A Case of Osteomyelitis of the Mandibular Condyle Secondary to Bisphosphonate-related Osteonecrosis of the Jaw

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We present a case of osteomyelitis of the condyle secondary to bisphosphonate-related osteonecrosis of the jaw. A 77-year-old female was referred to our clinic with complaints of swelling in the left mandibular molar regions. The patient had been suffering from myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) associated vasculitis and had been treated with glucocorticoids for 8 years, and oral bisphosphonates had been prescribed to prevent osteopenia secondary to glucocorticoids. Imaging examinations showed radiolucency of the left mandibular body. Based on the diagnosis of osteomyelitis of the mandibular body secondary to bisphosphonate-related osteonecrosis, the patient received antimicrobial therapy and was well-healed. However, the patient returned 8 weeks later complaining of acute left preauricular swelling. Computed tomography showed the destructive changes in the mandibular condyle. We speculated that the infection was caused by the local spread from osteomyelitis of the left mandibular body. The risk of jaw necrosis related to antiresorptive therapy is well known. In recent years, the number of older patients being administered glucocorticoids with bisphosphonates has increased; therefore, we must be attentive to the signs of infectious diseases of the jawbone in the aging because it can easily shift to osteomyelitis or osteonecrosis and spread infection through the marrow.

Key words: osteomyelitis, osteoporosis, mandibular condyle, bisphosphonate-related osteonecrosis of the jaw (BRONJ), medication-related osteonecrosis of the jaw (MRONJ)

INTRODUCTION

Osteomyelitis, which is an inflammatory condition of the bone and bone marrow, is classified into 2 major categories by the presence of etiological factors: primary and secondary osteomyelitis. Primary osteomyelitis cases are those in which no apparent etiological factor can be found, while secondary osteomyelitis cases have apparent etiological factors, such as osteoradionecrosis, bacterial infection of odontogenic origin, or medication-related osteonecrosis in the oral and maxillofacial region [1]. In addition, the risk of secondary osteomyelitis increases by osteoporosis in the oral and maxillofacial region.

Osteoporosis is a skeletal disorder leading to bone fragility, particularly in post-menopausal women, older men, and patients taking glucocorticoids. Generally, osteoporosis increases the risk of fragility fractures, such as hip and vertebral fractures [2]. Osteoporosis also provides an entry point for bacterial infection and osteomyelitis in the jawbone.

Oral bisphosphonates are antiresorptive medications approved for the treatment of osteoporosis because of their ability to decrease the risk of osteoporotic fractures, while intravenous bisphosphonates are antiresorptive medications used to manage cancer-related conditions, including hypercalcemia of malignancy and skeletal-related events associated with bone metastases in the context of solid tumors. However, the risk of jaw necrosis related to antiresorptive therapy is well known [2].

In recent years, the number of older patients administered glucocorticoids with bisphosphonates has increased; therefore, we must be attentive to the signs of infectious disease of the maxillofacial bone in older patients because this can easily shift to osteomyelitis or osteonecrosis and spread infection through the bone marrow. In this study, we report a case of an older woman with osteomyelitis of the condyle secondary to bisphosphonate-related osteonecrosis of the jaw.

CASE REPORT

A 77-year-old female was referred to the Department of Oral and Maxillofacial Surgery, Tokai University School of Medicine, with complaints of swelling and pain in the left mandibular molar regions. At that time, she had a 4-week history of swelling, with exacerbation of pain in the prior 2 weeks. There was no swelling of the left cheek or restriction of the mouth opening upon physical examination. However, intraoral examination revealed gingival swelling in the left mandibular molar regions, and the extrusion of the left upper second premolar tooth, first and second molar teeth, with the loss of the left lower second premolar tooth, and the first and second molar teeth. The extruded teeth were biting the lower swelling gingiva with gingival fistulas (Fig. 1), and her oral hygiene condition was insufficient due to the poor oral

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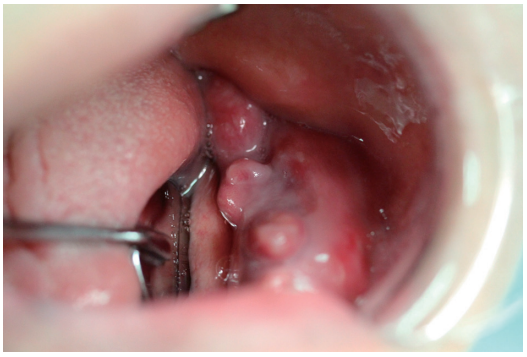

Fig. 1 An intraoral picture showing gingival swelling with fistulas in the left mandibular molar regions with the loss of the lower second premolar tooth and the first and second molar teeth.

hygiene maintenance including daily tooth brushing. A panoramic radiograph and computed tomography (CT) showed radiolucency of the left mandibular body of the lost teeth regions (Fig. 2A–C). The patient had been suffering from myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA) associated vasculitis with mild renal dysfunction (serum creatinine levels: 1.1–1.4 mg/dl) for 8 years. The therapy was initiated with high dosages of intravenously administered prednisolone (30 mg) for six consecutive days followed by oral prednisolone in tapering regimen (At the time, oral predninolone at 7 mg/day was administered), and oral bisphosphonates (alendronate sodium hydrate, 35 mg once weekly) had been prescribed for 28 months to prevent osteopenia secondary to glucocorticoids. The differential diagnosis at this time included osteomyelitis caused by bisphosphonate-related osteonecrosis, and neoplasm. Cytodiagnosis of discharge fluid from the gingival fistulas ruled out neoplasm. The result was Class II. Laboratory studies disclosed the following values: white blood cells (WBCs) were 10,300/ul, with a marked shift to the left; C-reactive protein (CRP) was 4.44 mg/ml. The laboratory tests frequently showed increases of the WBC levels due to MPO-ANCA associated vasculitis. However, CRP levels were higher than the range of the marker during the stable management of the MPO-ANCA associated vasculitis. The patient was finally diagnosed with infection followed by osteomyelitis of the mandibular body secondary to bisphosphonate-related osteonecrosis. We speculated that the infection was caused by the biting wound in the lower gingiva by the extruded teeth. The patient received a dental treatment to cut the extruded teeth because of avoiding the masticatory trauma to the lower gingiva and an empiric antimicrobial therapy and was given a 6-day course of cefcapene pivoxil hydrochloride hydrate (CFPN-PI). The oral bisphosphonates were stopped by her attending physician. The left mandibular molar regions were well-healed after the treatments.

The patient returned 8 weeks later, however, complaining of acute left preauricular pain, swelling, and trismus. Physical examination revealed extensive swelling in the left preauricular regions, and limited mouth opening of less than 20 mm. Oral pharyngeal examination was unremarkable. The CT scan of the patient's head showed a lytic lesion in the left condyle of the mandible. The lesion had destroyed the outer cortical plates of the condyle. In addition, left masseter enlargement was evident (Fig. 3A and B). Magnetic resonance imaging (MRI) confirmed the destroyed outer cortical plates of the condyle and the enlargement of the soft tissue at the outside of the left condyle head and the left masseter. The lesion including the bone marrow of the left condyle head was a high-intensity signal on T2-weighted images (Fig. 3C). A bone scan revealed the increased successive uptake from the region of the left mandibular body of the lost teeth to the left condylar process (Fig. 3D and E). The laboratory tests showed an increase in the WBC and CRP levels. The WBCs were 11,100/ul, and the CRP was 8.56 mg/ml. We speculated that the infection was caused by the local spread from an adjacent lesion, which was the left mandibular body of the lost teeth regions. The patient was diagnosed with infection followed by osteomyelitis of the condylar process secondary to the local spread from an adjacent bisphosphonate-related osteonecrosis. Intravenous antibiotics ceftriaxone sodium hydrate (CTRX) was initiated at a dosage of 1000 mg once daily for 3 days.

The patient was given a prescription for Minomycin, 100 mg 2 times daily for 2 months. Needle aspiration of the left preauricular abscess capsule was performed for drainage and to obtain a tissue culture, and minimal sanious fluid with viscosity was obtained (Fig. 4A and B). We confirmed the nonmalignant nature and Gram-positive rods in gram staining. However, the bacteria did not grow. We speculated that the non-growth of bacteria was caused by the administration of the antibiotics before the drainage. One week later, we extracted the left lower first premolar tooth with severe caries and periapical lesion because of suspicion of the source of infection. The left preauricular pain, swelling, and trismus improved and levels of WBC and CRP decreased (9,200/ul and 0.1 mg/ml, respectively) after the treatments.

The 9-month follow-up CT demonstrated full recovery of the lytic lesion in the left condyle of the mandible (Fig. 5). There has been no recurrence in the 12 months since the last treatments (Fig. 6).

DISCUSSION

In recent years, the risk of jaw necrosis related to antiresorptive or antiangiogenic therapy has been well known. Antiresorptive medications, such as bisphosphonates and denosumab, are administered for osteoporosis and malignancy patients, and inhibit osteoclast

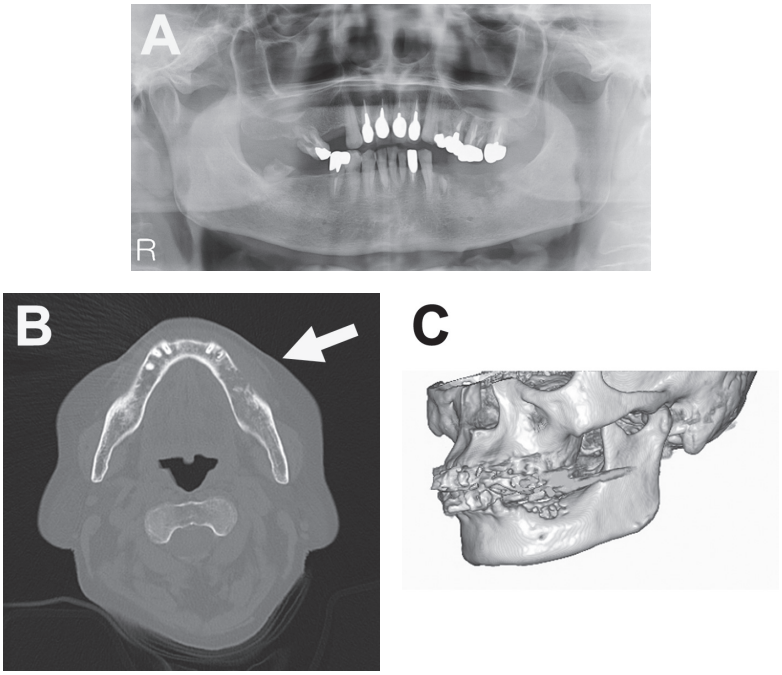

Fig. 2 **A)** A panoramic radiograph showing radiolucency of the left mandibular body of the loss of the lower second premolar tooth, first and second molar teeth. The extrusion of the left upper second premolar tooth, the first and second molar teeth, and the left lower first premolar tooth with the severe caries and periapical lesion. **B)** and **C)** CT and three-dimensional CT images showing radiolucency due to the destruction of the outer cortical plates of the left mandibular body (white arrow).

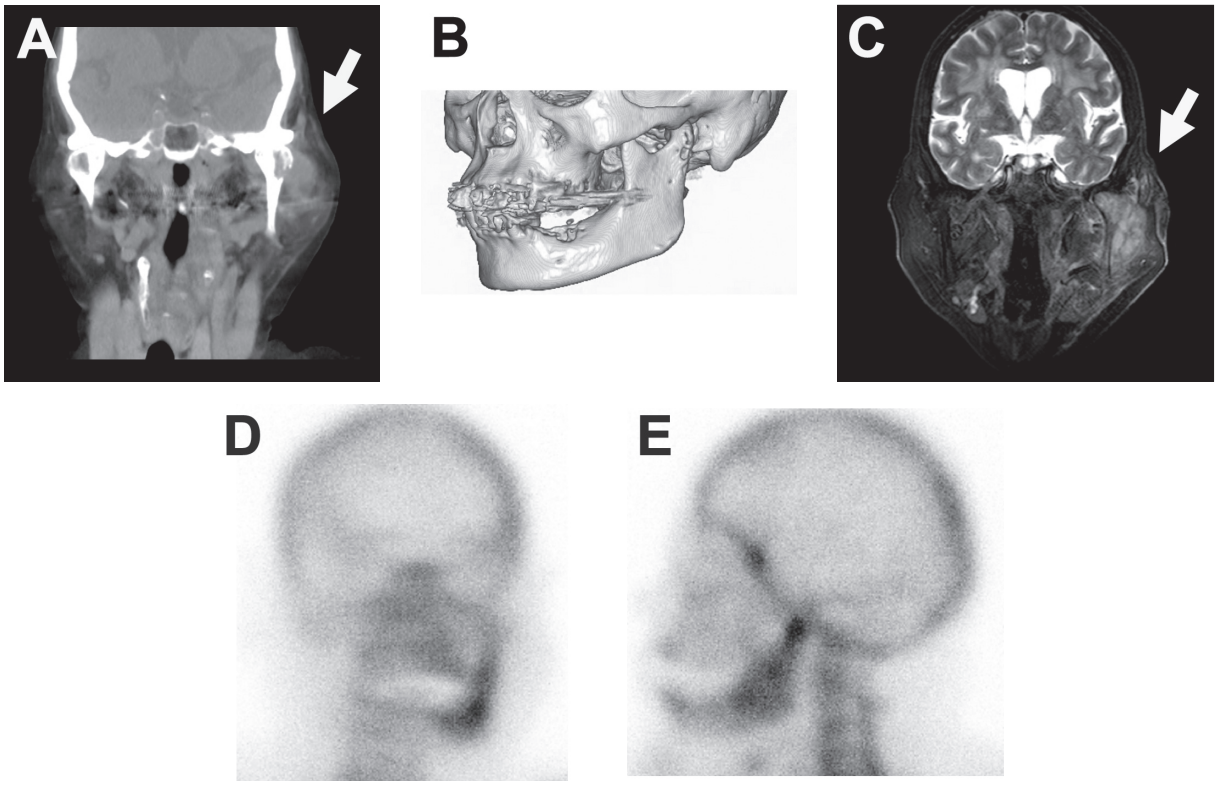

Fig. 3 **A)** and **B)** CT and 3-dimensional CT images showing radiolucency due to the destruction of the outer cortical plates of the left condyle and the left masseter enlargement (white arrow). **C)** Axial T2-weighted MRI showing a high-intensity signal at the bone marrow of the left condyle head. In addition, the MRI shows the destroyed outer cortical plates of the left condyle, the enlargement region of the soft tissue at the outside of the left condyle head, and the left masseter with a high-intensity signal (white arrow). **D)** and **E)** The bone scan showing the increased successive uptake from the region of the left mandibular body of the lost teeth to the left condylar process.

differentiation and function while increasing apoptosis, which leads to decreased bone resorption and remodeling [2]. By contrast, antiangiogenic medications, such as bevacizumab, are administered only for malignancy

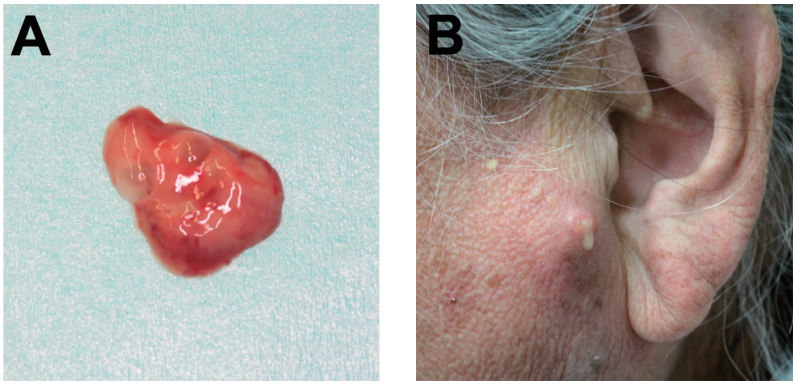

Fig. 4 **A)** The sanious fluid with viscosity obtained from the left preauricular abscess capsule by needle aspiration.
B) The lasting pus discharge from the left preauricular enlargement after needle aspiration.

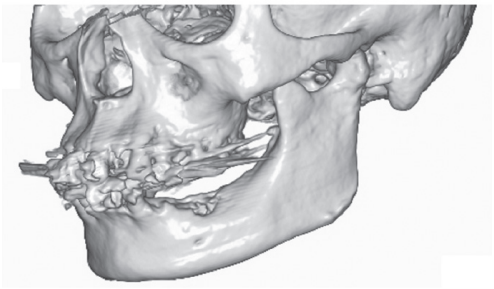

Fig. 5 The 9-month follow-up 3-dimensional CT images showing full recovery of the lytic lesion in the left condyle and partial recovery of the lytic lesion in the left mandibular body.

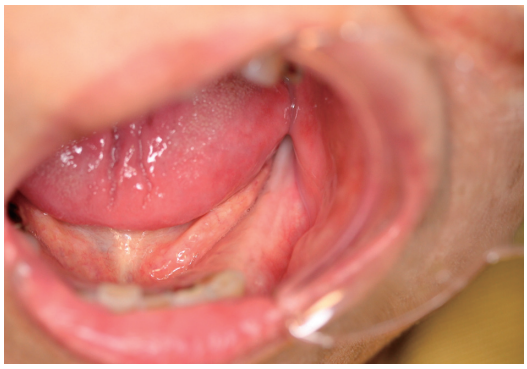

Fig. 6 An intraoral picture showing full recovery of the gingival swelling with fistulas in the left mandibular molar regions.

patients, and interfere with the formation of new blood vessels by binding to various signaling molecules, thus disrupting the angiogenesis-signaling cascade [3].

Medication-related osteonecrosis of the jaw (MRONJ) is defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS) as a condition characterized by exposure of bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for more than 8 weeks in a patient who has taken current or previous treatment with antiresorptive or antiangiogenic agents and who has no history of therapeutic radiation to the jaws [4]. Our case was diagnosed as MRONJ because of the condition characterized by exposure of bone that could be probed through the intraoral fistula in the mandibular region persisting for more than 8 weeks in the patient, who had recently received treatment with antiresorptive agents and who had no history of therapeutic radiation to the jaws.

Although the pathophysiology of the MRONJ has not been fully elucidated, proposed hypotheses that attempt to explain the unique localization of MRONJ exclusively to the jaws include altered bone remodeling or oversuppression of bone resorption, angiogenesis inhibition, constant microtrauma, suppression of innate or acquired immunity, vitamin D deficiency, soft tissue bisphosphonate toxicity, and inflammation or infection [5–8]. Inflammation or bacterial infection, in particular, has long been considered important components of MRONJ [4]. Moreover, there are various risk factors for MRONJ, such as aging, the duration of antiresorptive therapy, dentoalveolar surgery, and corticosteroid medications. Our case had several risk factors, such as bacterial infection in the left mandibular molar regions, aging, and corticosteroid medication. Therefore, our case was classified as high-risk for MRONJ.

The staging criteria of MRONJ are a set of 4 stages from 0 to 3, and the treatment strategy for each stage is suggested by the AAOMS. The clinical management of MRONJ is controversial [9]. It is currently still recommended that the management of MRONJ should be decided according to the stage of the disease; conservative treatment is preferred in the early stages without symptoms, while surgical management is preferred in cases of bone exposure with symptoms [9]. Conservative management includes the reinforcement of oral hygiene, periodic dental checks, oral rinses with chlorhexidine, and antibiotic treatment. In this regard, the most widely used antibiotics are amoxicillin, with or without clavulanic acid, clindamycin, azithromycin, and in some cases, a combination of metronidazole with beta lactams. In most of the studies, this approach

resulted in the stabilization of osteonecrosis or simply the improvement of symptoms [10]. In our case, at the time of the first medical examination, MRONJ was stage 2, which is defined as exposed and necrotic bone or fistulas that probe to bone associated with infection. We administered CFPN-PI, which is a third-generation cephalosporin, because it offers a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative bacteria [11]. CFPN-PI was effective, and pain, gingival swelling, and erythema abated. However, 8 weeks later, the patient's condition turned worse, becoming stage 3, which included osteolysis of the condyle head extending beyond the region of the alveolar bone with left masseter enlargement. At first, we intravenously administered ceftriaxone to cure the acute inflammation in the outpatient department. We selected the third-generation parenteral cephalosporin, which has a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative bacteria, because this made possible a once-daily dosage schedule by the long elimination half-life [12]. After improving the acute inflammation, we administered minocycline for 8 weeks. It was effective, and the left preauricular pain, swelling, and trismus improved. Nine months later, CT scans demonstrated a full recovery of the lytic lesion in the left condyle of the mandible. Minocycline is a semisynthetic, broad-spectrum, second-generation tetracycline antibiotic. The bacteriostatic activity of tetracycline antibiotics results from binding to the bacterial 30S ribosomal subunit, thus inhibiting protein synthesis [13, 14]. Minocycline also has good tissue penetrance, including biofilms, because it is a lipid-soluble drug. Moreover, the MIC for the anaerobic bacterium of the odontogenic infection is low. Therefore, minocycline is suitable for the dosage to osteomyelitis and osteonecrosis in the maxillofacial bone [14]. The most common adverse events of minocycline are gastrointestinal symptoms and central nervous system effects, such as dizziness and vertigo. In our case, there were no adverse events. Another adverse event is staining of the permanent dentition, which occurs during tooth development, between the ages of 4 months and 12 years. Therefore, its administration to infants and pregnant women should be avoided [15].

Osteomyelitis of the condylar process is a rare disease. Local spread from an adjacent lesion, trauma, or blood-borne infection is reported to be the cause of osteomyelitis of the condylar process [16]. In our case, local spread from the mandibular osteomyelitis secondary to bisphosphonate-related osteonecrosis of the jaw in the molar region was suspected as the source of the infection because of increasing successive uptake from the region of the left mandibular body of the lost teeth to the left condylar process on the bone scan and the absorption of the bone marrow from the left mandibular body to the condyle head on the CT scan. In addition, osteoporosis due to aging and glucocorticoid medication promoted the spread of infection to the marrow.

In recent years, the number of older patients administered glucocorticoids with bisphosphonates or denosumab has increased; therefore, we must be attentive to the possible signs of infectious disease of the maxillofacial bone in such older patients because it can easily shift to osteomyelitis or osteonecrosis and spread the infection through the marrow.

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