Case Report and Review of the Literature

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ABSTRACT. At initial presentation, chronic recurrent multifocal osteomyelitis may mimic acute hematogenous osteomyelitis; however, cultures of affected bone are sterile. Nuclear scintigraphy identifies additional foci of involvement that present concurrently or sequentially. Unlike acute bacterial osteomyelitis, chronic recurrent multifocal osteomyelitis seems unaffected by antibiotic therapy and typically responds to treatment with antiinflammatory drugs. Surgical decortication has been reported for refractory cases. The case presented here illustrates the rare involvement of the mandible after initial presentation in the spine of a 4-year-old girl and the refractory nature of the disease over 6 years despite treatment with various medical and surgical therapies. Pediatrics 2004;113:e380–e384. URL: http://www.pediatrics.org/cgi/content/full/113/4/e380; bone diseases, osteitis, hyperostosis.

ABBREVIATIONS. CRMO, chronic recurrent multifocal osteomyelitis; MRI, magnetic resonance imaging; ESR, erythrocyte sedimentation rate; CT, computed tomography; AFB, acid-fast bacilli; Ig, immunoglobulin; PCR, polymerase chain reaction; DSO, diffuse sclerosing osteomyelitis; SAPHO, synovitis, acne, palmoplantar pustulosis, hyperostosis, ostitis syndrome.

Giedion et al1 first described acquired, culture-negative, multifocal osteomyelitis in children in 1972 and named the syndrome “subacute and chronic symmetrical osteomyelitis.” In the original report, the disorder involved the metaphyses of long bones either simultaneously or successively. Subsequent publications reported involvement of additional bone sites and referred to the disorder as chronic multifocal osteomyelitis2 and chronic recurrent multifocal osteomyelitis (CRMO).3 Pediatric cases with mandibular involvement have been reported in the oral surgery, radiology, orthopedics, and dermatology literature.

Unlike the previously reported 4 cases of CRMO with mandibular involvement in the English-language literature,4–7 this patient developed CRMO initially in the spine and thereafter developed mandibular involvement. She did not have prior dental infection or skin manifestations associated with CRMO. Additional aspects of interest include the progressive nature of the mandibular involvement and the disease refractoriness to different therapies over 6 years.

CASE REPORT

Year 1

In February 1997, a previously healthy, 4-year, 2-month-old white female was seen in the clinic for left-sided lumbar pain and a fever to 104°F. There was no history of trauma, and the examination was normal. She was treated for muscle strain with ibuprofen. Over the next 3 months, the pain persisted and woke her at night, and she refused to run or jump. A bone scan revealed increased uptake at the left side of the S1 vertebra on delayed images. Magnetic resonance imaging (MRI) revealed a well-circumscribed, irregularly shaped lytic lesion of S1 extending into the sacral ala (Fig 1). Her erythrocyte sedimentation rate (ESR) was 27 mm/hour, and she underwent a computed tomography (CT)-guided percutaneous needle biopsy of the S1 vertebra in June 1997. The histopathology reported probable osteoblastoma; cultures for bacteria (including acid-fast bacilli [AFB]) and fungus were negative. No treatment was prescribed.

During the subsequent 6 weeks, the lumbar pain persisted, and the patient underwent an open posterior biopsy of S1 in July 1997. The histopathology examination revealed normal bone; bacterial cultures were negative, and ESR was 28 mm/hour. She was not treated with antibiotics.

Six weeks after biopsy, she was evaluated for recurrent left-sided lumbar pain. ESR was 49 mm/hour. A CT scan of the lumbar spine revealed extension of the previously noted lesion, now lytic and sclerotic, across the growth plate into the S1 vertebral body and left posterior S1 elements, and an enlarged L5-S1 disk that compressed the nerve root. The patient underwent an open anterior biopsy of S1 in October 1997. Histopathologic findings demonstrated changes consistent with chronic osteomyelitis; bacterial cultures were negative. The girl was treated with oral cepalexin (55 mg/kg per day) for 4 months, with no improvement in back pain.

Year 2

The patient was treated with intravenous cefuroxime (140 mg/kg per day) for 1 month, followed by 7 days of oral azithromycin (10 mg/kg on day 1, then 5 mg/kg on days 2–5) for lobar pneumonia. During February through March 1998, she was treated with 6 weeks of intravenous nafcillin (200 mg/kg per day) for persistent back pain. With nafcillin treatment, the back pain improved, and the ESR decreased to 29 mm/hour. Treatment then was switched to oral clindamycin (40 mg/kg per day). During the sixth month of clindamycin therapy, the patient developed diffuse pain and swelling of the entire left mandible. She had no evidence or history of dental caries or periodontal disease. She underwent an intraoral biopsy of the mandible in October 1998. The pathology report revealed histiocytes in the marrow cavity and evidence of bone remodeling. Aerobic and anaerobic bacterial cultures grew oral flora; AFB and fungal cultures were negative. The culture results were attributed to contamination from the intraoral surgical approach. During the next 4 months, she was treated for the working diagnosis of CRMO with indomethacin (2–3 mg/kg per day). ESR remained elevated at 38 to 52 mm/hour. The back pain, mandibular pain, and left-sided soft tissue swelling over the mandible resolved; however, bony enlargement of the left mandible persisted.

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Year 3

The patient discontinued indomethacin treatment due to abdominal pain and nausea. In March 1999, she was treated with a 4-week course of amoxicillin-clavulanate (100 mg/kg per day, amoxicillin component) with indomethacin as needed for mandible pain; however, this did not affect the bony enlargement, intermittent pain, and soft tissue swelling of the left mandible.

In June 1999, the patient developed recurrent left-sided lumbar pain and mandible pain that disrupted her sleep. Despite Naprosyn (10–20 mg/kg per day), she experienced daily pain and swelling of the left mandible and back pain over the next 3 months.

Additional tests were performed, including serologies for Coxiella burnetii, Brucella, and Francisella tularensis, which were negative. The serum Bartonella henselae immunoglobulin (Ig)G was positive at 1:128 with a negative IgM. The serum Bartonella quintana IgG was equivocal at 1:64 with a negative IgM. A CT scan revealed an increased number of luencies within a thickened, densely sclerotic left mandible (Fig 2). The patient underwent a mandible decortication via an extraoral approach and excision of an adjacent enlarged lymph node in September 1999. Histopathology of the bone revealed scattered acute and chronic inflammatory cells within fibrotic bone consistent with chronic osteomyelitis. Routine and anaerobic cultures of the bone were negative, as were cultures for fungus, AFB, and Nocardia. Polymerase chain reaction (PCR) tests of the bone for Mycobacterium tuberculosis, B henselae, and B quintana were negative. Histologic examination of the node revealed follicular hyperplasia. M tuberculosis PCR of the node was negative. After surgery, the patient resumed Naprosyn, receiving it every 12 hours. Over the following 6 months, the patient reported intermittent mandible pain and no back pain. She resumed full-time school attendance and extracurricular activities.

Year 4

While receiving daily Naprosyn, the patient developed pain localized to the right sacral area in March 2000. Examination findings were normal. MRI of the lumbosacral spine revealed signal abnormalities involving the right and left S1 vertebral body and sacral alae (Fig 3). Four months later, during Naprosyn treatment, the patient developed increased bony enlargement of the left mandible and numbness attributed to bone impingement of the mental nerve foramen. After discussion with the maxillofacial surgical consultant and review of the case report by Gallagher et al, a 3-month trial of interferon-γ (50 μg/m² subcutaneously, 3 days per week) was administered. During therapy, the mandible pain resolved, and the mandible swelling and back pain were improved significantly.

Year 5

After completing the interferon course, the left mandible pain and swelling recurred and were refractory to Naprosyn therapy. She underwent a repeat left mandible decortication via an extraoral approach in May 2001. Histopathologic examination revealed histiocytes, chronic inflammatory cells, and a few giant cells consistent with chronic osteomyelitis. Cultures for bacteria...
(routine and anaerobic), AFB, and fungus were negative. The patient was treated with 3 weeks of oral clindamycin (40 mg/kg per day) and Naprosyn as needed for pain.

In October 2001, the patient developed bony swelling and tenderness of the right mandible. An MRI study demonstrated soft tissue swelling medial to the right side of the mandible and mucosal changes consistent with sinusitis. She received treatment with amoxicillin-clavulanate for 14 days, which did not affect the mandible symptoms. A panoramic radiograph demonstrated multiple lytic lesions in the right mandible.

Year 6

From November 2001 to February 2002, the patient experienced worsening right mandible pain daily and 2 episodes of fever with soft tissue swelling lateral to the ramus; these were treated with Naprosyn and acetaminophen. A CT scan performed January 2002 showed diffuse thickening of the body of the right mandible and the entire left mandible to the condyle (Fig 4). Lytic lesions appeared throughout the mandible except for the right ramus and condyle. Treatment with a second course of interferon-γ was attempted but discontinued after 2 weeks because of drug-related side effects. Beginning May 2002, the patient was treated with oral prednisone and subcutaneous methotrexate (titrated to 0.8 mg/kg weekly), during which her mandible and back pains resolved and the ESR decreased to 29 mm/hour. A panoramic radiograph demonstrated sclerosis at sites of prior lytic lesions in the left mandible with persistent lytic lesions on the right. However, methotrexate was discontinued after 11 months because of oral ulcers, nausea, and vomiting refractory to adjunctive therapy. ESR increased to 50 to 60 mm/hour. The patient began treatment with alendronate in February 2003 along with continued prednisone. ESR and C-reactive protein remained elevated.

It has been 6.5 years since onset of the initial lumbar pain, 5 years since onset of left mandible symptoms, and 1.5 years since onset of the right mandible symptoms. The patient is managed currently with oral prednisone, alendronate, and Naprosyn as needed for pain. In addition to daily lower-dose prednisone, she has received 2 courses at 2 mg/kg per day of prednisone for 7 days to treat episodes of acute soft tissue swelling anterolateral to the left ramus associated with trismus. She has persistent facial deformity due to diffuse bilateral mandible enlargement; however, she is otherwise growing and developing normally and participating in school and extracurricular activities.

DISCUSSION

CRMO is a relapsing inflammatory disease affecting a variety of bones (such as the pelvis, sternum, and scapula) in addition to the originally described long bones. The disease is rare, accounting for 2% to 5% of all osteomyelitis cases, and primarily affects young girls, with a female/male ratio of 5:1. In a 5-year follow-up study of 23 patients published in 2002, the median age of onset was 10 years with a reported range of 4 to 14 years. It primarily affects children and demonstrates no racial predilection.

Cases of mandibular CRMO previously published include 1 adult and 5 children. The adult case in-
volved a 40-year-old woman whose 3-year disease course initially involved inflammation of the right first and second ribs. She then developed symptomatic left mandibular disease, treated medically and with partial mandibular resection. Bone scan results revealed additional asymptomatic sites of involvement including the frontal bone of the skull, left first rib, and fifth lumbar vertebra. A case report of a 12-year-old girl reported a 1-year course of CRMO with involvement of the right mandible, right foot, left groin, and left ankle accompanied by palmoplantar pustulosis. Flygare et al reported the 8-month course of CRMO involving the right maxilla and right mandible in a 14-year-old who thereafter developed a symptomatic focus in the left radius. This patient developed an episode of significant soft tissue inflammation adjacent to the ramus, affecting the masseter and pterygoid muscles, similar to what occurred in our patient on 2 separate occasions during corticosteroid treatment. Otsuka et al reported a 4-month course of CRMO in a 4-year-old girl who developed right and then left mandibular involvement after a root canal treatment of a right mandibular tooth. Thereafter, pain and swelling developed over the bilateral tibia and right fibula, and bony involvement was confirmed by bone scan. In the French literature, Lavis et al reported a 4-month course of CRMO affecting a 14-year-old boy who initially presented with painful swelling of the left mandible. His dental examination at presentation was normal. The mandibular lesion was biopsied, and the bacterial culture grew Streptococcus oralis. After 10 days of intravenous antibiotics, 2 additional areas of tender swelling developed in the mandible. A bone scan performed thereafter revealed an additional focus in the right proximal humerus.

As more cases of culture-negative chronic osteomyelitis involving the mandible have been characterized, investigators recognize that diffuse sclerosing osteomyelitis (DSO) of the mandible has identical presentation, histopathologic findings, and refractory clinical course as CRMO. DSO may be a limited presentation of CRMO. Additional supportive evidence includes similar skin findings associated with either DSO or CRMO. Palmoplantar pustulosis has been described with both CRMO and DSO. Psoriasis has also been described with both CRMO and DSO. The European rheumatology literature includes CRMO as part of the spondyloarthropathy spectrum, acne, palmoplantar pustulosis, hyperostosis, osteitis (SAPHO) syndrome. Additional cases of mandibular CRMO are reported in the European SAPHO literature. In the maxillofacial surgery literature, SAPHO has been described as including DSO and CRMO. Both SAPHO syndrome and CRMO are considered types of seronegative spondyloarthropathies.

CRMO was attributed originally to an infectious agent, because the presentation includes an elevated ESR, mild leukocytosis, low-grade fever, and inflammatory and radiologic findings localized to bone in areas typical for acute hematogenous bacterial osteomyelitis. Patients undergo bone biopsy because the presentation, radiographic, and nuclear scintigraphic findings can mimic acute hematogenous osteomyelitis, neoplasia, eosinophilic granuloma, osteoblastoma, and osteoid osteoma. Patients usually are treated with systemic antibiotics at initial presentation; however, cultures of bone are typically negative. Our patient had extensive serologic testing of serum, various cultures of biopsied bone, and various PCR tests of bone and tissue, all of which were negative. The multifocality of disease involvement, the typically negative cultures of bone, and the remitting-relapsing nature of the disorder distinguish CRMO from subacute bacterial osteomyelitis. The following diagnostic criteria were proposed by Manson et al in 1989: 1) ≥2 radiographically confirmed bone lesions; 2) at least 6 months of remissions and exacerbations of signs and symptoms; 3) radiographic and bone scan evidence of osteomyelitis; 4) lack of response to antimicrobial therapy at least 1 month in duration; and 5) lack of an identifiable cause.

A possible immune-mediated etiology has been speculated, given the reports of clinical improvement and reduced sedimentation rates with nonsteroidal antiinflammatory drugs and corticosteroids. However, immunologic evaluations of cases have not revealed abnormalities in Ig, mononuclear cell response to mitogens, T-cell subsets, oxidative burst of phagocytic cells, neutrophil chemotaxis, or phagocytosis. There was no association with HLA-B27, antinuclear antibody, or rheumatoid factor.

There have been no controlled trials evaluating or comparing different drug therapies or surgical interventions. With the relapsing-remitting course of CRMO, it is unknown whether long-term medical therapy, intermittent courses of medical therapy, and surgery impact the natural history. There is general agreement that antibiotics have no effect on the clinical course of CRMO. There are anecdotal reports of a variety of medical therapies (Table 1).

In a retrospective review 13 years after initial diagnosis, Huber et al described 23 patients, of whom 17 were in remission. Among the group in remission, the median duration of active CRMO was 5.6 years (range: 0.1–19 years). Of the 6 patients with continued CRMO activity, 2 had intermittent relapses and discontinuations.
4 had chronic pain. Five patients had psoriasis, and 2 had recurrent pustular rashes. Of the 23 patients, 18 (78%) had minimal or no impairment of physical function, 4 had mild impairment, and 1 had severe persistent disease and moderately severe impairment. Eleven patients had significant bony deformities, including 7 with leg-length discrepancies, 3 with bony overgrowth, and 1 patient with both. The study was unable to identify characteristics that differentiated those patients with persistently active CRMO from those who went into remission.

Coinde et al. reported a retrospective review of 17 children with an average of 4 years of follow-up (range: 6 months to 25 years). Eight children had developed a related skin disorder during the first year of their illness (4 with palmoplantar pustulosis and 4 with psoriasis). Six children had sacroiliitis. Four patients were lost to follow-up 6 months after diagnosis. Three patients were in full remission without treatment. Two patients had chronic pain despite therapy. Twelve patients had intermittent relapses treated with antiinflammatory drugs. The authors suggest that intermittent treatment of acute relapses is as effective as long-term therapy, although supporting evidence is not provided.

Given the uncommon occurrence of CRMO, a controlled trial evaluating different treatment regimens is unlikely. Although anecdotal reports and case series advocate treatment with antiinflammatory drugs, the case presented illustrates the refractory nature of CRMO despite treatment with extended regimens of antiinflammatory medications.

Clinicians caring for children should be familiar with CRMO, because it typically occurs during childhood and should be included in the differential diagnosis of patients presenting with signs and symptoms of unifocal osteomyelitis. Because other sites of bone involvement may be asymptomatic, a bone scan is recommended for patients with negative bacterial cultures of bone biopsy and for those presenting with mandibular inflammation. Prompt diagnosis of CRMO will allow patients to avoid the risks associated with lengthy courses of antibiotic therapy and repeat bone biopsies.

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REFERENCES

Chronic Recurrent Multifocal Osteomyelitis of the Spine and Mandible: Case Report and Review of the Literature
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