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Isolated chronic nonbacterial osteomyelitis of the mandible: Favorable response to anti-TNF treatment

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Abstract

Chronic Nonbacterial Osteomyelitis (CNO) is an autoinflammatory bone disease affecting the long bones. Lesions may appear at any site in the skeleton, but isolated mandibular involvement is rare. This presentation is not well recognized in the dentistry literature. We present two patients with bilateral mandibular CNO. Both patients showed satisfactory response to tumor necrosis factor-alpha- blocking (TNF- α) therapy with etanercept. This report highlights the need of awareness of CNO as a differential diagnosis of the chronic mandible swelling and the effectiveness of biologic treatment.

Keywords

Chronic nonbacterial osteomyelitis; mandible; autoinflammatory; TNF- α inhibitor

Introduction

Chronic Nonbacterial Osteomyelitis (CNO) is a rare childhood sterile inflammatory osteitis classified among the autoinflammatory bone diseases. Typically, it characterized by an insidious onset of recurrent multiple painful swollen lesions affecting the metaphysis of long bones [1]. However, lesions may appear at any site in the skeleton. The mandible can be affected as part of multiple skeletal lesions, but isolated mandibular involvement is very rare [2]. The precise etiology and pathophysiology are poorly understood. However, several studies related the pathogenesis of autoinflammatory bone diseases including CNO to the imbalance between certain pro-inflammatory cytokines and anti-inflammatory cytokines; abnormal regulation of interleukin 1β (IL-1β) axis may be involved in pathophysiology [3]. Moreover, in a mouse model, tumor necrosis factor- α (TNF-α) has been implicated in the pathogenesis of bone resorption and inflammation [1,4]. However, how these cytokines imbalance led to bone resorption in CNO is still poorly understood and needs further investigations. Because of lack of diagnostic criteria, CNO remains a diagnosis

of exclusion. Imaging alone is not enough to make the diagnosis. Therefore, bone biopsy is mandatory to exclude other causes. Mandibular CNO can sometimes be misdiagnosed as bacterial osteomyelitis and treated unnecessarily with antibiotics. Other differential diagnosis comprise fibro-osseous lesions included ossifying fibroma and fibrous dysplasia, namely Cherubism and neoplastic disorders such as histiocytosis X and lymphoma. Different medications including non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids and bisphosphonates have been used for CNO treatment with good clinical response. However, a number of reports showed successful use of biologic agents in patients with partial response or refractory to other medications [5]. The available published data from Saudi Arabia about the clinical spectrum and the long-term follow-up of autoinflammatory bone diseases particularly; mandibular involvement is very limited.

In this report, we present two patients with bilateral mandibular CNO with a satisfactory response to TNF- œ inhibitors and highlight the need of awareness of CNO as a differential diagnosis of the chronic mandible swelling.

Case Report

Case I

A 14-year-old girl was referred to us at the age of 10 years because of a bilateral painful jaw swelling and limited mouth opening. She had intermittent exacerbation with a progressive course. There was no history of fever, systemic or cutaneous manifestations. She was evaluated by different specialties in different hospitals; her initial work-up revealed normal total Complete cell count (CBC) but elevated Erythrocyte Sedimentation Rate (ESR) 35mm/hr and C-reactive protein (CRP) (16 mg/L). Mandible X-ray and Computed Tomography (CT) revealed expansion of the mandibular body with cystic lesions, sclerosis and small foci of poorly defined lytic destruction with periosteal reaction at the condyle and proximal ramus associated with thickening of the masticator muscle, while magnetic resonance imaging (MRI) demonstrated bilateral patchy heterogeneous mandibular bone marrow signal alteration with enhancement suggesting osteomyelitis (Figure 1 and 2A). Bone scintigraphy revealed increased uptake only along both mandibles (Figure 3). She underwent a bone biopsy which revealed nonspecific chronic inflammatory changes with predominant lymphocytic infiltrates, some marrow edema and mild fibrosis. There was no evidence of neoplastic process. All bacterial cultures including tuberculosis were negative. Initially, she was managed as bacterial mandibular osteomyelitis, but a six weeks course of antibiotics and naproxen 250 mg twice daily failed to improve her symptoms. Few months later, she was seen at our institution, based on the clinical, laboratory including histopathology and negative culture and imaging findings, she was diagnosed as a case of mandibular CNO. She showed improvement on the initial treatment with oral prednisone (1mg/kg/ day) besides intravenous pamidronate (1 mg/kg/ dose, maximum 60 mg) every 3 months for six doses. However, she had reactivation of her disease with weaning of prednisone dose, so methotrexate (0.5 mg/kg/ week) and TNF- œ inhibitor therapy with etanercept (0.8 mg/kg/ week) were given with good response, pain and swelling disappeared. Few months later, methotrexate stopped and maintained on etanercept. Fortunately, she had sustained clinical remission and repeated CT and MRI showed significant improvement in the bone

size with minimal enhancement (Figure 2B).

Case II

A 13-year-old girl presented with a one-year history of an intermittent bilateral jaw swelling associated with pain and limited mouth opening. There was no history of fever or systemic manifestations. She was managed at other hospital with prolonged antibiotics without beneficial effects. Her investigations showed normal CBC with an elevated ESR (26 mm/hr) and CRP (12 mg/L). CT and MRI showed mandibular expansion and enhancement with heterogeneous signal intensity (Figure IV-A). Bone scintigraphy revealed increased uptake only along both mandibles. To exclude other causes, an open bone biopsy of the left mandible was obtained. Histopathology revealed chronic inflammation with lymphocytic cells infiltration and patchy fibrosis without evidence of malignant cells. All bacterial and fungal stains and cultures were negative. The diagnosis of CNO was then established, and she started on naproxen 250 mg twice daily and intravenous methylprednisolone (30 mg/kg/dose), followed by oral prednisone (1 mg/kg/day) and intravenous pamidronate (1 mg/kg/dose) every 3 months with clinical improvement. Unfortunately, her symptoms recurred; it was therefore introduced methotrexate (0.5 mg/kg/ week) and etanercept (0.8 mg/kg/week). Four months later, she showed significant improvement; pain disappeared and swelling regressed. Follow-up visits revealed sustained clinical improvement with normalized inflammatory markers and a significant improvement in CT and MRI of the mandible (Figure IV-B).

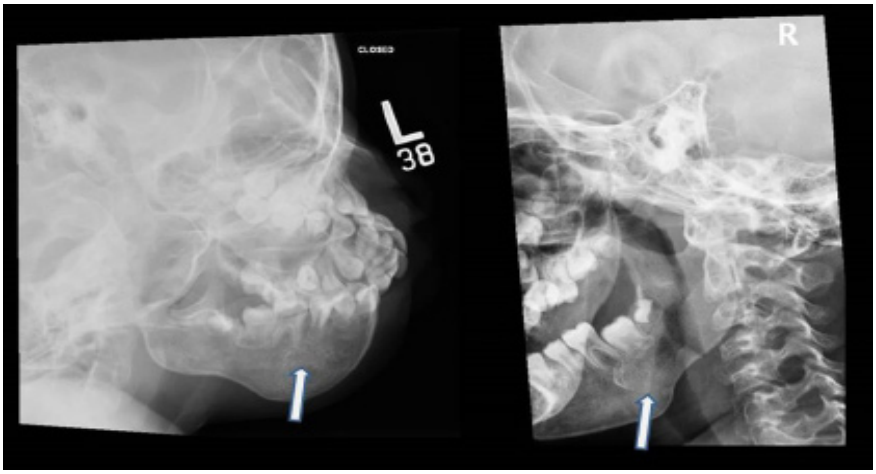

Figure 1: Bilateral Oblique mandible x-ray of case I showing heterogeneous patchy sclerotic and lytic expansive bone lesions.

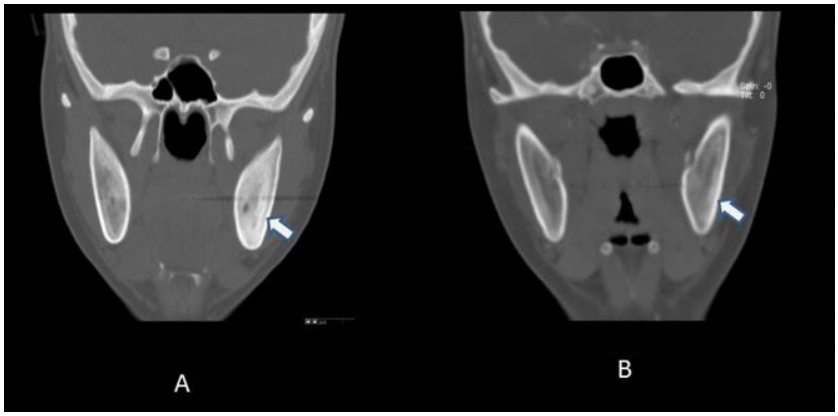

Figure 2: (**A**)Coronal reformatted CT mandible of case I showing the sclerotic thick mandible more on the left side with an area of periosteal reaction and cystic focus. **(B)** Six months after treatment CT mandible of case I, showing regression and improvement in the soft tissue and bone size.

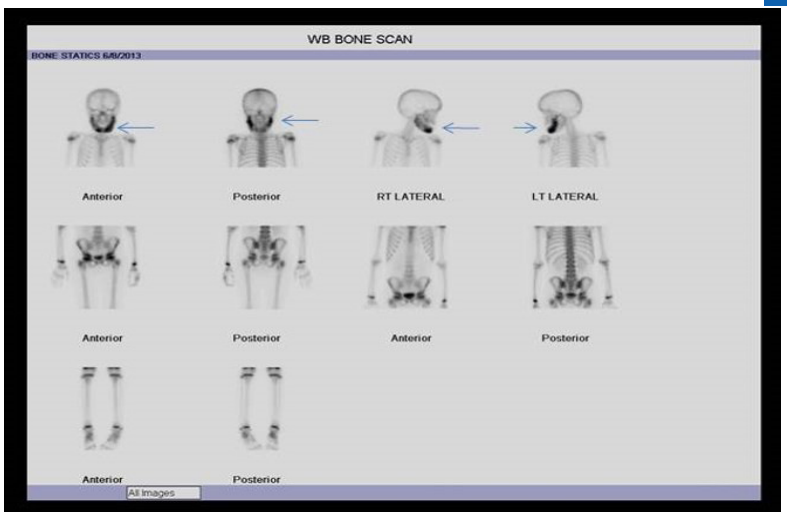

Figure 3: Delayed Bone scan of case I showing the patchy increased uptake of the radioactive materials only noted at the mandible.

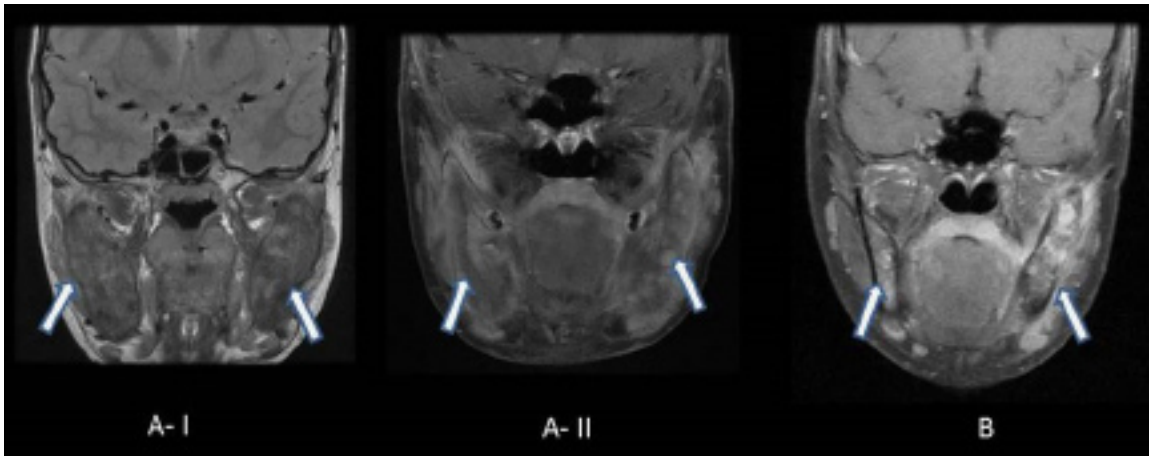

Figure 4 (A&B): (A-I) DCoronal Proton Density MRI of case II showing the expansive mandibular heterogeneous bone marrow; soft tissue lesions replacing the normal bone marrow with extra-osseous involvement and periosteal enhancement. **(A-II)** Coronal MRI T1 of case II with fat suppression post contrast (Dotarem) injection showing the heterogeneous bone and soft tissue enhancement with the periosteal reaction. **(B)** Four months after treatment, coronal MRI of case II showing improvement in the soft tissue and bone size.

Discussion

Autoinflammatory bone diseases including CNO are characterized by chronic sterile bone inflammation. The exact etiopathogenesis of CNO is unknown. However, sterile bone inflammation is the hallmark of CNO. The current pathophysiological understanding of CNO is based on a disturbed regulation of the innate immune system lead to imbalance of the pro-inflammatory cytokines expression, namely interleukin IL-1 and IL-6 and TNF- α and anti-inflammatory cytokines such as IL-10 and subsequent increased osteoclast activity and inflammatory cellular infiltration of the bone. CNO is regarded as a polygenic disease without definite gene variants linkage. However, certain genetic factors play a role in the disease's development; familial inherited cases of CNO have been described with specific gene mutations [6].

CNO present in childhood and adolescence with bone pain, localized swelling and warmth. It has been reported in association with systemic or cutaneous manifestation such as Crohn's disease, arthritis and psoriasis [7]. The clinical presentation is variable, ranging from focal lesion with mild and short disease

course to multifocal involvement with severe course and recurrent attacks. The isolated mandible CNO is a very rare inflammatory osteitis, which is characterized by recurrent attacks of unilateral or bilateral jaw pain and swelling, which may affect mouth opening and chewing [7,8]. Although imaging findings are nonspecific and not diagnostic, they are helpful in localizing the lesions and assessment of the surrounding soft tissue. Plain radiographs may be normal but may show findings such as radiolucency, sclerosis, osteolytic lesions or bone expansion as a consequence of chronic bone inflammation. However, MRI and CT with and without contrast are more sensitive during the early phases; bone edema, increased signal intensity and enhancement suggesting active lesions. In contrast, whole bone scintigraphy is important to rule out asymptomatic lesions. Bone biopsy is a crucial step to exclude other differential diagnosis such as malignancy and fibro-osseous lesions. Furthermore, nature and distribution of inflammatory cells either neutrophils or lymphocytes are correlated with the disease phase [9]. The diagnosis of CNO should be made based on the clinical manifestations, imaging findings, histopathology and microbial culture.

To date, there are no consensus treatment strategies for CNO because of lack of placebo controlled randomized trails. Currently, choosing the treatment depends on the location of the lesions and disease severity, different treatment options, including NSAIDs, glucocorticoids, bisphosphonates and immunosuppressive drugs have been used with good clinical response. However, occasionally, there is disassociation between the clinical and radiographic remission [6]. Most patients achieve symptom free status without vanishing the radiographic findings. Unfortunately, there is no cure for autoinflammatory bone diseases, and the complete remission rate is variable among the published data [7]. Knowing the cytokine profile imbalance namely, increased TNF production led to use of anti-TNF- œ agents in CNO patients with successful results [10]. Given the safety profile of anti-TNF- α agents in patients with juvenile idiopathic arthritis, these agents should be considered for patients with CNO involving critical sites such as vertebrae and mandible particularly, in patients who did not achieve clinical remission with previous treatment [10]. We presented two patients suffered painful swelling of both mandibles and significant limited mouth opening. There was no response to various antibiotics, but cyclic pamidronate and various anti-inflammatory medications including NSAIDs and systemic corticosteroids had shown only partial and transient improvement. Fortunately, they had favorable sustained response, with pain and swelling resolution with anti-TNF- α therapy. Because of lack of randomized placebo-controlled trails, the optimal therapeutic approach to the management of CNO remains unknown.

Our observation shows that isolated mandibular CNO may be overlooked. Early diagnosis, based on clinical presentation, imaging and histopathological findings are required to avoid prolonged antibiotic courses and potential complications. Furthermore, anti-TNF- œ therapy may be an effective therapeutic option in resistant cases of isolated mandibular CNO.

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