CASE REPORT

Chronic recurrent multifocal osteomyelitis of the mandible: report of three cases

Luciana B. Paim,1 Bernadete Lourdes Liphaus,2 André C. Rocha,3 Aura Ligia Z. Castellanos,4 Clovis Artur A. Silva5

Abstract

Objective: To report three cases of chronic recurrent multifocal osteomyelitis of the mandible, an inflammatory disease affecting one or more bones with absence of isolated microorganisms in affected areas.

Description: The first case is a 13 year-old female presenting with pain and fever after dental treatment. The patient received antibiotic treatment for osteomyelitis, but developed progressive enlargement of the mandible and palmoplantar pustulosis. Bone scintigraphy showed intense and diffuse uptake in the mandible. The swelling decreased after indomethacin and hyperbaric oxygen therapy. Case 2 is a 9 year-old female patient with recurrent pain and edema of the right mandible for three years. The diagnosis of osteomyelitis was established and amoxicillin introduced. After three months, tomography showed diffuse mandible osteolysis. Indomethacin and hyperbaric oxygen therapy were introduced, however the patient presented a relapse and was treated with prednisone, rofecoxib and methotrexate. Patient 3, a 10 year-old male, had palmoplantar pustulosis and recurrent enlargement of the mandible. Tomography showed diffuse mandible osteolysis and scintigraphy revealed intense and diffuse uptake in the mandible. The patient was treated with prednisone. Rofecoxib was replaced after two relapses.

Comments: Chronic recurrent multifocal osteomyelitis of the mandible is often associated with prolonged pain periods and periods of activity and remission of the inflammatory process. Its recognition is important to prevent the patient from being submitted to prolonged antibiotic therapy and unnecessary invasive procedures.


Introduction

Chronic recurrent multifocal osteomyelitis (CRMO) is a rare inflammatory bone disease which affects one or more bones with periods of exacerbation and remission and generally without any infectious agents being isolated from affected areas.1-6 Systemic involvement is exceptional and associated cutaneous lesions are common, particularly pustulosis palmoplantaris.2,4,6 The most often affected bones are sternum, clavicle, ribs, spine, pelvis and peripheral long bones.1,2 Isolated involvement of the mandible is rare and multiple lesions may occur.7
Radiographic findings are similar to with septic osteomyelitis, with osteolytic lesions and circumscribed sclerosis. Bone scintigraphy is of help in locating asymptomatic lesions. Biopsies do not generally find evidence of infectious agents. Prognosis is uncertain and clinical course can be painful and prolonged. Treatment is habitually given with non-hormonal anti-inflammatories, corticosteroids, sulfasalazine and/or methotrexate.

The objective of the present study is to describe three cases of CRMO of the mandible monitored at the Pediatric Rheumatology Unit at the Children’s Institute at the Hospital das Clínicas of the Medical faculty of the Universidade de São Paulo during the period between 1998 and 2003.

Case descriptions

**Case 1**

Female patient, white, 13 years and 3 months old, in March 1995 developed diffuse mandibular pain after dental treatment with local hyperemia and fever. Was given a number of antibiotics (crystalline penicillin, amoxycillin, clindamycin and metronidazole) diagnosed with osteomyelitis, progressing with periods of improvement and periods of exacerbation of the mandibular tumorization. In November 1998 she was interned at our unit for investigation of diffuse mandible tumors, associated with a restricted ability to open the mouth and pustulosis palmoplantaris. Complementary examinations revealed: computerized tomography (CT) with diffuse mandibular osteitis (ground-glass appearance), with no collections present; mandibular biopsy revealed giant cells with fusiform cell stroma and inflammatory neutrophil infiltration and a culture from the biopsy isolated *Propionibacterium sp*. Bone scintigraphy found accentuated and homogeneous diffuse hyper-deposition of the radiolabeled drug along the entire extent of the mandible, to a lesser degree in the mandibular rami. Erythrocyte sedimentation velocity (ESV) was 55 mm in the first hour and C-reactive protein (CRP) was 80 mg/dl. Complete hemogram, urea, creatinine, coagulation test, urine I and radiography of the entire spine and long bones were all normal. The HLA-B27 antigen, anti-nuclear factor (ANF), rheumatoid factor (RF) assays were negative. Blood and urine cultures were also negative. The patient was treated with roxithromycin for three months. Despite the antibiotic therapy the patient evolved with periods of improvement and regression of the mandibular tumorization. In July 2000 indomethacin was suspended as the patient had been asymptomatic for more than a year and inflammatory tests were negative. In May 2001 the patient presented relapse, with pain and localized edema, requiring the reintroduction of indomethacin. She is currently asymptomatic, using indomethacin, has an ESV of 16 mm for the first hour and CRP is negative.

**Case 2**

White female patient, nine years and five months, presented high intensity pain and recurrent mandibular edema for three years. No fever, purulent secretion or local traumas. Odontological investigation did not uncover evidence of any oral abnormalities. In November of 2000, the patient was referred to the Mouth and Jaw Service. The initial physical examination found evidence of painful right side submandibular tumorization, without erythema and with no local heat; restricted ability to open the mouth and light edema on gums. The initial diagnostic hypothesis was osteomyelitis and aspiration puncture was performed and amoxacillin instigated. After three months of treatment, without clinical or laboratory improvement she was referred to the Children’s Institute and naproxen and amoxycillin were introduced. The latter was used for eight months, until ESV normalized. The patient evolved with bilateral enlargement of the mandible, painful to the touch and with restricted opening. Complementary examinations revealed ESV at 26 mm for the first hour, CRP 7.0 mg/dl. Complete hemogram, urea, creatinine, coagulation test, urine I and radiography of the thorax and long bones were all normal. Tests for HLA-B27 antigen, ANF and RF were negative as were blood and urine cultures. Computerized tomography of the mandible found thickening, sclerosis of the mandibular rami and a body with osteolytic, rounded area (ground-glass pattern), compatible with bone dysplasia. A diagnosis of CRMO was established and indomethacin and hyperbaric chamber (a total of 80 sessions) were introduced. In November of 2001 the patient presented with relapse (significant pain and increased mandibular volume). Examination by CT found bilateral volumetric enlargement of the mandible with an osteodysplasic aspect with light tumefaction of soft areas adjacent to bone cysts. The patient received prednisone for a month with improvement and once more presented relapse when it was suspended, with the use of rofecoxib 25 mg/day and methotrexate 20 mg/week becoming necessary. After two months the patient presented clinical improvement and currently ESV is at 32 mm for the first hour.

**Case 3**

White male patient, 10 years old, presented pustulosis palmoplantaris and diffuse bilateral mandibular enlargement from August 2000 onwards with pain, heat, fever and restricted mouth opening which improved after a non-hormonal antiinflammatory was used (diclofenac). He was referred to the Mouth and Jaw Service and Pediatric Rheumatology Unit in November 2001 because of recurrent pain. Complementary examinations revealed: CT with thickening, sclerosis of diffuse mandibular
osteitis areas (ground-glass appearance), compatible with bone dysplasia; mandible biopsy found evidence of chronic inflammatory processes and fibrosis. Bone scintigraphy found diffuse hyper deposition. Initial ESV was 50 mm for the first hour and CRP was 6.0 mg/dl. Panoramic radiography of the mandible found osteolytic lesions and cortical thickening. Complete hemogram and radiography of the whole spine and the long bones were normal. Assays for the HLA-B27 antigen, ANF and RF were negative. Blood and urine cultures were also negative. A diagnosis of CRMO was established and the patient was initially treated with prednisone for one month. The patient presented two relapses (January and February of 2002), and was maintained on 25 mg/day of rofecoxib. There is currently total regression of the tumorization. Panoramic mandible radiography shows improvement to the cortical thickening.

Discussion

Patients with chronic recurrent multifocal osteomyelitis CRMO present with an insidious onset involving heat and edema of soft tissues, restricted to one or more bones. Systemic manifestations including fever and weight loss habitually occur during the acute phase of the disease, as was the case with two of our patients. Effects are usually symmetrical and multifocal (there may only be one bone affected). Clinical course is intermittent with periods of remission and exacerbation. Lower limb bones are the most often affected 55%, followed by the axial skeleton pelvis in 55%, spine in 15%, thoracic wall in 13% and clavicle (8%). Rarely the disease can affect the mandible in isolation, and multiple lesions can occur, as were observed with our patients. Benedetta et al. described 260 pediatric patients with CRMO, and mandibles were involved in just 13 cases 5%.

Chronic recurrent multifocal osteomyelitis within the pediatric age group can be associated with a number of cutaneous manifestations: pustulosis palmpoplantar, diffuse pustulosis; psoriasis vulgaris; acne; SAPHO syndrome and pyoderma gangrenosum. Two of our patients presented pustulosis palmpoplantar. Test results ESV and CRP are elevated during the acute phase and normalize during remissions. Cultures are habitually negative for bacteria, fungi and mycobacteria, however, Propionibacterium acnes in bone aspirate may be associated with OCMR. Radiography shows osteolytic destruction in the metaphyseal regions of long bones, followed by progressive sclerosis. Bone scintigraphy is useful for detecting silent lesions, showing an increase in depositing in the affected areas. Nuclear magnetic resonance or computerized tomography, while not essential to diagnosis, are useful to show the extent of lesions and the involvement of joints and adjacent soft tissues.

Biopsies show that lesions are not septic and that this agent functions as a trigger for the immunological and inflammatory reactions; as was observed in case 1. Histopathological investigation of the bone lesions returns variable results. The initial lesion is characterized by the presence of neutrophils, and is classed as a pseudo-abscess. The chronic lesion has a predominance of lymphocytes with the occasional presence of plasmocytes, histiocytes and fibrosis.

Recent studies suggest the following criteria for a diagnosis of CRMO: a duration of more than three months; histological evidence of chronic bone inflammation, excluding other diseases and an absence of bacterial growth in cultures.

Some authors consider CRMO to be part of the spectrum of the SAPHO syndrome (synovitis, acne, pustulosis palmpoplantar, hyperostosis and osteitis). This acronym emphasizes the association between bone inflammation and cutaneous manifestations. An association is described between the SAPHO syndrome and spondylo-arthropathies and the HLA-B27 antigen. The prevalence of the HLA-B27 antigen is 9% among European pediatric patients with OCMR, particularly among pediatric patients with osteolytic lesions and cutaneous involvement. Our three patients did not present the HLA-B27 antigen.

Other authors define CRMO located exclusively in the mandible as diffuse sclerosing osteomyelitis of the mandible (DSOM). Due to the clinical, radiological, scintigraphic and histological similarities with the SAPHO syndrome the hypothesis that DSOM may be a localized manifestation of the same entity has been suggested.

The use of antimicrobial therapy with CRMO does not alter the course of the disease. Nonsteroidal anti-inflammatories (naproxen, indomethacin or aspirin) constitute initial treatment and a rapid course of corticosteroids is recommended in refractory cases. Nonsteroidal anti-inflammatories which inhibit the cyclooxygenase2, such as meloxicam, have been used with CRMO cases which do not respond to naproxen. Two of our patients received rofecoxib at a dosage of 0.6 mg/kg/day, following the dosage previously used for juvenile rheumatoid arthritis. Other treatments such as sulfasalazine, methotrexate and a hyperbaric chamber, are indicated in painful and refractory cases, as was the case with two of our patients.

The hyperbaric chamber or hyperbaric oxygenation is a safe and efficient procedure for cases of acute and chronic osteomyelitis and can be used with patients suffering intense pain and be maintained. Hyperbaric oxygen aids healing stimulating fibroblasts, and increasing the production of collagen and angiogenesis.

Prognosis is doubtful with CRMO which can present a prolonged and painful clinical course with intervals of inflammatory process activity and remission.
It is important that pediatricians recognize CRMO, and differentiate between it and acute osteomyelitis avoiding prolonged, unnecessary antibiotic therapy. The presence of recurrent or chronic (more than three months) painful mandibular tumorization alert us to the diagnosis. Scintigraphy, tomography or resonance are useful to identify osteolytic lesions. Biopsy is necessary in order to rule out bone tumors and infectious osteomyelitis. Initial treatment includes non-hormonal anti-inflammatories and/or corticosteroids. A hyperbaric chamber or methotrexate can be used in refractory cases with significant or prolonged pain.

References