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Bone inflammation and chronic recurrent multifocal osteomyelitis

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Abstract. – Chronic recurrent multifocal osteomyelitis (CRMO) is a sporadic condition of inflammatory bone pain that occurs as recurrent flares because of osteomyelitis, which presents in the form of multiple aseptic foci. The estimated prevalence of CRMO is 1-2 per million, affecting mostly children, in the age group of 2 to 17. Main symptoms of CRMO are bone inflammation and pain, which are generally worse at night. Other symptoms seen on radiographs indicate osteolytic lesions surrounded by sclerosis, at later stages of the disease. Markers of inflammation, viz. tumor necrosis factor a and C-reactive protein are elevated in many cases. Because of similar symptoms, differential diagnosis is needed to confirm CRMO from infectious osteomyelitis, bone tumors, and other diseases. The genetic component is likely in some cases such as Majeed syndrome, deficiency of IL-1 antagonist, etc. Imaging is the essential part of diagnosing CRMO, and magnetic resonance imaging of the whole body is the most widely used and recommended method for the evaluation of multiple foci, as compared to radiography for reasons of sensitivity as well as prevention of excessive exposure of affected children to radiation. CRMO is considered an autoimmune and auto-inflammatory disorder, but its precise pathophysiology is not clear. Current treatment options are non-steroid anti-inflammatory drugs like naproxen, as the primary choice, and the bisphosphonates such as pamidronate as the second choice, to counter the symptoms and to reduce bone lesions. The surgical option is the choice for recalcitrant cases, even though recurrence may still be a problem.

Key Words:
Chronic recurrent multifocal osteomyelitis, Bone lesions, Osteomyelitis, Magnetic resonance imaging, Bone scintigraphy, Auto-inflammatory disorder.

Introduction

Chronic recurrent multifocal osteomyelitis (CRMO), often referred to chronic nonbacterial osteomyelitis (CNO), manifests reappearing bouts of inflammatory bone pain due to osteomyelitis lesions present in the form of multiple aseptic foci. CRMO is considered as an orphan disease; epidemiological estimates indicate its prevalence at 1-2 per million (Orphanet.net), affecting mostly children, with the onset of the disease being at about 10 years[1,2]. However, its incidence may have been underestimated due to misdiagnosis. While CRMO or CNO are common terms used in pediatric cases, a very similar disease (if not exactly the same) is termed acne, synovitis, hyperostosis osteitis (SAPHO) syndrome, and pustulosis in adults. It is not clear if these disease entities are the same in children and adults[3,4]. As the name implies, CNO is culture negative sterile inflammatory osteitis. This pathological condition was initially described in 1972 by Giedion et al[5] in four children with sub-acute and chronic osteomyelitis accompanied by multiple, symmetrically distributed foci of aseptic osteomyelitis, affecting mainly the long bones and it was called chronic symmetric osteomyelitis. This condition was later studied more extensively and termed as chronic recurrent multifocal osteomyelitis (CRMO) by Björksten et al[6]. Main symptoms are bone inflammation presenting with severe bone pain, particularly at night time, and radiographs indicating osteolytic lesions surrounded by sclerosis at later stages of the disease. Laboratory parameters such as circulating levels of C-reactive protein, erythrocyte sedimentation rate, or total blood count, are often normal or show only minor changes[4]. Even though a history of inflammatory diseases in the affected families is noticed in few cases, only a small proportion (6%) of these affected families have more than one person with CRMO[1]. CRMO diagnosis is primarily ascertained by the exclusion of osteomyelitis due to infection, presence of a tumor, and other related diseases. Radiological imaging plays an essen-

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tial role in the evaluation of CRMO, and thus, a knowledgeable imaging specialist on the different aspects of CRMO is helpful for early diagnosis and appropriate treatment[7].

Clinical Features and Epidemiology

CRMO predominantly affects children between 2 and 17 years of age (median age = 10 years). There appears to be a female preponderance of CRMO, with female to male ratio in many case series at 2:1. Symptoms are often heterogeneous, and the patients show swelling of the affected area and also complain of severe bone pain at night, along with the occasional presentation of other systemic symptoms such as fever, malaise, and weight loss[8]. Markers of inflammation, tumor necrosis factor α and C-reactive protein are seen elevated in the circulation in many cases[9,10]. Even though there may not be any permanent consequences in children with CRMO, if it is resolved, there are chances of permanent bone deformity primarily because of pathologic fractures, deformities due to vertebral compression that result in scoliosis and discrepancy in leg length. There can be functional sequelae due to hyperostosis[2]. Characteristically, CRMO presents up to 20 affected bone sites and these lesions are found throughout the axial and appendicular skeleton, with the metaphysis of long bones being affected more[9,11]. Apparently, bones of lower extremities, particularly the distal femur and tibia and proximal tibia, seem to be more frequently affected followed by the pelvis, vertebrae, clavicle, and the small bones of hands and feet, etc.[9,12]. Bones such as the ribs, sternum or mandible, are rarely affected[13]. CRMO initiates with a single location of the lesion followed by spreading with the appearance of multifocal disease. Approximate time from the appearance of disease symptoms till diagnosis is 18 months and can vary anywhere from few weeks to few years and there is a high probability of family history[1,14].

Etiology and Diagnosis of CRMO

Pathophysiology and etiology of CRMO are not clearly understood. CRMO is considered an autoimmune and auto-inflammatory disorder. There are many other diseases that are often associated with CRMO, particularly with inflammatory diseases of intestinal tract and skin; these additional inflammatory disorders are also seen in family members of CRMP patients, suggesting common underlying pathogenic mechanisms[4]. Nearly 20-50% of CRMO cases are associated with palmoplantar pustulosis, which often appeared synchronously with the osseous exacerbations[14,15]. Other associated skin diseases include psoriasis vulgaris, dermatomyositis, etc., and gastrointestinal diseases include Crohn disease, ulcerative colitis, etc.[16]. These associated diseases often play an important part in the proper diagnosis of CRMO, which should be dependent on the unique presentation of the disease with fluctuating course, recurrent bouts of pain and also the atypical presence of the multifocal lesions and compatible imaging findings (Table I). The evaluation of patients with acute bone pain for potential CRMO can often get complicated by infections. Another common situation that needs a differential diagnosis is acute hematogenous osteomyelitis in infancy and childhood, which also involves multiple bones and symmetrical distribution of the lesions, with significant resemblance to CRMO (Table I). Hematogenous vertebral osteomyelitis[17] and pyogenic vertebral osteomyelitis[18] are some of the rare forms of chronic osteomyelitis that are associated with infections. Thus, an extensive laboratory tests for infection is imperative for proper evaluation of a patient for suffering possibly from CRMO[16]. There is also likely a genetic component for the development of CRMO. CRMO may also be caused by 2 monogenic syn-

Table I. Diseases that warrant differential diagnosis of CRMO.

Main disease entity	Subclass of the disease identified
Infectious osteomyelitis	Brucellosis Typhoid fever Tuberculosis *Kingella kingae*
Genetic defects	Majeed syndrome Cherubism Deficiency of IL-1 receptor antagonist Hypophosphatasia
Juvenile idiopathic arthritis	Enthesitis-related arthritis Psoriatic arthritis
Benign bone lesions	Osteoid osteoma Osteoblastoma
Malignant tumors	Osteosarcoma Ewing's sarcoma Neuroblastoma Leukemia Lymphoma
Bone fracture	

dromes, which are rare. Mutations in the LIPIN2 gene lead to a syndrome that is inherited in an autosomal recessive manner, called Majeed syndrome. Characteristics of Majeed syndrome include dyserythropoietic anemia and early-onset CRMO[19]. Another monogenetic autosomal recessive, auto-inflammatory disorder and potentially life-threatening associates with CRMO, is the interleukin-1 receptor antagonist deficiency, caused by a mutated IL1RN gene. This disorder presents systemic inflammation, generalized pustulosis, osteitis, and periostitis during the neonatal period[4,20]. Other genetic deficiencies that potentially relate to CRMO are cherubism, caused by mutations in SH3BP2 gene[21], and hypophosphatasia, which results from a defect in the gene coding for tissue-nonspecific alkaline phosphatase[22]. Certain forms of cancer are also known to mimic many symptoms of CRMO, thus needing to be considered for differential diagnosis (Table I). These include non-Hodgkin lymphoma, which also presents fatigue, weight loss and bone pain, and also as a single lesion with swelling and even a pathologic fracture[23,24]. Neuroblastoma is also known to present bone pain as it can metastasize to bone marrow and cortical bone[25]. Another important malignant carcinoma is that needs to be differentially diagnosed in patients with potential CRMO is osteosarcoma, which is common among young adults aged 15 to 19. Osteosarcoma also primarily affects metaphyses of long bones, in particular, the distal femur, proximal humerus and proximal tibia in children, similar to the situation with CRMO[26]. Because of these similarities between bone tumors and CRMO, it is important to undertake analysis of bone lesion biopsies, and this is particularly important when the focus of the disease is on single symptoms and in this case, bones pain and lesions.

Imaging and CRMO Diagnosis

Imaging is the essential part of diagnosing CRMO and radiography is the primary choice for the examination of bone pain in children. The first diagnostic description of CRMO utilized radiological examination of children to describe osteolysis[5]. According to radiological examination, the first changes generally seen during the development of CRMO are in the metaphysis next to the physis[27], associated with the presence of osteolysis enclosed by a thin sclerotic rim, without periosteal elevation or sequestra formation[2]. Radiographic appearance of bone may become normal over the course of time by about 2 years, due to healing of the damaged areas of bone by sclerosis[28]. Even in early stages of the disease, the radiographs can be normal whereas the presence of several lesions in the metaphysis can be seen in more advanced stages of CRMO[28]. Even though radiography can be useful in identifying asymptomatic foci, being a radiological technique, this involves high doses of radiation; also, the results are often difficult to be interpreted in case of symmetric metaphyseal lesions, which are often mistaken for normal growth plate uptake, thus limiting the use of this technique[29]. Magnetic resonance imaging (MRI) is relatively more sensitive and has the advantage of avoiding exposure to radiation and is useful in determining the involvement of soft tissues as well as the bone[13]. Whole body scanning with MRI or bone scintigraphy is advised when a patient is suspected of having CRMO. Identification of symptomatic lesions was found to be easier by bone scintigraphy employing the property of bone hydroxyapatite to adsorb chemicals such as methylene diphosphonate or hydroxymethylene diphosphonate labeled technetium-99m. This technique was also found to be helpful in assessing multiple asymptomatic lesions of CRMO[30,31]. It has been reported that MRI is more sensitive compared to bone scintigraphy for the evaluation of spinal, pelvic and femoral lesions, in particular symptomatic lesions[9,32]. It should also be kept in mind that MRI has certain short comings as an MRI conducted only in the coronal plane is likely unable to detect lesions present at extreme anterior or posterior regions of the bone, as in the case of sternoclavicular and costovertebral joints[33]. Also, MRI examination is influenced by motion, which can introduce artifacts, and thus, patient sedation is often required. However, an important consideration is the exposure time. It takes about 45 minutes to acquire whole body MR images, usually without the use of sedation[34], whereas, the three-phase bone-scintigraphy scanning needs about 3-4 hours and this long exposure time to radiation, particularly in the case of children, is not in accordance to the practice mandate of "as low-as-reasonably achievable"[29]. Therefore, whole body MRI is the more widely used and recommended method for the evaluation of multiple foci in CRMO. Short tau inversion recovery (STIR), a fat suppression technique is employed for MRI examination of the soft tissues. These types of techniques are very useful for the diagnosis of CRMO patients and subsequent follow-up. Also, gadolinium mediated enhancement of imaging has been shown to provide imaging with a better

resolution, of the lesions and associated inflammatory activity[35]. A recent study[36] suggested that CNO/CRMO is increasingly diagnosed using MRI rather than bone histological examinations.

Pathophysiology of CRMO

Besides the main observation that CNO/CRMO is an inflammatory disease, the molecular basis is not completely understood. Attesting to this are the observations that CRMO displays onset different from the usual sites like clavicle and pelvis, though on rare occasions. Thus, it has been reported that neurocranium and skull may also be sites of disease onset[37,38], which further complicates our understanding of the molecular basis of this disease. Because of this, there is a lack of specific biomarkers for following the progress or treatment of CRMO, even though some of the classical inflammation markers such as C-reactive protein, erythrocyte sedimentation rate, etc., have been used clinically[39]. It has been suggested that altered levels of a set of nine serum markers including IL-12, eotaxin, IL-1RA, sIL-2R, IL-6, MCP-1, MIG, MIP-1b, and RANTES, positively identifies CRMO patients and distinguishes them from patients with Crohn disease and healthy people[40]. Although it is known that heredity plays a significant role in the pathogenesis of CNO/CRMO[41], in most of the affected patients, the precise contributing molecular defect is not known. Many of the previously suggested genetic defects seen in other related diseases such as Crohn disease, PAPA syndrome, etc., have been eliminated as possible causes for CRMO[39,42]. Despite the accumulation of several polymorphisms in the promoter region of the immune regulatory cytokine IL-10 gene, its expression in monocytes was not responsive to inflammatory stimuli in CRMO patients. Insufficient or lack of activation of MAPK (mitogen-activated protein kinases) and ERK1/2 (extracellular signal-regulated kinases) in these patients was found responsible for the reduced transcriptional activation of the IL-10 promoter and expression of IL-10 and also some of the other similar immune function genes such as IL-19 and IL-20[43-45]. It has also been observed that activation and expression of inflammasome components, including ASC, NLRP3, and caspase-1, are elevated in CRMO patients and contribute to pathogenesis[45,46]. Thus, it appears that CNO/CRMO is likely to result from defects in several signaling pathways that control the expression of critical immune regulatory components, rather than from a single pathway defect. We still need to precisely define the underlying molecular defects for these derangements.

Treatment Options

Management of CRMO often presents difficulty in identifying the patients who are likely to have spontaneous resolution of symptoms and those who are likely to suffer in the long-term. The severe bone pain in affected patients with active disease needs to be attended as it disrupts quality of life and leads to deformities of bones[47]. Pain is often reduced by using non-steroidal anti-inflammatory drugs (NSAIDS), which are basically the first line of treatment for CRMO patients, with nearly 80% patients being responsive (Figure 1). In a study of 37 children with CRMO,

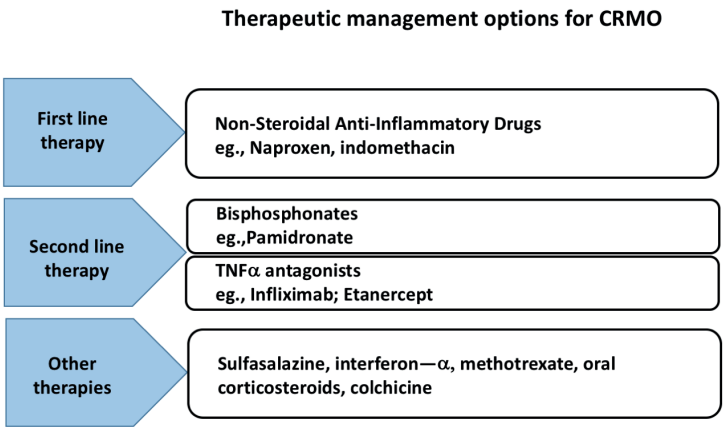

Figure 1. Therapeutic management options for CRMO. Primary choice of treatment for chronic recurrent multifocal osteomyelitis (CRMO) is the use of NSAIDs such as naproxen, indomethacin, etc. Bisphosphonates like pamidronate are very effective in cases where NSAIDs are unable to relive pain and in cases of CRMO associated with bone remodeling and bone sclerosis. Other treatment options are not well established clinically.

it has been observed that naproxen treatment for 6 months led to asymptomatic disease in 43% of the cases, with a significant progressive improvement in pain, functional impairment, and swelling[14]. Addition of sulfasalazine in 5 of these patients who were not responsive to naproxen led to significant improvement[14]. Some reports indicated that patients with relapsing CRMO are generally less responsive than those with non-relapsing CRMO (42% *vs.* 100%, respectively). Even though there are more numbers of side effects, indomethacin was found to be more effective than naproxen in relapsing patients[48]. Bisphosphonates, which inhibit osteoclastic bone resorption have been used as effective therapeutics against CRMO (Figure 1). Thus, a treatment with pamidronate for 3-day period was able to greatly reduce pain in all the patients tested and further treatment for six months lead to almost complete resolution of bone inflammation as attested by MRI. Myalgia and/or fever were the main side effects reported in few patients. Pamidronate was found to be effective in naproxen non-responsive patients and many cases of CRMO[49-51]. Bisphosphonate therapy is likely to be efficacious in cases of bone remodeling accompanied by bone sclerosis. Blockers of TNF-α action are also suggested to be effective in CRMO patients, particularly those with marked inflammation, for lowering symptoms[52]. Other drugs such as steroids, methotrexate, colchicine, α-interferon, etc., have been tried with varying success and not enough information is available on the efficacy of these agents in CRMO patients (Figure 1)[16,47].

Conclusions

CRMO is a rare but recurrent auto-inflammatory bone disease with characteristic presence of multiple foci of aseptic osteomyelitis, affecting mostly children. Main symptoms of CRMO are fever, bone inflammation and pain, which is generally worse at night. Inflammatory markers are elevated in many cases. Differential diagnosis is needed to confirm CRMO from infectious osteomyelitis, bone tumors, and other diseases, because of similar symptomatology. The genetic component is likely in some cases such as Majeed syndrome, lack of IL-1 antagonist, etc. Whole body magnetic resonance imaging is the recommended and more widely used method for the evaluation of multiple foci in CRMO, as compared to radiography for reasons of sensitivity as well as prevention of excessive exposure of affected children to radiation. Current treatment options are non-steroid anti-inflammatory drugs as primary choice, and bisphosphonates as the second choice to counter the symptoms and reduce bone lesions, with surgical option as the choice for recalcitrant cases.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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