiple biopsies and long-term antibiotic treatment in children with CRMO.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is an idiopathic inflammatory disorder of bone seen primarily in children and adolescents. The syndrome of CRMO was originally described in 1972 in four children, under the name “subacute and chronic recurrent osteomyelitis” (1). It is characterized by multifocal nonpyogenic inflammatory bone lesions, a course of exacerbations and remissions, and an association with other inflammatory disorders (2). Since its original description, there have been multiple case reports and studies of this disorder under a number of different names. These include subacute and chronic symmetric osteomyelitis, subacute
symmetric osteomyelitis, chronic multifocal symmetric osteomyelitis, chronic multifocal cleidometaphyseal osteomyelitis of childhood, and chronic recurrent multifocal osteomyelitis (1,3–6).

The term CRMO was first used by Probst and colleagues (3,5) and encompasses the typical clinical features of this entity: chronicity with a protracted course, involvement of more than one site, multiple exacerbations and relapses at old and new sites, and disease at sites that are typical of osteomyelitis in children. Although primarily a disease of children, it has been reported in older patients up to the age of 55 years (7,8). Since its original description more than 3 decades ago, several hundred cases of CRMO have been reported, likely owing to an increasing awareness of this disease. Because CRMO is a diagnosis of exclusion, it is likely that its actual prevalence is higher than reported in the literature.

As imaging plays an important role in the evaluation of this disorder, it is important that radiologists be familiar with its various manifestations. Suggestion of the diagnosis by a radiologist could help avoid unnecessary diagnostic procedures and antibiotic therapy and initiate an appropriate therapy. In this article, we present our clinical experience with CRMO and review its epidemiologic, etiologic, clinical, and histopathologic features. We then describe the imaging approach, imaging appearances, and specific disease sites: tubular bones, clavicle, spine, pelvis, mandible, and hands and feet. Finally, we discuss differential diagnosis and outcomes and compare CRMO with SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome.

Clinical Experience
Between 2003 and 2008, 25 patients with CRMO were referred to the department of pediatric rheumatology at our institution. There were 10 male and 15 female patients with an average age at onset of symptoms of 8.3 years (range, 2.5–24 years). The three most common sites of disease at initial presentation were the lower extremities (39.7%), spine (25.9%), and pelvis (20.7%). During the course of follow-up, a total of 121 bone lesions were seen in this patient population, with the most common site of disease being the lower extremities (tibia, 15%; femur, 12%). Metaphyseal lesions were the most common, accounting for 49% of all long bone lesions.

The diagnosis of CRMO in our patient population was confirmed by means of bone biopsy and negative cultures in 23 of the 25 cases. Biopsy was not performed in two cases owing to a typical clinical picture and the presence of comorbid conditions (Crohn disease in one case and a pustular rash in the other), which supported the diagnosis of CRMO. The images from these cases have been used to illustrate this pictorial review of CRMO.

Epidemiologic Features
CRMO is primarily a disease of childhood, with most patients presenting between 9 and 14 years of age. However, it has been described in infants as young as 6 months and in adults as old as 55 years (7,9–11). Several studies have demonstrated a female predominance, with a male-to-female ratio of 1:2.1 (12–15). Although most of the initial reports of CRMO came from Europe, cases have been reported worldwide (1,10,11,16–19). The true prevalence of this condition remains unknown, with more than 250 cases of CRMO reported in the literature (12,13). Given the fact that it is a diagnosis of exclusion, it is likely that the actual prevalence of CRMO is higher than realized.

Etiologic Factors
The cause of CRMO remains elusive. Initial reports suggested an infectious origin, with suspected organisms including *Staphylococcus aureus*, *Mycoplasma hominis*, *Propionibacterium acnes*, and *Chlamydia* (7,9,20). However, larger studies have shown no common infectious agent responsible for CRMO (8,21). The coexistence of skin organisms (such as diphtheroids and coagulase-negative staphylococci) in the biopsy cultures and the failure of CRMO symptoms to improve with antibiotic therapy suggest that the organisms are likely contaminants of biopsy specimens (19,22).

The association of CRMO with dermatologic disorders (such as psoriasis) and inflammatory bowel disease and its response to steroids have led to the suggestion of an autoimmune cause (23–25). More recently, a genetic origin for CRMO has been suggested secondary to observation of disease in siblings and monozygotic twins (10,11,26–28). By means of a family-based association study, a susceptibility locus has been identified at 18q21.3–22 (29).

The genetic origin of CRMO is further supported by the identification of mutations of the LPIN2 gene in Majed syndrome (10,11,30,31). This rare autosomal-recessive syndrome is phenotypically characterized by a triad of CRMO, congenital dyserythropoietic anemia, and an inflammatory dermatosis. Spontaneously occurring
mouse models of CRMO have been identified that show an autosomal-recessive gene defect localized to the murine *psipip2* gene (27,32,33). Biopsy samples from these mice show histologic features similar to those seen in CRMO (27,32,33).

**Clinical Features**

Patients typically present with nonspecific complaints such as pain, tenderness, swelling, or limited range of motion at one or more sites. Systemic manifestations such as fever, weight loss, and lethargy may be present but are unusual. The duration of symptoms can vary from days to several years (19). In the series of Mandell et al (34), children were symptomatic for 3 days to 2 years before initial presentation. The duration of symptoms can often be hard to assess because of the insidious onset and vague nature of the symptoms. Laboratory findings at initial presentation are essentially nonspecific, with the most common findings being mildly elevated erythrocyte sedimentation rate and C-reactive protein level with a normal white blood cell count (26).

Although most patients present with a single symptomatic site, other sites of disease become apparent at imaging or during clinical follow-up (Fig 1). At any one time, the number of osteomyelitis lesions can range from one to 18 (34,35). Although most patients with CRMO have recurrent and multifocal disease, a significant number of children with nonbacterial osteomyelitis may have only a single lesion, which exhibits the same clinical, radiologic, and histologic features as multifocal disease (Fig 2). The term *chronic nonbacterial osteomyelitis* has been suggested for this entity (21).
CRMO has been reported in association with skin lesions including palmoplantar pustulosis, psoriasis vulgaris, Sweet syndrome, and pyoderma gangrenosum (16,19,23,24,36,37) (Table). In the review by Schultz et al (37), the prevalence of cutaneous lesions in children with CRMO was reported to be 25%, with pustulosis being the most common, followed by psoriasis. An association between CRMO and inflammatory bowel disease, especially Crohn disease, has also been reported (Fig 3) (25,37,38).

**Histopathologic Findings**

Because the imaging findings of CRMO can be nonspecific, especially early in the course of the disease or in the presence of a solitary lesion, microbiologic and histopathologic analysis are essential to exclude infectious osteomyelitis and neoplastic lesions. At histologic evaluation, CRMO bone lesions show nonspecific inflammatory changes with granulocytic infiltration (8,19). In the acute stages, there is a predominance of polymorphonuclear leukocytes and osteoclastic bone resorption with or without multinucleated giant cells. As the disease progresses, the predominant features are lymphocytes, plasma cells, histiocytes with occasional granulomas, and increased osteoblast activity (8).

The histologic findings correlate relatively well with the radiologic appearance; however, some studies have shown poor correlation between the histologic findings and the duration of clinical disease (15,45). Biopsy specimens may show acute, subacute, and chronic changes mixed in the same lesion (45).

**Imaging Approach**

The imaging evaluation of CRMO should start with radiographic evaluation of the symptomatic sites. If the radiographs are negative in the presence of significant clinical symptoms, further evaluation with MR imaging should be considered to evaluate for marrow edema. When a diagnosis of CRMO is considered on the basis of clinical findings and initial imaging evaluation, further evaluation of the whole body is
Although bilateral disease is morphologically symmetric, it typically lacks clinical and temporal symmetry. The identification of additional sites of disease can aid in the diagnosis of CRMO, especially when disease is present at typical locations like the anterior chest wall or when disease is symmetrically distributed (Figs 4, 5). In addition, the identification of all sites of disease aids in the follow-up of disease activity.

**Imaging Appearances**

The findings at imaging studies can be suggestive of a diagnosis of CRMO but are not pathognomonic. Common sites of skeletal involvement include the long tubular bones and clavicle, but lesions have been described throughout the skeleton, including the spine, pelvis, sacroiliac joint, ribs, sternum, scapula, mandible, and hands and feet. Involvement of the lower extremity has been reported to be three times more frequent than in the upper extremity, with the distal femur and proximal tibia being the most common sites. Lesions may present as lytic or sclerotic areas, or a combination of both, with or without associated soft tissue swelling.

**Teaching Point**

Whole-body imaging can demonstrate clinically occult sites of disease, confirming the multifocal nature of disease. In the series of Yu et al (49), imaging demonstrated 20 additional sites of disease in seven children, who had clinically apparent disease at only 14 sites. In another series of patients, scintigraphy demonstrated an average of six lesions per patient, even though 12 of the 14 cases had a unifocal presentation (34). In addition, 64% of the cases in that series were found to have bilateral disease at scintigraphy.
Figure 6. CRMO in a 12-year-old girl with a 7-month history of ankle pain. (a) Anteroposterior radiograph of the ankle shows multiple pyramid-shaped lytic lesions with surrounding sclerosis in the metaphyses of the tibia and fibula (straight arrow); the lesions extend across the growth plate into the epiphysis (wavy arrow). Multiple apophyseal lesions are also present in the tarsal bones (arrowheads). Also note the generalized osteopenia. (b) Photomicrograph (original magnification, ×100; hematoxylin-eosin stain) shows fragments of bone surrounded by fibrous stroma, in which there are scattered inflammatory cells and macrophages. Results of microbiologic analysis were negative and thus supportive of the diagnosis of CRMO.

Figure 7. CRMO in a 5-year-old patient with right knee pain. (a) Lateral radiograph of the knee shows a permeative lytic pattern in the patella (arrow) with overlying soft-tissue swelling. (b) Sagittal fat-saturated T2-weighted MR image shows erosive changes of the ossification center of the patellar apophysis (arrow), whereas the surrounding cartilage appears intact. Other sites of nonbacterial inflammation developed in both femora and tibiae over the next 3 years. The diagnosis of CRMO was confirmed with histopathologic analysis and negative culture results from bone biopsy.

The distribution of CRMO, specifically its tendency to involve the metaphyses and metaphyseal equivalents, is reminiscent of hematogenous osteomyelitis in children. However, CRMO is unique in its tendency to involve the clavicle—an uncommon site for hematogenous osteomyelitis.

In the early stages, plain radiographs typically demonstrate an osteolytic lesion located...
Figure 8. CRMO in a 7-year-old patient with a 4-month history of leg pain. 
(a) Anteroposterior radiograph of the ankle shows a small lytic lesion adjacent to the physis. (b) Follow-up radiograph obtained 3 months later shows the enlarging lytic lesion with surrounding sclerosis that fades away from the lesion. (c) Radiograph obtained 3 months later shows other lytic areas adjacent to the physis. (d) On a radiograph obtained 4 months later, the lesions appear to coalesce and heal without significant periosteal reaction or sclerosis.

adjacent to the growth plate in the metaphysis. With time, progressive sclerosis is seen around the lytic lesion, so that chronic lesions may be predominantly sclerotic with associated hyperostosis. The appearance of CRMO lesions can range between purely osteolytic, osteolytic with a sclerotic rim, mixed lytic and sclerotic, and purely sclerotic (Fig 8). Multiple metaphyseal lesions may be present extending along a growth plate (Figs 6, 8). The radiographic findings may indicate a process of longer duration than suggested by the patient’s clinical symptoms, likely due to the insidious nature of the clinical symptoms (Fig 9) (49). Radiographic findings of exacerbations include new areas of lytic destruction and periosteal reaction, which develop sclerosis with time, resulting in progressive hyperostosis and sclerosis.
Figure 9. CRMO in a 6-year-old girl with a 1-week history of right leg pain. Anteroposterior (a) and lateral (b) radiographs of the right tibia and fibula show sclerosis of the proximal tibia with cortical thickening, which extends into the distal diaphysis. A small lytic lesion is present in the mid fibula with mild associated periosteal reaction. Bone scintigraphy showed uptake in these lesions and in the right femur. The histopathologic, clinical, and culture findings were compatible with CRMO.

![Image of a 6-year-old girl's right leg showing CRMO](image)

Figure 10. CRMO in an 11-year-old patient with multifocal bone pain. (a) Oblique radiograph of the right ankle shows a lytic lesion of the metaphysis that appears to extend across the growth plate (arrow). There is a suggestion of overlying soft-tissue swelling. (b) Sagittal fat-saturated T2-weighted MR image shows edema involving the distal metaphysis and extending across the physis into the epiphysis. There is associated soft-tissue inflammation and periosteal reaction.

![Image of an 11-year-old patient's right ankle showing CRMO](image)
Figure 11. Soft-tissue inflammation in an 11-year-old girl with known CRMO and a 2-year history of chest pain. (a) Posteroanterior radiograph of the chest shows an expanded right third rib (arrow). (b) Axial contrast material–enhanced T1-weighted MR image of the chest shows marked soft-tissue inflammatory changes around the rib (arrow), a finding that can mimic a malignancy like Ewing sarcoma. Biopsy revealed sterile inflammation.

MR imaging is useful both for determining the extent of disease and for surveillance. During the active phase of the disease, MR imaging shows typical findings of marrow edema, which appears hypointense on T1-weighted images and hyperintense on T2-weighted images. MR imaging can demonstrate associated periostitis, soft-tissue inflammation, and transphyseal disease—findings that are typically underestimated on radiographs (Figs 10, 11) (39,51). The detection of transphyseal involvement may have prognostic significance by allowing identification of patients at higher risk for growth deformities due to formation of physeal bars (22).

Clinically occult joint effusions adjacent to the osseous lesions can be demonstrated with MR imaging (28). In a series of 66 patients with CRMO, 30% were noted to have joint involvement with synovial thickening, joint effusion, or destruction of joint cartilage and subchondral bone (52). MR imaging may show small fluid collections or areas of necrotic bone, features that have been demonstrated in histologic studies of CRMO as well (8). However, the presence of a large fluid collection or abscess, fistulous tract, or sequestrum makes the diagnosis of infectious osteomyelitis more likely than CRMO (51).

MR imaging is useful for follow-up of lesions during exacerbation of disease, especially when radiographs show marked sclerosis or hyperostosis. Areas of new activity demonstrate high signal intensity on T2-weighted images and contrast enhancement due to marrow edema, with the surrounding sclerotic bone appearing hypointense on both T1- and T2-weighted images.

Note that CRMO shares many features with chronic sclerosing osteomyelitis of Garré. Both entities are seen in children and adolescents and are characterized by an insidious onset, a relapsing-remitting course, negative culture results, and lack of suppuration. Both entities tend to involve the long tubular bones—mainly the femur or tibia. It is likely that CRMO and chronic sclerosing osteomyelitis of Garré are different names given to the same disease (45).

**Tubular Bones**

The most common location of disease in the tubular bones is the metaphysis adjacent to the growth plate (over 50%), followed by the diaphysis, diaphyseal-metaphyseal region, and metaphyseal-epiphyseal region (34). The typical finding in the long tubular bones is a round or column-shaped osteolytic metaphyseal lesion abutting the growth plate (Fig 6). The lytic lesion becomes surrounded by a thin, sclerotic zone within 1–2 weeks (15). As the inflammatory process extends into the cortex, periosteal reaction develops, which can be quite extensive in long tubular bones.

The amount of periosteal reaction depends on both the duration of disease and the anatomic site involved. Although small-diameter bones like the fibula and metacarpals-metatarsals can have extensive periosteal reaction and soft-tissue inflammation, lesions in large-diameter bones like the femur can have a predominantly lytic-sclerotic process with minimal surrounding reaction (Fig 12). It has been suggested that small-diameter bones demonstrate more periosteal reaction owing to earlier extension of the inflammatory process from the medullary space into the cortex (22). The marked
periosteal reaction and sclerosis seen with CRMO lesions of tubular bones has also been referred to as “tumorous osteomyelitis” (Fig 2) (20).

Chronic inflammation at the metaphysis can result in abnormal tubulation of the long bones with metaphyseal expansion and sclerosis, a useful imaging finding in long-standing CRMO (Fig 12). Although the inflammation can extend into the cortex, the presence of cortical disruption should raise concern for an aggressive lesion, such as a malignancy, and further evaluation with a biopsy should be performed (53).

Clavicle

CRMO of the clavicle most commonly manifests with local swelling, pain, or impairment of shoulder movement and may cause thoracic outlet syndrome (54). Like CRMO in other parts of the body, clavicular involvement appears to be more common in female patients than in male patients. CRMO is the most common nonneoplastic process involving the clavicle in patients less than 20 years of age (55). It is also the most common disease process to involve the medial third of the clavicle in all age groups (55). Up to 30% of all CRMO lesions are located in the clavicle (40). Given the preceding facts, the diagnosis of CRMO should be considered in the differential diagnosis of a sclerotic expanded lesion affecting the medial third of the clavicle in children and adolescents (Fig 13). Considering this diagnosis can help avoid unnecessary biopsies and anxiety for patients, secondary to a misdiagnosis of a malignancy such as Ewing sarcoma (55,56).

Clavicular CRMO is unique compared with the other common sites of disease in CRMO, in that hematogenous osteomyelitis of the clavicle is extremely uncommon. CRMO of the clavicle has been referred to by several different names, including recurrent hyperostosis of the clavicle, sternocostoclavicular hyperostosis, idiopathic cortical hyperostosis, and condensing osteitis of the clavicle (56,57). There seems to be a higher prevalence of clavicular disease in CRMO patients with palmoplantar pustulosis and acne fulminans (14).

Clavicular disease typically manifests as a lytic medullary process in the medial part of the clavicle with surrounding periosteal reaction, which may have an “onion skin” appearance. During remissions, the lesions heal with progressive sclerosis. With each exacerbation, the disease tends to extend laterally, although the most lateral part of the clavicle remains unaffected (58). CRMO
in children is characterized by progressive hyperostosis and sclerosis of the medial end of the clavicle without involvement of the sternoclavicular joint. This is in contradistinction to clavicular involvement in adults with CRMO; such involvement occurs as a subphenotype of SAPHO syndrome, in which clavicular disease is often accompanied by arthritic changes of the joint space (58). Also, the ligamentous ossification and bony bridging across the sternoclavicular joint reported in adults have not been described in children.

Radiographic evaluation of the clavicle can be limited due to overlapping structures. CT can more clearly demonstrate the extent of disease with lytic areas and surrounding sclerosis and hyperostosis. MR imaging reveals bone marrow edema with surrounding periosteal reaction. Inflammatory changes can also be seen extending into the surrounding soft tissues and muscles; these changes may give the appearance of an aggressive process such as Ewing sarcoma, lymphoma, or histiocytosis (54). With increasing sclerosis and hyperostosis, both T1- and T2-weighted images show markedly hypointense areas. New areas of activity can be identified in the hyperostotic clavicle as hyperintense lesions on T2-weighted images, in cases where radiographic evaluation may be limited due to overlapping structures and hyperostosis. Whereas the metaphyseal lesions of long bones can heal completely, the sclerotic-hyperostotic clavicular lesions tend to persist for several years and can cause thoracic outlet syndrome (41).

**Spine**

Spinal involvement, although less common than disease in the long tubular bones, has been reported in CRMO. In a review of 35 cases of CRMO with 157 lesions, only 3% of lesions were present in the vertebral bodies (12). However, CRMO of the vertebral body is the most common site to be complicated by a pathologic fracture (28). Spinal disease may be detected incidentally during the radiologic work-up of suspected CRMO, or it may be the site of primary presentation. Presenting symptoms can include back pain, scoliosis or kyphosis, and rarely cord compression (59).

Radiologic findings include partial or complete loss in height of the vertebral body. A lytic lesion with surrounding sclerosis or a purely sclerotic appearance may be seen in the vertebral body with or without extension into the pedicle (Fig 14). The thoracic spine is the most common site of disease (accounting for 46 of 65 spinal lesions in one review), followed by the lumbar spine (13 of 65), while disease in the cervical spine and sacrum is less common (60).
Figure 15. CRMO of the spine in a 6-year-old boy with multifocal bone pain for 1 year. (a) Anteroposterior radiograph shows marked loss in height of the T4 vertebral body (arrow) and partial collapse of the T7 and T8 vertebral bodies with endplate irregularity (arrowhead). (b) Sagittal T2-weighted MR image shows a vertebra plana at T4. Spondylodiskitis is seen at T7-8 with endplate irregularity, but disk height and signal intensity are preserved.

Figure 16. CRMO of the spine in a 6-year-old girl with a history of back pain. Radiography showed some loss in height of the T9 vertebral body. (a) Sagittal T1-weighted MR image shows loss of normal marrow signal intensity in the T2, T9, T10, and T12 vertebral bodies with loss in height of T9. (b) T2-weighted MR image shows edema in the T9 vertebral body with a low-signal-intensity line paralleling the inferior endplate (arrow). Note that the intervertebral disk space appears unremarkable even in the presence of contiguous vertebral body disease.
Figure 17. CRMO of the pelvis in a 9-year-old girl with multifocal bone pain since the age of 2 years. Anteroposterior radiograph of the pelvis shows multiple lytic lesions with sclerotic margins at both ischiopubic synchondroses (arrows); the lesions extend into the ischial tuberosities.

MR imaging demonstrates altered signal intensity of the vertebral marrow and partial or complete loss in height of the vertebral body. The adjacent disk may show some loss in height or altered signal intensity; however, to our knowledge, none of the reported cases have shown extension of disease across the intervertebral disk space—a feature that can help differentiate CRMO from infectious osteomyelitis (Fig 15) (60,61). A subchondral fracture-like line has also been reported in CRMO patients with vertebral collapse, but there are no data on the specificity of this finding for a diagnosis of CRMO (Fig 16) (60). MR imaging often demonstrates additional sites of disease in the spine that are occult at clinical examination, radiography, or scintigraphy (Fig 16) (61,62).

Involvement of multiple noncontiguous vertebral bodies with sparing of the intervening disks helps differentiate CRMO from infectious osteomyelitis. Although histiocytosis X remains the most common cause of vertebra plana in children, CRMO is another disease that can cause vertebra plana (49). Since the initial description in 1989, several cases of vertebra plana secondary to CRMO have been reported (49,51,63–65). Unlike in vertebra plana caused by eosinophilic granuloma, restitution of vertebral body height has not been observed in vertebra plana caused by CRMO (49).

Pelvis
CRMO of the pelvis is less common. The sites of predilection in the pelvis include the metaphyseal equivalents—such as the ischiopubic synchondrosis and the sacroiliac joints—sites that are prone to hematogenous osteomyelitis as well (Fig 17). These lesions may be subtle on radiographs; however, cross-sectional imaging with CT will clearly demonstrate the osteolysis with surrounding periosteal reaction and sclerosis. MR imaging shows edema in active lesions with surrounding periostitis and associated soft-tissue inflammation.

Because the synchondroses have avidity for $^{99m}$Tc, bone scans should be evaluated carefully at single-photon-emission CT for any asymmetry of activity, to identify pathologic sites. CRMO of the pelvic synchondrosis tends to heal without significant sequelae (66). Pelvic disease can also manifest as sclerosis of bones such as the iliac wings. During evaluation of the pelvis, close attention should be paid to the sacroiliac joints, as patients with CRMO are at increased risk of developing spondyloarthropathy with unilateral sacroiliitis (Fig 18) (42).
Mandible
CRMO can involve the mandible in about 5% of cases (40). Mandibular CRMO has also been referred to as diffuse sclerosing osteomyelitis of the mandible (67–69). It typically manifests as chronic mandibular pain, although associated jaw swelling may also occur. Mandibular disease can be isolated or accompanied by disease at other sites in the body. In a review of 12 adult cases of diffuse sclerosing osteomyelitis of the mandible, 50% were found to have disease at other sites such as the anterior chest and spine (68). Mandibular disease has also been shown to be associated with lesions in other skull or facial bones such as the maxilla and zygoma (Figs 1, 19) (69,70).

Radiographic findings are similar to those in other sites of disease, with initial stages demonstrating a lytic process with associated variable amounts of sclerosis. Cross-sectional imaging often reveals associated soft-tissue inflammation as well, without evidence of discrete abscess formation. As the mandibular disease progresses, increasing sclerosis with hyperostosis and progressive enlargement of the mandible develop. Biopsy results reveal a culture-negative chronic osteomyelitis. Awareness of this entity, especially among oral surgeons, is essential to avoid unnecessary antibiotic therapy and multiple invasive procedures (Fig 5).

Hands and Feet
CRMO is more common in the small bones of the feet than in the hands. It can involve the tarsal bones such as the calcaneus and talus, which are metaphyseal equivalents, or the short tubular bones including the metatarsals and phalanges (Fig 20). The short tubular bones typically demonstrate lytic lesions with surrounding sclerosis, periosteal reaction, and associated soft-tissue inflammation (Fig 21). CRMO of the metatarsals and phalanges has been reported to cause premature physeal closure (22).

Differential Diagnosis
The differential diagnosis of CRMO includes subacute and chronic infectious osteomyelitis, histiocytosis, hypophosphatasia, and malignancies like leukemia, lymphoma, and Ewing sarcoma (71). Although the typical imaging findings of CRMO can aid in suggesting the correct diagnosis, they are not pathognomonic.

Clinical and radiographic features that help in differentiating CRMO from infectious osteomyelitis and tumors include the following: (a) a prolonged clinical course, with most patients being...
healthy between recurrent episodes; (b) an unusual location of lesions in comparison with those of infectious osteomyelitis, such as involvement of the clavicle, bilateral symmetry, and frequent multifocality; (c) radiographs showing multiple foci of osteolysis with associated sclerosis or hyperostosis; (d) lack of abscess formation, fistulas, or sequestra; (e) lack of response to antibiotics; and (f) comorbid inflammatory disorders such as psoriasis, palmoplantar pustulosis, or inflammatory bowel disease (19,51). Because the imaging findings of CRMO can be nonspecific, especially early in the course of the disease, evaluation of the osseous lesions with biopsy and culture is required to establish a diagnosis of CRMO.

Outcomes

The disease course of CRMO is unpredictable. Although most cases undergo spontaneous resolution in several months to several years, patients have been found to be symptomatic for as long as 25 years after the initial diagnosis (72). In a study of 13 patients, Jurik et al (66) found all cases to be symptomatic after a follow-up period of 16 years, although in most cases symptoms related to the initial lesions had resolved. In contrast, long-term follow-up of a German cohort revealed all cases to be in remission (19). In a follow-up study of 23 patients, Huber et al (50) showed that 25% of subjects had persistent signs of disease activity when evaluated at a median time of 12.4 years after diagnosis. In the follow-up study of Duffy et al (72), the shortest duration of symptoms was 2.5 years and the longest duration was 20 years.
Although most CRMO lesions heal to become occult at radiography, others can demonstrate persistent sclerosis. Persistent sclerosis appears to be the pattern in older patients, in whom the normal modeling and growth process of bone is already complete. Lesions occurring in skeletally immature children may undergo restitution to normal bone. This might not be true in bones that have developed marked hyperostosis, with sclerosis extending into the medullary cavity. One example of this is the clavicle, where the hyperostosis can produce a palpable bump and be a source of thoracic outlet obstruction (41). Another residual deformity is thoracic kyphosis secondary to vertebral body compression (37,66).

CRMO of long bones can result in orthopedic complications like bony overgrowth, angular deformities, and limb-length discrepancy at maturity (72). Owing to its tendency to occur near the physes, CRMO can cause premature physeal closure, resulting in growth arrest. Manson et al (22) described six sites of premature physeal fusion among 29 sites of disease in seven patients with CRMO. Premature physeal fusion has been reported most often in the metatarsals, followed by the tibia and femur (22,41). Limb-length discrepancy has been reported to be the most common physical deformity in patients with a history of CRMO, with the affected limb being shorter in most cases (72). The hyperemia caused by chronic inflammation may result in diffuse demineralization, predisposing to fractures (73).

An increased risk of chronic spondyloarthropathy, unilateral sacroiliitis, and enthesitis has also been suggested in children with a history of CRMO in the absence of a human leukocyte antigen (HLA)–B27 association (21,42,43). In the study of Vittecoq et al (42), 12 of 15 patients with CRMO developed spondyloarthropathy that met the criteria of the European Spondyloarthropathy Study Group, with spine involvement developing after a median follow-up of 5.63 years.

**CRMO versus SAPHO Syndrome**

SAPHO syndrome is the adult equivalent of CRMO. Whereas CRMO typically manifests in the first decade of life, the mean age of onset for SAPHO syndrome is 28 years (74). However, adults with CRMO and children with SAPHO syndrome have been reported (40,75). The prevalence of skin lesions like palmoplantar pustulosis is much higher in SAPHO syndrome than in CRMO. Furthermore, the skin lesions may manifest several years after the first bone lesion in children with CRMO (43).

Whereas chest wall and pelvic disease predominates in SAPHO syndrome, the long bones are the most common sites of disease in CRMO. This is likely related to the presence of open physes in children predisposing to a higher prevalence of metaphyseal lesions, as is seen in hematogenous osteomyelitis. CRMO and SAPHO syndrome differ in the type of disease seen at the anterior chest wall. Although involvement of the sternoclavicular and first sternocostal joint and ossification of the costoclavicular ligaments are frequent in SAPHO syndrome, these findings are not reported in CRMO.

Adults with SAPHO syndrome can have arthritis of peripheral joints and ossification of ligaments and entheses, features not typically seen with CRMO (66). Children with CRMO have been reported to have arthritis at sites distant from the osteomyelitis lesions. Whether CRMO and SAPHO syndrome are distinct diseases or the same disease process with differences in phenotype based on age of onset remains to be determined.

**Summary**

CRMO is an established clinicopathologic entity, although its cause remains elusive. Along with the variability in its initial presentation, there is great variability in the numbers of sites affected, recurrence rates, and prognosis. The typical clinical picture of CRMO is a child or young adult with a history of chronic multifocal bone pain, in whom biopsy of osseous lesions shows osteomyelitis with failure to culture any organisms. The typical radiographic appearance is a lytic lesion at a metaphysis or metaphyseal equivalent that develops progressive sclerosis and hyperostosis over time.

With the exception of CRMO in the context of Majeed syndrome, there is no diagnostic test for CRMO and it remains a diagnosis of exclusion. The presence of disease in typical sites such as the medial clavicle, the presence of bilateral disease in a symmetric distribution, and the presence of skin findings such as palmoplantar pustulosis support the diagnosis. Diagnosis of CRMO requires a team approach between the pediatric rheumatologist, orthopedic surgeon, radiologist, and pathologist. Radiologists need to be familiar with the imaging findings because they may be the first to suggest this diagnosis. This can help minimize the number of unnecessary interventions in the form of repeated biopsies, surgeries, and antibiotic therapy.
References

75. Schilling F. Chronic recurrent multifocal osteomyelitis (CRMO) [in German]. Rofo 1998;168:115–127.
The identification of additional sites of disease can aid in the diagnosis of CRMO, especially when disease is present at typical locations like the anterior chest wall or when disease is symmetrically distributed (Figs 4, 5).

Common sites of skeletal involvement include the long tubular bones and clavicle, but lesions have been described throughout the skeleton, including the spine, pelvis, sacroiliac joint, ribs, sternum, scapula, mandible, and hands and feet.

The most common sites of disease are the metaphyses or metaphyseal equivalents, accounting for approximately 75% of all lesions in the series of Mandell et al (34) (Figs 6, 7).

Chronic inflammation at the metaphysis can result in abnormal tubulation of the long bones with metaphyseal expansion and sclerosis, a useful imaging finding in long-standing CRMO (Fig 12).

It is also the most common disease process to involve the medial third of the clavicle in all age groups (55).
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