Chronic Recurrent Multifocal Osteomyelitis: Two Cases of Sacral Disease Responsive to Corticosteroids

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Chronic recurrent multifocal osteomyelitis is a rare inflammatory form of osteomyelitis of unknown etiology. It affects children and adolescents, and signs and symptoms include recurrent episodes of bone pain, tenderness, possible constitutional upset, and increased inflammatory markers. We present 2 patients with cases of chronic recurrent multifocal osteomyelitis affecting the sacrum who responded dramatically to treatment with corticosteroids.

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare condition of unknown etiology. The diagnosis should be considered at an early stage for children with suspected osteomyelitis to avoid unnecessary and ineffective antibiotic and surgical therapy. CRMO usually affects children and adolescents, and signs and symptoms include recurrent episodes of bone pain, tenderness, and possible swelling affecting >1 site. There may be mild constitutional upset and fever, but patients are generally healthy between episodes. The most common sites affected are the metaphyses of long bones. Results of radiography and MRI are suggestive of osteomyelitis, but culture of the affected sites yields negative results, and there is no response to antibiotics. Patients are often treated with multiple courses of intravenous and oral antibiotics and with surgical procedures (sometimes for years) before the diagnosis is considered. CRMO has been said to be a relapsing and self-limiting condition, although permanent disability may be common. Deformities may be exacerbated by inappropriate surgical procedures. CRMO is generally treated symptomatically with nonsteroidal antiinflammatory drugs (NSAIDs) and analgesics.

CRMO has been reported at many sites, the most common being the distal tibia, femur, and clavicle, as well as the mandible and spine. To our knowledge, there have been no reports of disease affecting the sacrum. We describe 2 patients with cases of CRMO affecting the sacrum, both of whom showed a dramatic response to corticosteroids in terms of lessened pain, reduction in C-reactive protein (CRP) levels, and improved appearance on MRI.

**Patient 1.** A 27-year-old woman presented with a 13-year history of recurrent episodes of low back and right leg pain associated with increased inflammatory markers. The back pain had started after a fall when she was 14 years old, although there had been no penetrating injury. The episodes of back pain were unresponsive to treatment with simple analgesics and NSAIDs. At the age of 19 years, patient 1 was admitted to the hospital because of low back and right thigh pain. Radiography and a bone scan revealed lesions suggestive of osteomyelitis in the sacrum, distal femur, and 1 rib. Although culture of the sacral aspirate yielded negative results, a presumptive diagnosis of osteomyelitis was made, and patient 1 was treated with intravenous and oral antibiotics for a total of 3 months. During the next 3 years, she continued to experience episodes of back and thigh pain and received several courses of both oral and intravenous antibiotics, all to no effect, and she declined further follow-up. Two years later, she was referred for a second opinion because of further back and hip pain. Her erythrocyte sedimentation rate (ESR) was 114 mm/h, and her CRP level was 97 mg/L. Results of radiography and MRI again were suggestive of osteomyelitis (figure 1). She was treated with azithromycin and underwent surgical excision of a presumed focus of osteomyelitis in the right distal femur. Cultures once again yielded negative results, and she was treated postoperatively with vancomycin and meropenem, followed by doxycycline and ciprofloxacin, for a total of 6 months. She improved symptomatically, her ESR fell to 45 mm/h, and her CRP fell to 42 mg/L. However, 7 months later, her symptoms returned, with pain now spreading below the right knee. MRI revealed a new right tibial lesion. Her CRP level was 109 mg/L. She was treated with a further course of azithromycin, but the pain worsened. She received 1 g of methylprednisolone on 2 consecutive days and, within 2 days, had a dramatic response in terms of both pain reduction and improved inflammatory markers. Seven months later, her CRP level remained normal at <8 mg/L, and she reported no pain. MRI of the right leg showed disappearance of the tibial lesion within 2 days after receipt of methylprednisolone (figure 2).
Figure 1. MRI of the sacrum of patient 1, showing bone marrow edema in all sacral segments, right sacroiliitis, and edema in right iliac blade consistent with chronic recurrent multifocal osteomyelitis.

**Patient 2.** A 10-year-old boy presented with a 10-month history of pain and swelling affecting the right heel. There were no constitutional symptoms, although his ESR was elevated at 28 mm/h. MRI showed edema within the calcaneum. The symptoms subsided spontaneously, but 6 months later, patient 2 developed similar pain and tenderness in the left foot and difficulty running. MRI of the left foot revealed a focal well-defined lesion of the metaphysis of the first metatarsal, with a sclerotic rim and surrounding soft tissue edema. There was a similar lesion in the second metatarsal. The patient underwent biopsy of the metatarsal lesions to exclude osteomyelitis. Culture of biopsy samples yielded negative results, and histological examination revealed a mixed acute and chronic inflammatory cell infiltrate with lymphocytes, macrophages, occasional plasma cells, and polymorphonuclear leukocytes. Two weeks after the biopsy, the patient presented with pain in the sacrum, and MRI revealed increased uptake in the lower 3 sacral segments, consistent with a diagnosis of chronic recurrent multifocal osteomyelitis. The patient was given a 1-week course of 50 mg of prednisolone daily. Within 2 days after receipt, he reported no pain, and an additional MRI showed improvement of the sacral lesions (figure 3). Patient 2 remained asymptomatic 6 months later.

**Discussion.** CRMO is a rare condition of unknown etiology. It was first described by Giedion et al. [1] in 1972. It presents with episodes of recurrent bone pain, tenderness, and sometimes swelling, and it is occasionally associated with constitutional disturbance, fevers, and raised inflammatory markers. It usually affects children and adolescents, although cases in adults have been described [2]. CRMO has been described in association with inflammatory bowel disease [3], pustulosis palmoplantaris [4], and SAPHO syndrome (i.e., synovitis, acne, pustulosis, hyperostosis, and osteitis) [5], although most cases are idiopathic. King et al. [6] described 3 diagnostic criteria that need to be fulfilled: multifocal (≥2) bone lesions; a prolonged course (>6 months) with patients remaining healthy between acute episodes of pain; and lack of response to antibiotic therapy for ≥1 month. CRMO most commonly affects the metaphyseal regions of long bones, such as the distal tibia, femur, and clavicle, as well as the mandible and spine [7]. Radiographic findings are often suggestive of osteomyelitis, but the diagnosis of CRMO is usually confirmed by isotope bone scanning and MRI. A 99mTc bone scan commonly reveals multiple, often asymptomatic, foci of high uptake, and MRI shows lytic lesions surrounded by sclerotic areas and variable amounts of bone and soft tissue edema. MRI is the most sensitive method of determining the extent of bony and spinal involvement [7]. It has been suggested that typical MRI features can distinguish bacterial osteomyelitis from CRMO [8], although biopsy remains essential to exclude infections or tumors, such as Ewing’s sarcoma. Culture of affected bone in CRMO is invariably sterile, although *Mycoplasma hominis* [9] and coagulase-negative staphylococci [6]—possibly a contaminant—have been identified. Histological examination of early lesions reveals noncharacteristic features of acute and chronic inflammation, with predominant polymorphonuclear cells and occasional areas of necrosis. Later lesions show mainly infiltration with lymphocytes and plasma cells, with areas of necrosis and new bone formation [4, 6, 10].

CRMO has a relapsing and remitting course with a variable prognosis. In some cases, a good outcome can be expected, with remission in late childhood and no permanent sequelae, but in others, a prolonged course occurs. Premature epiphyseal fusion can occur and lead to inequality in leg lengths and consequent disability [11]. Progressive thoracic kyphosis has also been reported. Frequent surgical procedures performed for diagnostic and therapeutic purposes may compound the eventual disability. Most patients receive multiple courses of both oral and intravenous antibiotics with no lasting effects before the diagnosis is eventually considered. Macrolide antibiotics have been shown to have antiinflammatory effects both in vitro and in vivo. The exact mechanisms are unclear, but they include...
Figure 2. MRIs of the femur and tibia of patient 1 before (A) and after (B) treatment with methylprednisolone, showing improvement of tibial edema.

Figure 3. MRIs of the sacrum of patient 2 before (A) and after (B) prednisolone treatment, showing improvement in inflammation in the upper sacral segment.
stimulation of neutrophil degranulation and the oxidative burst in phagocytes and inhibition of various cytokines, including prostaglandin E₂ and TNF-α [12]. The clinical effects of these phenomena are unknown. Azithromycin was reported to be of benefit in 7 of 13 cases of CRMO in one series [13], although antibiotics are considered to be largely ineffective. Management is therefore usually symptomatic with analgesics and NSAIDs [14]. Corticosteroids are commonly cited as being of benefit in CRMO, although there has to our knowledge been only 1 case report of treatment with oral corticosteroids [15] and none with intravenous corticosteroids. There is no consensus about the most appropriate dose, preparation, or duration of treatment. There have been case reports of response to IFN-α, IFN-γ, sulfasalazine, pamidronate, and infliximab [3], but the varied mechanism of action of these drugs and the relapsing and remitting nature of the condition suggest that the response is unpredictable at best. CRMO is considered to be an inflammatory, rather than an infective, osteomyelitis [6], and this might explain the dramatic resolution of symptoms and signs in our 2 patients after treatment with corticosteroids.

CRMO is a rare but important diagnosis of exclusion. It should be considered at an early stage in suspected cases of osteomyelitis in children or adolescents to avoid prolonged and inappropriate treatment with antibiotics or surgery. The diagnosis should be confirmed by isotope bone scanning and MRI of affected sites. Azithromycin may be beneficial for some patients, but corticosteroids should be considered for treating patients unresponsive to NSAIDs and analgesics. Surgery should be avoided if possible, because inappropriate excision of large areas of bone could worsen the eventual outcome.

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References