Case Reports

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Chronic recurrent multifocal osteomyelitis of the left femur associated with ulcerative colitis: a case report

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Abstract

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare condition characterized by chronic relapsing noninfectious bone inflammation of unknown etiology. Although CRMO is considered an extraintestinal manifestation in patients with inflammatory bowel disease, most cases of CRMO are associated with Crohn's disease; very few are associated with ulcerative colitis (UC). We herein describe a 21-year-old patient with UC who developed recurrent left thigh pain. The patient was diagnosed with CRMO associated with UC, which was well controlled with azathioprine treatment.

Keywords

Chronic recurrent multifocal osteomyelitis, ulcerative colitis, bone inflammation, magnetic resonance imaging, azathioprine, case report

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Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is associated with various extraintestinal manifestations.[1] Among them, musculoskeletal manifestations ranging from articular and periarticular features to muscular and bone involvement are the

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most common extraintestinal features of IBD, with a prevalence of 6% to 46%.[2,3]

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare condition characterized by chronic relapsing noninfectious bone inflammation of unknown etiology.[4] Since the first published report of CRMO associated with CD by Bognar et al.,[5] CRMO has been considered an extraintestinal manifestation of IBD; however, the relationship between CRMO and IBD is poorly understood.

Although several cases of CRMO associated with CD have been reported, cases of CRMO associated with UC have been rarely reported, especially in adults. We herein describe an adult patient with UC who developed CRMO of the left femur that was well controlled with azathioprine treatment.

Case report

The reporting of this study conforms to the CARE guidelines.[6] A 21-year-old man was transferred from the emergency room to the orthopedics department with a 1-month history of severe pain in the left thigh that had begun after riding a bike. He had been diagnosed with UC 3 months earlier based on the results of colonoscopy and biopsy for symptoms of abdominal pain, bloody stool, and diarrhea. His symptoms were well controlled with oral and suppository mesalazine treatment.

The patient was a nonsmoker and a nonalcoholic. His vital signs at the time of admission were as follows: blood pressure, 120/70 mm Hg; pulse rate, 120 beats/minute; respiratory rate, 20 breaths/minute; and body temperature, 36.6°C. Laboratory findings included a white blood cell count of 11,420/mm^3 (neutrophils, 64.8%), hemoglobin level of 16.5 g/dL, and platelet count of 290,000/mm^3. His erythrocyte sedimentation rate and C-reactive protein level were increased to 87 mm/hour and 6.87 mg/dL, respectively. Physical examination revealed mild swelling and tenderness in the left thigh, but there was no redness or increased warmth.

Magnetic resonance imaging (MRI) of the left thigh revealed slightly low to intermediate signal intensity on T1-weighted imaging (WI), enhancement of the periosteum and adjacent soft tissue on gadolinium contrast-enhanced T1WI, and very high signal intensity on T2WI at the left femoral shaft, consistent with osteomyelitis (Figure 1). Although the evidence of infection was insufficient, a first-generation cephalosporin was empirically prescribed along with a nonsteroidal anti-inflammatory drugs (NSAID) for pain control. However, even after 7 days of treatment, the left thigh pain did not significantly improve. Therefore, bone curettage of the left femur was performed to identify other causes, revealing periosteal reaction, cortex avulsion, and inflammation of the surrounding soft tissues on the posterior side of the left femur. However, there were no suspicious findings of neoplasia and no evidence of infection in the microbiological examination. Pathological examination of the bone specimen confirmed osteomyelitis with sterile inflammation, fibrosis, and periosteal reactive bone formation (Figure 2).

On day 12 of treatment, the patient was referred to the gastroenterology department for recurrence of abdominal pain and bloody diarrhea. Sigmoidoscopy revealed edematous and friable mucosa, marked erythema, and ulcers with spontaneous bleeding from the rectum to the sigmoid colon. A stool test for *Clostridium difficile* toxins and immunohistochemical analysis for the presence of cytomegalovirus in the tissues revealed negative results. Treatment with prednisolone (30 mg) was initiated after discontinuation of treatment with NSAIDs, which dramatically improved the symptoms of UC and left thigh pain. On the basis of the patient's clinical course, the final

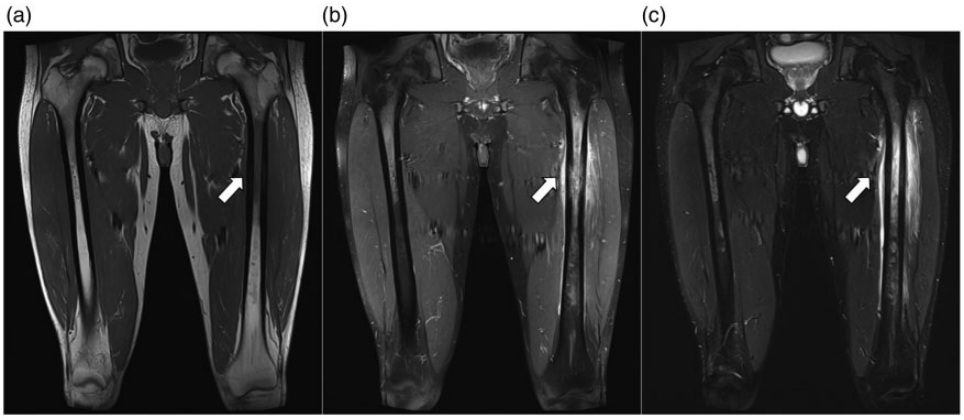

Figure 1. Magnetic resonance imaging of the left thigh showed (a) slightly low to intermediate signal intensity on T1-weighted imaging, (b) enhancement of the periosteum and adjacent soft tissue on gadolinium contrast-enhanced T1-weighted imaging, and (c) very high signal intensity on T2-weighted imaging at the left femoral shaft.

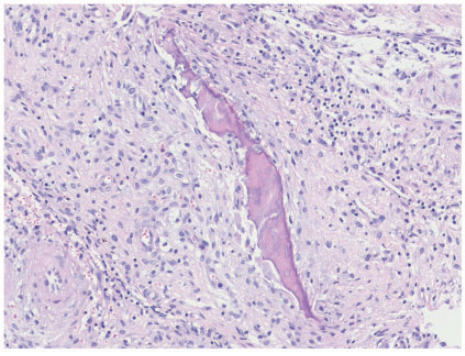

Figure 2. Histological findings. Microscopically, dense marrow fibrosis with granulation tissue is seen. Some lymphoplasmacytic cell infiltration is also observed. The fragment of the bone has been reabsorbed by osteoclasts. These features are consistent with osteomyelitis (hematoxylin and eosin stain, ×100).

diagnosis of CRMO associated with UC was confirmed.

Treatment with mesalazine was continued, while that with prednisolone was tapered over 2 months. One month after discontinuation of the steroid treatment, the left thigh pain recurred; however, there was no deterioration of UC symptoms. Treatment with prednisolone (40 mg) and azathioprine (100 mg) was initiated. Treatment with prednisolone was tapered over 2 months; only treatment with azathioprine (100 mg) was maintained. The left thigh pain was well controlled thereafter. At the time of this writing, the patient was being followed up in the outpatient department and had shown no recurrence of symptoms associated with CRMO and UC for 3 years.

Discussion

CRMO was first described by Giedion[7] in 1972 as "an unusual form of multifocal bone lesions with subacute and chronic symmetrical osteomyelitis." This disorder is a rare idiopathic inflammatory bone disease that occurs primarily in children and adolescents and is characterized by multifocal non-pyogenic inflammatory bone lesions. Patients with CRMO typically present with gradual-onset bone pain, local tenderness, and swelling that are usually self-limiting with a course of exacerbations and remissions.[8]

About 25% of patients with CRMO have associated inflammatory disorders such as psoriasis, palmoplantar pustulosis, Sweet's syndrome, Takayasu's arteritis, Wegener's granulomatosis, spondyloarthropathy, pyoderma gangrenosum, and IBD.[8,9] The association of CRMO and IBD was mentioned for the first time by Kahn, who reported in a letter not published in the literature that of 30 patients with CRMO, 5 had IBD (4 with CD and 1 with UC).[10] Although several cases of CRMO associated with CD have been reported, very few cases of CRMO associated with UC have been reported. In addition, most cases of CRMO associated with IBD have been reported in children and adolescents; very few cases have been reported in adults. In most previously reported cases of CRMO associated with IBD, bony symptoms preceded IBD symptoms by months or years, whereas IBD symptoms preceded bony symptoms in some cases; in a few cases, IBD and bony symptoms appeared simultaneously. In other words, most clinical presentations of CRMO appear to be independent of the intestinal inflammation.

Although the etiology of CRMO is uncertain, the strong association with an inflammatory disorder suggests a shared pathophysiology such as an autoimmune process and supports a genetic component to disease susceptibility. Several previous studies have shown that bone inflammation in patients with CRMO is caused by an abnormal immune response directed against the bone, and IBD is similarly caused by an activated immune system. Several hypotheses have been proposed, including the following. First, cytokines released by the inflamed intestine, particularly interleukin 1, interleukin 6, and tumor necrosis factor-α, can potentially mediate bone inflammation as an extraintestinal manifestation of IBD.[9] Second, common inciting agents cause chronic inflammation in both the bone and intestine.[11] In addition, the genetic contribution to CRMO disease susceptibility is further supported by the identification of *LPIN2*, *MEFV*, *PSTPIP1*,*2*, *IL1RN*, and *CARD15*/*NOD2* gene mutations; the latter two gene mutations are also associated with IBD.[12,13]

The diagnosis of CRMO is made by exclusion of other diseases such as infection and neoplasia; therefore, it commonly requires laboratory tests; imaging such as X-rays, bone scanning, or MRI; and bone biopsy. Although laboratory test results are normal in most people, elevated levels of inflammatory markers might be detected in others. Altered or damaged bone can be seen on X-ray; however, MRI is more sensitive than radiography for assessing the extent and activity of the disease. Bone biopsy may be needed to exclude infection or neoplasia.[14]

The treatment of CRMO has not been standardized and is largely empiric. Because of the rare nature of the disease, no randomized trial has been performed, although a few prospective studies have focused on the treatment of CRMO. NSAIDs are often the first-line treatment; however, they are relatively contraindicated because of their association with colitis flare. Other agents have also been used, including oral corticosteroids, methotrexate, sulfasalazine, and colchicine.[15] Recently, many cases of successful resolution of refractory CRMO with biological agents such as tumor necrosis factor-α antagonists has also been reported.[16–19]

In the present case, the bowel symptoms of UC worsened a few days after initial treatment, which may be considered an exacerbation of UC associated with the bony inflammation in CRMO. However, it might have been more likely due to the use of NSAIDs for pain control without recognition of CRMO, an extraintestinal manifestation of UC. The symptoms associated with UC and CRMO remarkably

improved after azathioprine treatment, and the patient remained relapse-free for a long time. This corresponds with the results of previous reports, which indicated that IBD therapy was generally associated with improvement in bony symptoms.[20]

In conclusion, CRMO associated with UC is relatively rare; however, it can be controlled with IBD therapy. Physicians should be aware of the possibility of CRMO associated with UC when they encounter unexplained bone-related symptoms in patients with UC.

Ethics and consent statements

The patient provided written informed consent and agreed to the use of his medical records and images for publication of this case report. The patient's details were de-identified. Approval by an ethics committee was not required because all data used in this study were obtained from previous medical records.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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