Case Report

Pamidronate Treatment of Chronic Noninfectious Inflammatory Lesions of the Mandible in Children

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ABSTRACT. Noninfectious inflammatory lesions of the mandible occur in chronic recurrent multifocal osteomyelitis (CRMO). Diffuse sclerosing osteomyelitis of the mandible (DSOM) is a condition thought to be a localized form of CRMO. Recently, bisphosphonate therapy, and particularly intravenous pamidronate, has been proposed as a treatment for patients with both CRMO and DSOM who do not improve with nonsteroidal antiinflammatory drug treatment. We report our experience using pamidronate in 2 children with chronic noninfectious osteomyelitis affecting the mandible. We describe the clinical and radiographic features and the treatment, side effects, and clinical and radiographic responses. Our experience suggests that pamidronate is an effective second-line therapy. (J Rheumatol 2007;34:1585–9)

Key Indexing Terms:
CHRONIC RECURRENT MULTIFOCAL OSTEOMYELITIS MANDIBLE PAMIDRONATE
DIFFUSE SCLEROSING OSTEOMYELITIS OF THE MANDIBLE BISPHOSPHONATES

Chronic recurrent multifocal osteomyelitis (CRMO)[1] is an uncommon inflammatory disorder characterized by multifocal bony lesions associated with recurrent pain, swelling, and sometimes skin lesions[2]. SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), described in young to middle-aged adults, includes similar bony lesions[3]. A recent series suggested that unifocal and/or nonrecurrent diseases may represent different levels of severity within the same clinical entity, CRMO being the most severe manifestation[4]. CRMO typically involves the metaphyses of the long bones of the lower limbs, while chest wall, pelvis, and spine involvement are rare compared to SAPHO syndrome[2,3]. In CRMO, mandibular involvement is rare[5-7]. When limited to the mandible, the condition is also termed diffuse sclerosing osteomyelitis of the mandible (DSOM). In DSOM, clinical, radiographic, and histologic features are similar to those seen in CRMO and SAPHO[8,9]. Radiologically, early mandibular changes, usually diffuse and extensive, include resorption of cortical and trabecular bone with cortical disruption. Sclerosis and periosteal reaction with ossification are responsible for bone enlargement and sequestration. In chronic stages, a mixed pattern of sclerotic changes and milder osteolytic changes occurs[10,11].

For patients with CRMO whose symptoms and signs persist despite nonsteroidal antiinflammatory drug (NSAID) treatment, alternative therapies using anti-tumor necrosis factor (TNF) agents and bisphosphonates have been proposed[12,13]. We describe our experience using pamidronate in 2 children with mandibular osteolytic lesions.

CASE REPORTS

Patient 1. A previously healthy 4-year, 10-month-old girl presented with a 1 month history of distal left thigh pain, limp, and low grade fever. Radiographs and magnetic resonance imaging (MRI) revealed a lytic lesion of the left distal femoral metaphysis consistent with subacute osteomyelitis. Blood cultures were negative. Her symptoms subsided following 3 weeks of ibuprofen and intravenous cephalexin. Four months later, she developed pain and swelling in the region of the left hemi-mandible associated with cervical lymphadenopathy, mild dysphagia, and flu-like symptoms. Because of an incomplete response to a second course of antibiotics (10 days of cloxacillin, amoxicillin, and cefaclor), she was referred to the Hospital for Sick Children 4 months after the initial symptoms. Examination revealed localized swelling and tenderness of the left mandible with no increased heat or redness. The remainder of her examination was normal. Blood tests showed elevated inflammatory markers [white blood cell count 12.4×10^9/l, platelet count 543×10^9/l, erythrocyte sedimentation rate (ESR) 41 mm/h, and C-reactive protein (CRP) 21.8 mg/l] and negative HLA-B27. Bone scintigraphy showed increased uptake limited to the region of the left mandible. Computed tomography (CT) scan showed mandibular abnormalities including multiple lucencies and ground-glass sclerosis with extensive periosteal reaction and masseter muscle swelling (Figure 1A). Bone histopathology showed fibrotic marrow with minimal chronic inflammation; cultures were negative. She had a third course of intravenous (IV) antibiotics (3 months of clindamycin and cephalexin), with no clinical response. The diagnosis of CRMO was made

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based on the existence of 2 foci of osteomyelitis in the absence of an identifiable infectious cause. One month later, treatment with indomethacin 3 mg/kg/day was begun, with a good initial response. However, because of recurrent flares on indomethacin and unresponsiveness to a trial of celecoxib, IV pamidronate was initiated 1 year after initial presentation. She received pamidronate 0.5 mg/kg and 1 mg/kg one day apart. She experienced nausea and developed fever during the first infusion. No further pamidronate was given as she developed mild hypocalcemia (2.05 mmol/l) immediately after the second infusion. Her pain assessed by visual analog scale (VAS) resolved completely and the swelling decreased substantially within 1 week after the last infusion. Bone scintigraphy, performed the day of the second pamidronate infusion, showed decreased local uptake. CT scan performed 11 months after pamidronate showed absence of osteolytic changes and remodeling with a mandibular shape close to normal (Figure 1C). One year after pamidronate infusion, some markers of inflammation remained elevated (ESR 26 mm/h), while platelet count and hemoglobin normalized. Two years after pamidronate infusion, she has not experienced any recurrence of symptoms or signs in the mandible. However, she developed a new lesion in the right proximal tibial metaphysis 17 months after pamidronate that was successfully managed with indomethacin.

Patient 2. At age 6 years, 8 months, a previously healthy girl developed swelling, pain, and tenderness of the left hemi-mandible. Radiographs and CT scan showed enlargement and thickening with a lucent lesion involving the ascending mandibular ramus and mandibular condyle associated with prominent soft tissue involvement (Figure 1B). ESR and CRP were normal (ESR 10 mm/h and CRP 0.9 mg/dl). Bone histopathology was consistent with chronic osteomyelitis with prominent collections of inflammatory cells and necrotic bone fragments. Microbiology of the bone biopsy was negative. The diagnosis of DSOM was suspected. Pain and swelling persisted despite sequential trials of ibuprofen, naproxen, and rofecoxib. A 3-week course of low-dose oral corticosteroid therapy (0.5 mg/kg/day) provided incomplete and unsustained symptom control. Nine months after symptoms onset, the lesion was

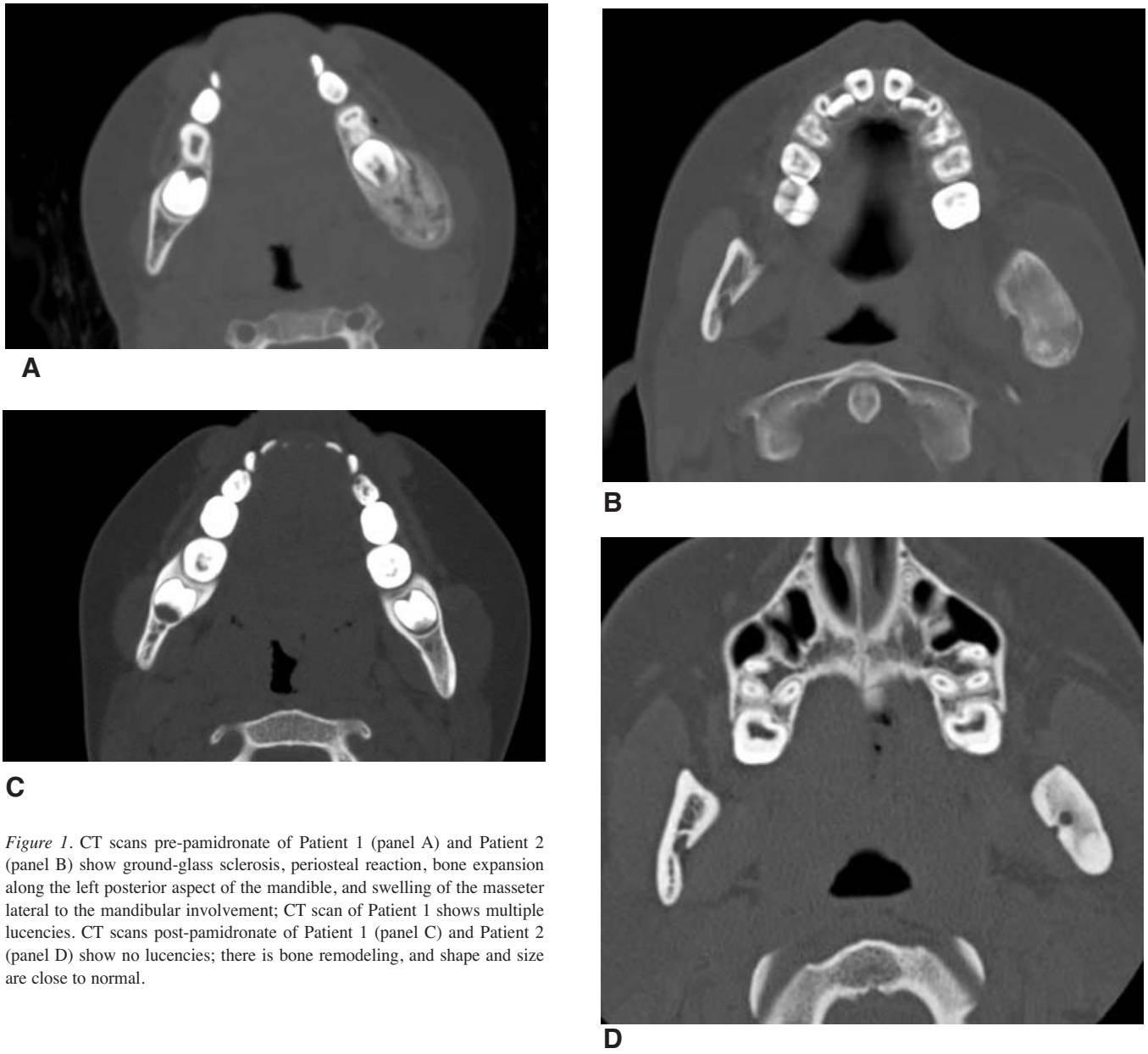

Figure 1. CT scans pre-pamidronate of Patient 1 (panel A) and Patient 2 (panel B) show ground-glass sclerosis, periosteal reaction, bone expansion along the left posterior aspect of the mandible, and swelling of the masseter lateral to the mandibular involvement; CT scan of Patient 1 shows multiple lucencies. CT scans post-pamidronate of Patient 1 (panel C) and Patient 2 (panel D) show no lucencies; there is bone remodeling, and shape and size are close to normal.

debrided and a coronoidectomy performed in an attempt to obtain pain control. Although microbiological studies were negative, she was started on antibiotic therapy (clindamycin) for 3 months, but gastrointestinal intolerance resulted in a switch to oral roxithromycin therapy that continued for 1 year. Three years after initial presentation, because of persistent pain, the mandibular lesion was again debrided. She required daily opioid analgesia (fentanyl transdermally for a period of 3 years). She was referred to the pediatric rheumatic disease program, University of Saskatchewan, 5 years after the initial presentation because of persistent pain. Pamidronate was started with an initial first-day dose of 0.5 mg/kg followed by 1 mg/kg on Days 2 and 3. Within several days, her symptoms of pain and swelling resolved and she remained symptom-free for 6 months, at which time isolated mild mandibular discomfort recurred. A second cycle of pamidronate (1 mg/kg/day × 3 days) was administered 6 months later and a third cycle 9 months after the second cycle. She did not experience any side effects related to pamidronate infusion. Inflammatory markers were not repeated after pamidronate infusions commenced. CT scan performed after the last cycle of pamidronate infusion showed absence of bone lucencies, almost normal mandibular size and shape, and bone remodeling (Figure 1D). After this report was accepted for publication, this patient had another pamidronate infusion and within 2 days developed extensive mouth ulcers, marked mandibular pain on the side of the lesion, and increased swelling. The previous infusion 3 months earlier was followed by the same constellation of features that settled in 2 weeks. In view of the 2 consecutive post-pamidronate reactions, no further pamidronate infusions are planned.

DISCUSSION

NSAID are first-line therapy in CRMO and are usually sufficient to manage the symptoms. When pain is unresponsive to NSAID therapy, a short course of corticosteroids is an alternative[4,5,7,14]. Increased local production of TNF-α in CRMO has prompted the use of TNF blocking agents, with efficacy in the small number of subjects reported to date[15-17] and in a teenager with bilateral mandibular involvement[12]. We elected not to use TNF-blocking agents in our patients as we technically could not confirm the increased local production of TNF-α and therefore could not justify the use of this medication given the few longterm data available.

The rationale for bisphosphonate therapy in CRMO/SAPHO/DSOM is based on its potential antiinflammatory properties[18] and its analgesic effect[13,19-23]. Inclusion criteria in the different reports of bisphosphonate use are mainly pain refractory to NSAID[13,19,20]. The treatment regimens have included single-dose to 3-day courses repeated as needed[13,19-23]. In the only pediatric study, pamidronate was given at a dose of 1 mg/kg (maximum 30 mg) daily for 3 consecutive days, every 3 months as required[13]. In our patients, the regimen used was slightly different as we used 0.5 mg/kg for the first infusion of the first course to evaluate tolerance to the medication and 1 mg/kg for the 2 remaining days. Pamidronate was repeated as needed and administered 3 days in a row at the dose of 1 mg/kg. Disodium clodronate has also been used in the treatment of DSOM, with reduction of pain at 6 months[24].

Immediate side effects from pamidronate may include brief episodes of fever, transient headaches, and flu-like symptoms, usually observed during the first infusion[13,19,20]. In our first patient, we observed nausea and fever during the first infusion and mild hypocalcemia after the second dose that led to cancellation of the third dose. Reports of osteonecrosis of the jaw in adults taking bisphosphonates especially after dental extraction have been reported. It is unclear whether this is related to bisphosphonates or to concomitant drugs, underlying diseases, or other comorbid risk factors in patients treated for cancer with chemotherapy and corticosteroids[25,26]. Good dental hygiene and close followup are recommended in patients at high risk of developing this complication. A case of irreversible bisphosphonate-induced osteopetrosis has been reported in one child who had received high cumulative dose of pamidronate over 3 years for isolated hyperphosphatasemia[27]. Of note, a plain radiograph performed 3 months after pamidronate infusion for knee pain in Patient 1 showed dense metaphyseal bands previously reported as bisphosphonate-induced radiographic changes in children (Figure 2)[28,29]. These thin, sclerotic metaphyseal bands at the site of rapid growth are consistent with cyclic administration of pamidronate and are thought to be reversible[28,30]. These sclerotic bands, along with increased bone mineral density, were observed in 32 children who received longterm cyclic pamidronate for osteogenesis imperfecta and cerebral palsy[29]. Given the potential risk of irreversible osteopetrosis, cautious monitoring is warranted when high cumulative doses of pamidronate are administered to the growing skeleton. To date, none of the patients with CRMO/SAPHO syndrome treated with bisphosphonates has experienced these complications. However, longterm data are limited in children. Until more data are available, caution should be exercised and close followup maintained in children with CRMO/DSOM treated with bisphosphonates.

In earlier studies, indicators of drug response included reduction of pain assessed either by VAS[20] or patient report[19], reduction of concomitant medications[20], reduced frequency of exacerbations[19,20], and decreased swelling[13]. Time to remission ranged from 3 days to several weeks after the last pamidronate infusion. In another study, the pain relief effect of another bisphosphonate, disodium clodronate, was delayed[24]. However, the effect of pamidronate was sustained over the time of followup, which ranged between 20 months and 2.8 years[13,20,22]. Both our patients had complete resolution of pain and swelling within a few days, with decreased requirement for other medications. While Patient 1 did not require additional courses of pamidronate, Patient 2 has been dependent on intermittent pamidronate infusions to maintain control.

Imaging has not been used to evaluate response to treatment in studies reporting the use of pamidronate in CRMO/SAPHO syndrome. CT scan is commonly used to stage and follow lesions involving the mandible as it is able to discern active from quiescent osteomyelitis. As a CT scan is a significant exposure to radiation, MRI is a safer alternative. However, it appears less sensitive to inflammatory changes, as marrow changes take months to normalize[10]. In our patients,

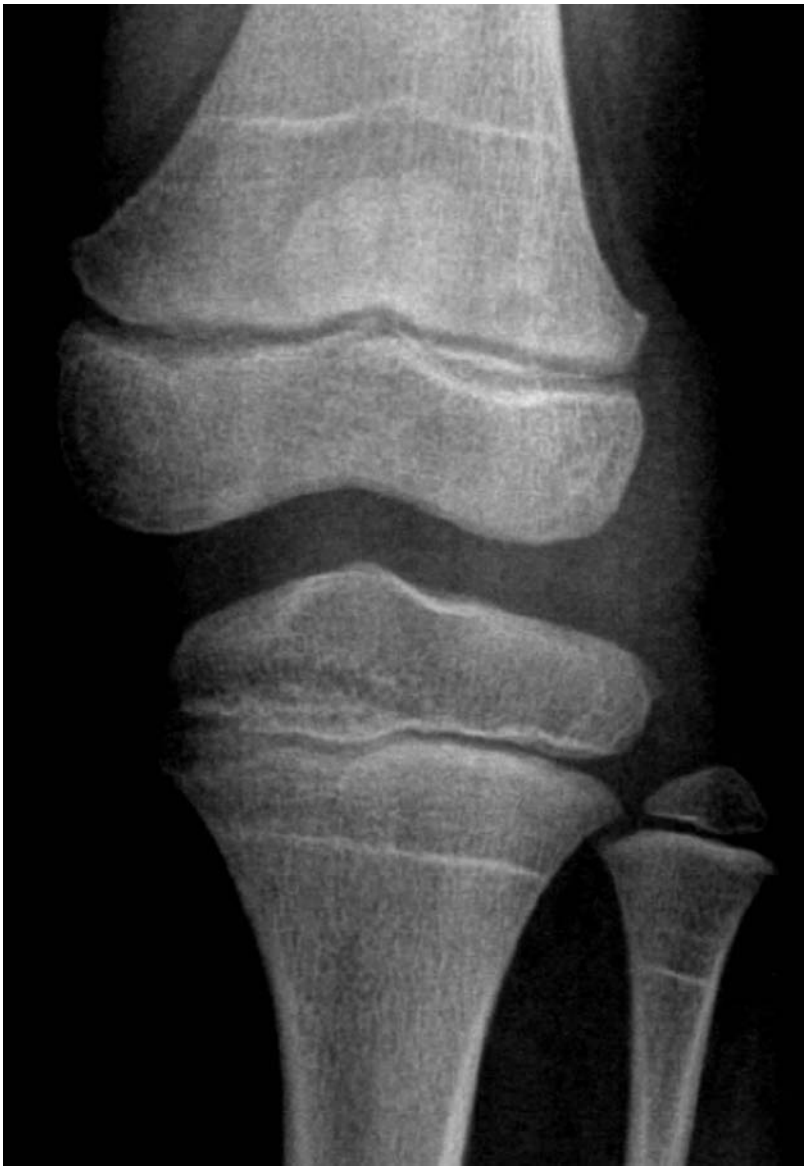

Figure 2. Radiograph of the knee (Patient 1) shows hyperdense metaphyseal bands described as bisphosphonate-induced radiographic changes.

imaging was helpful in evaluating response to treatment. In Patient 1, CT scan performed 13 months after pamidronate infusion displayed active remodeling with absence of lucency and almost normal bone size (Figure 1C). In 2 reports, no changes were seen on bone scan after pamidronate infusion despite a good clinical response[19,21]. Patient 1 had a decreased local uptake on the day of the second pamidronate infusion. Therefore, imaging may be useful in the assessment of disease activity in CRMO.

Both patients improved significantly in terms of pain and swelling taking bisphosphonates. Therefore, we can hypothesize that the bisphosphonate may have alleviated pain and reversed bone inflammation and associated soft tissue swelling caused by active resorption by its antiresorptive action. However, longterm remission was obtained, but mild systemic inflammation persisted in one patient, and both patients had subsequent recurrences (occurrence of another location for one and recurrence of symptoms for the other).

Decortication has been reported to improve symptoms in patients with DSOM[31]. Patient 2 had 2 debridements performed due to mandibular deformity and intractable pain, but has not required debridement since pamidronate administration.

Mandibular involvement, although rare in CRMO, is a therapeutic challenge due to intractable pain and the potential cosmetic effects. Pamidronate appears to be an efficacious alternative to conventional treatment in CRMO affecting the mandible, and may be an alternative to surgery when given early in the course of the disease. Further studies evaluating

the short- and longterm efficacy and safety of bisphosphonates as a second-line therapy in CRMO/DSOM are needed.

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