



[Case Report]

A case of intractable medication-associated osteonecrosis of the jaw complicated by cervical abscess and sepsis

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Abstract

[Background] Osteonecrosis of the jaw (ONJ) induced by bone resorption inhibitors is termed medication-related ONJ (MRONJ). Some papers have reported that bisphosphonates can cause MRONJ complicated by infections. However, there are few case reports of MRONJ associated with denosumab, and the detailed clinical course is unknown. This case report presents a case of MRONJ caused by bisphosphonate and denosumab, which was complicated by cervical abscess and sepsis.

[Case report] A 70-year-old woman was previously diagnosed with lung cancer with bone metastasis. Denosumab was subsequently administered along with a course of chemotherapy and radiation therapy for the cancer. Two years later, she developed ONJ on the right side, possibly due to denosumab, and treatment was initiated with irrigation and antibiotic administration. Despite continuous irrigation and antibiotic administration, she developed a cervical abscess with surrounding cellulitis and sepsis. The patient was immediately admitted for intensive care. The cervical abscess was surgically drained, and tracheostomy and artificial ventilation were performed due to the risk of airway obstruction after the cervical surgery. Antibiotic treatment was also continued. The patient recovered after intensive multidisciplinary treatments and was discharged 43 days after her hospitalization. No recurrence of the abscess was observed over the following 6 months with continual oral cleaning.

[Conclusion] MRONJ can be complicated with potentially fatal infections around the soft

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tissue and other regions around the jaw. Early diagnosis, appropriate management, and careful follow-up are necessary and should be conducted by a multidisciplinary team, including dentists.

Key words: abscess, bisphosphonate-associated osteonecrosis of the jaw, osteonecrosis, sepsis, case report

I . Introduction

Osteonecrosis of the jaw (ONJ) induced by bone resorption inhibitors is termed medication-related ONJ (MRONJ). It has been widely known that bisphosphonates can cause ONJ[1], and recent studies have also reported that another anti-resorptive agent, denosumab, is associated with ONJ development at a similar rate[2]. Denosumab is a human monoclonal antibody directed against the receptor activator of nuclear factor kappa B ligand (RANKL). It is widely used in patients with bone lesions due to osteoporosis, multiple myeloma, and solid tumor metastasis[3]. In Japan, denosumab has been widely used since 2011. Controlled trials conducted among patients with cancer have documented MRONJ in 1.3% and 1.8% of patients receiving bisphosphonate and denosumab, respectively [4]. There have been some reports of ONJ-induced infections caused by denosumab[5,6]. However, these have only been shown in results and tables in clinical trials and retrospective studies, and the detailed clinical course is unknown. This case report presents a case of MRONJ caused by bisphosphonate and denosumab, which was complicated by cervical abscess and sepsis.

II . Case

A 70-year-old woman presented to Chiba University Hospital complaining of dyspnea, redness, swelling, and pain around the right mandible. The patient first noticed these symptoms on the same morning. Four years prior, she was diagnosed with lung cancer of the left lower lobe with bone metastasis to the seventh cervical vertebra. The patient underwent simultaneous radiation therapy to the seventh cervical vertebra, avoiding the mandible area, and a course of chemotherapy with bisphosphonates (4 mg/month) for lung cancer, without

a dental consultation at the time of bisphosphonate-administration. After continued treatment with bisphosphonate for 10 months, the patient began monthly treatment of denosumab (120 mg/month). Eighteen months after the initiation of denosumab, she presented with right jaw pain and was referred to the dentist on suspicion of ONJ. Although she had swelling of the right lower jaw and showed bone exposure of the right jaw in the mouth, pantomography and computed tomography (CT) showed no sequestrum and abscess on the lower jaw, and she was diagnosed with stage 2 ONJ. Subsequently, dental procedures, including rinsing and administration of antimicrobials such as cefcapene pivoxil, levofloxacin, clarithromycin, and amoxicillin were performed. Although she underwent a crown removal one year after diagnosis of ONJ, her symptoms and CT findings showed no exacerbation after crown removal. Four months before presenting to the hospital, osimertinib was started as a sixth-line chemotherapy; however, it was discontinued 1 month before her hospitalization because of possible drug-induced interstitial pneumonia. Oral prednisolone (30 mg/day) was then administered for a week. Until hospitalization, administration of denosumab continued for 40 total months of treatment. She had no other relevant medical history and no prior use of bisphosphonates prior to her lung cancer diagnosis. Although she had undergone extraction of a tooth before the diagnosis of lung cancer, previous detailed history of dental treatment was unknown. However, she did not undergo extractions or dental procedures other than the crown removal after diagnosis of lung cancer. The patient was a social drinker but had no history of smoking.

Upon presentation to the hospital, the patient was immediately admitted for intensive care. Her weight and height were 49 kg and 155 cm respectively, and vital signs were as follows: Glasgow coma scale

score 15 (E4V5M6), blood pressure 82/47 mmHg, pulse rate 80 beats/minute, pulse oximetry 96% in room air, respiratory rate 22 breaths/minute, and body temperature 36.5 °C. Her quick sepsis-related organ failure assessment (qSOFA) score was 2 (respiratory rate ≥ 22 breaths/minute and systolic blood pressure ≤ 100 mmHg). Physical examination revealed swelling, redness, and pain in the right jaw, as well as bone exposure and discharge of pus from the right mandible in the oral cavity. Blood tests revealed inflammatory findings (white cell count $11.3 \times 10^4/\mu\text{L}$, C-reactive protein 3.10 mg/dL, and procalcitonin 1.57 ng/mL), and renal injury (blood urea nitrogen 24 mg/dL and creatinine 1.14 mg/dL). CT and chest radiography demonstrated the presence of lung cancer (which had

not worsened since the prior month) in the left lower lung and bilateral ground-glass opacity in the lung field. Cervical CT showed a low absorption area around the right lower jaw, with an abscess extending from the necrotic area (Fig. 1). In addition, inflammation of the soft tissue extended from the abscess to the periphery of the trachea, leading to narrowing of the airway (Fig. 1). CT of the bone showed a high-signal area in the right mandible, suggesting osteonecrosis of the jaw. Bronchoscopy showed that the pharynx and larynx were reddish, swollen, and narrowed due to the presence of purulent sputum (Fig. 2). Based on the results of these examinations, the patient was diagnosed with a cervical abscess and cellulitis around her right jaw and neck, as well as sepsis.

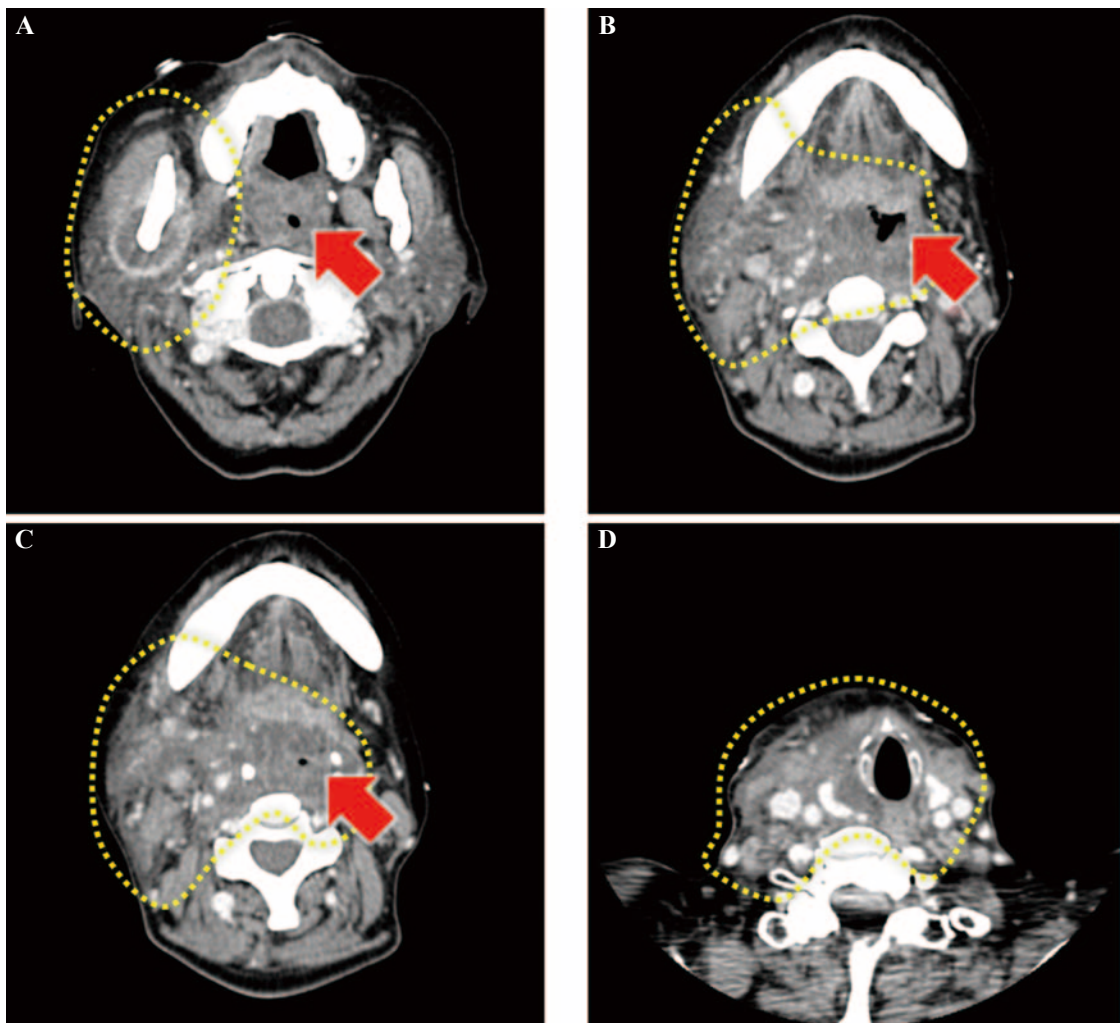


Fig. 1 Computed tomography of the neck on admission. Neck computed tomography revealed a low-absorption area around the right mandible and an abscess spreading from the osteonecrosis lesion. Moreover, inflammation of the soft tissue extended from the abscess to the periphery of the trachea (dotted area in A, B, C, D), and airway stenosis was observed (arrow in A, B, C).

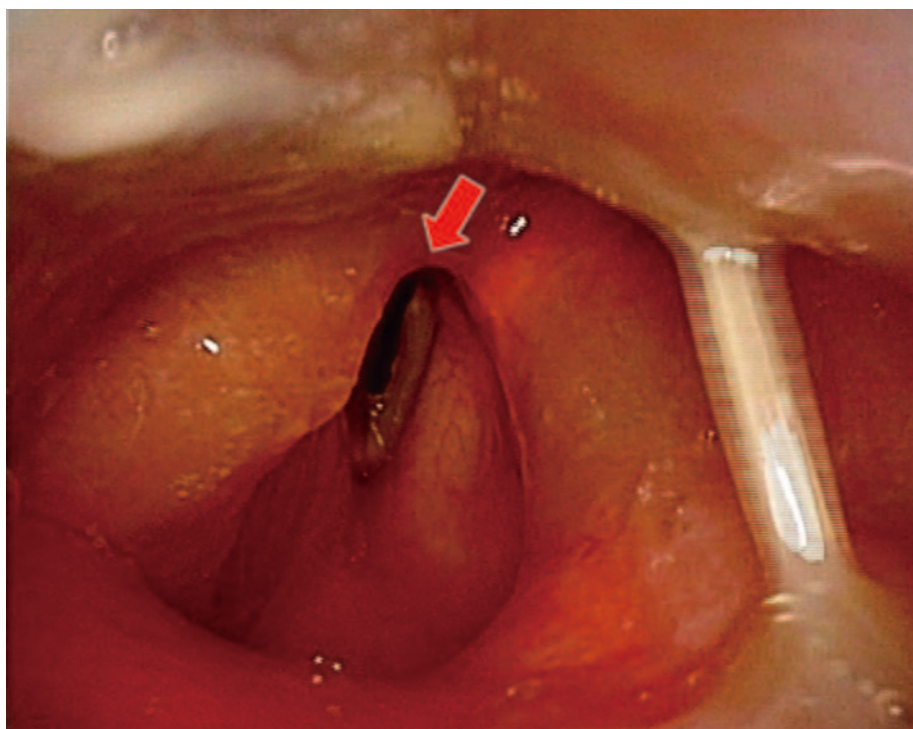


Fig. 2 Bronchoscopy on admission. Bronchoscopy showed that the pharynx and larynx were reddish and swollen, as well as narrowed due to the presence of purulent sputum.

Soon after hospital admittance, the patient's systolic blood pressure decreased to 70 mmHg, indicating septic shock. Therefore, large volume fluid replacement and noradrenaline infusion were initiated. At the same time, a total of five drain tubes were inserted into the lesions, draining grey pus with a foul odor from the cervical abscess (Fig. 3). *Streptococcus spp.*, *Staphylococcus spp.*, *Parvimonas micra*, and *Prevotella disiens* were cultured from the pus and therefore were considered to be the bacterial species that had originated from the ONJ and the oral cavity. A tracheostomy and artificial ventilation were performed due to the risk of airway obstruction after the cervical surgery, and prednisolone was tapered to discontinuation. Local cleaning was then performed. Antibiotics (cefepime 2 g given intravenously every 12 hours for 20 days and clindamycin 1200 mg given intravenously every 12 hours for 20 days) were also initiated. Since the patient's fever and right lower jaw swelling subsided after the intensive treatments, the drain tubes were removed on day 25. She was removed from artificial ventilation on day 34 and finally discharged on day 43, following the discontinuation of denosumab and chemotherapy

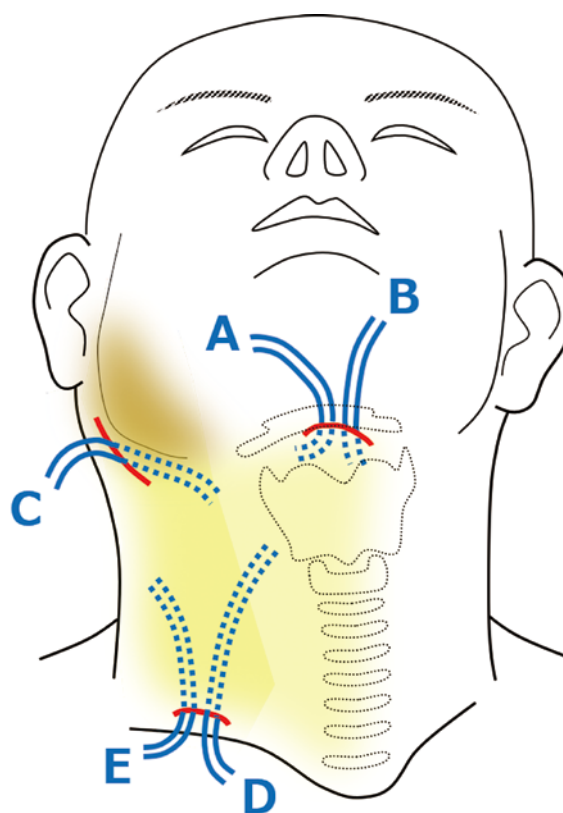


Fig. 3 Schema of lesion incision and drainage. Three incisions were made (red lines), and grayish-white pus with a foul odor was drained. Five drains were inserted into the incisions at the right side of the neck (A to E).

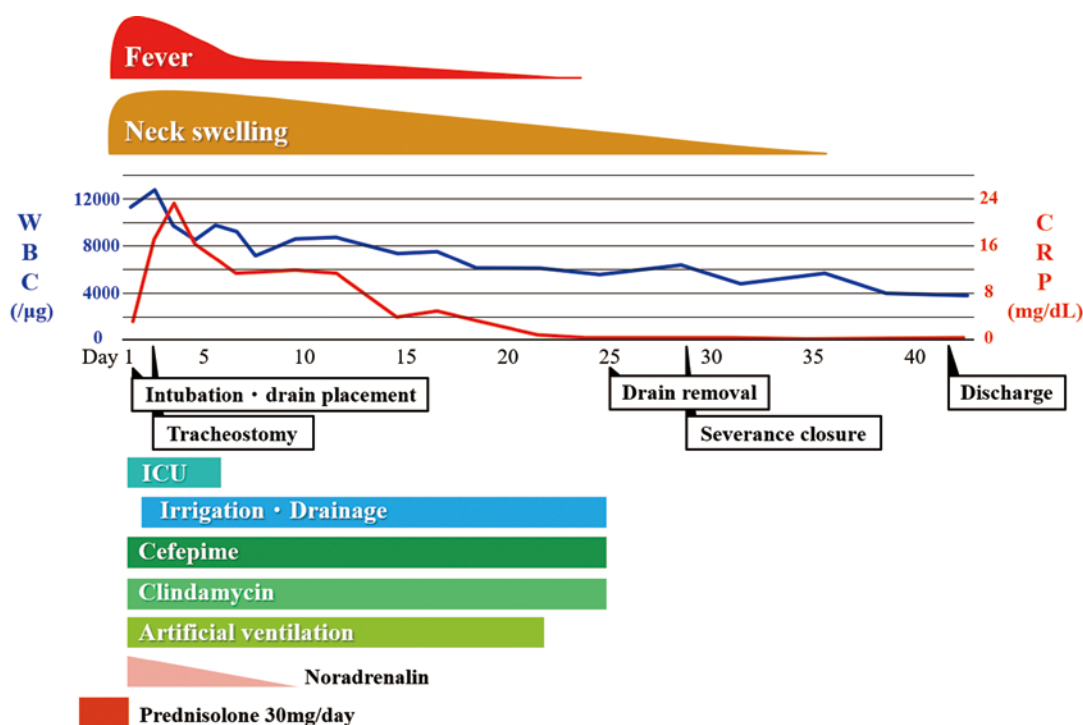


Fig. 4 Clinical course of the patient. Even after incisions were made for lesion drainage, a tracheostomy and ventilator management were performed due to the risk of airway obstruction. Prednisolone (30 mg/day) was simultaneously discontinued, and local cleaning and antibiotics were initiated. Fever and swelling of the lower right jaw reduced gradually with improvement of the inflammatory response, and noradrenalin was tapered to discontinuation. The patient had recovered enough to be transferred to a general ward; drain tubes were removed, and antibiotic administration was discontinued. No further relapse was observed, and the patient was discharged on day 43. CRP, C-reactive protein; ICU, intensive care unit; WBC, white blood cell

for the lung cancer (Fig. 4). The patient continued dental follow-up after discharge from the hospital. With continued oral cleaning with benzethonium chloride or povidone iodine, jaw pain persisted, but no drainage or swelling of the jaw and no recurrence of the abscess were observed. Six months later, the patient died due to respiratory failure secondary to lung cancer progression, which is unlikely to be associated with MRONJ.

The patient's husband provided informed consent to include the patient's information in this case report.

III. Discussion

Two clinical findings in this case report were noteworthy. Firstly, MRONJ caused by bisphosphonates and denosumab can cause an infection in the soft tissue and other regions around the jaw. Secondly, these complicating infections may be serious, potentially fatal, and result in sepsis; therefore, early diagnosis and appropriate therapeutic intervention are essential.

MRONJ is rarely complicated by infections such as brain and neck abscesses and necrotizing fasciitis. In the present case, the patient had been previously diagnosed with metastatic lung cancer and subsequently developed ONJ due to bisphosphonate and denosumab and complicating infection, which required multidisciplinary treatment. Denosumab suppresses the function of the molecule RANKL, which is essential for osteoclast differentiation and function, thus inhibiting resorption through suppression of osteoclast differentiation, function, and survival. As a result, it may cause a decrease in bone turnover and ONJ[3]. The frequency of infectious adverse events associated with denosumab and bisphosphonate administration has been reported to be 11.6% and 10.9%, respectively[2]. However, the rate of serious infection around the jaw complicated with MRONJ is unknown. The majority of the etiological agents are reported to be resident oral bacteria, which spread to the surrounding tissues of the jaw through the MRONJ lesion[7-13]. Serious infections that require

intensive care may result, despite dental intervention, and can sometimes be fatal[14-17]. In this case, resident oral bacteria were detected in the cervical cavity, and it is believed that the infection was transmitted from the oral cavity. Although the abscess and sepsis progressed rapidly in this patient, she was effectively treated by multidisciplinary treatments, including dental intervention. Indeed, this case report represents only one case, and the clinical course could not apply to all cases with serious infection-related MRONJ. However, collaboration with dentists may be required prior to the onset of MRONJ. Furthermore, patients should be educated that if mandible pain worsens, seeking immediate medical care is important for early detection. A high level of vigilance is required to monitor infectious complications after appropriate management to prevent potential morbidity in immunocompromised patients, such as the patient in this case report.

In Japan, clinicians adhere to a position paper on ONJ[18] based on international consensus[19], in which the severity of ONJ is classified from stage 0 to 3 according to the clinical symptoms and imaging results, and treatment recommendations are categorized depending on the severity. Risk factors for MRONJ include cancer-bearing status, chemotherapy and steroid administration, smoking, and the coexistence of cardiovascular disease and diabetes[20]. In addition, local risk factors include tooth extraction, periodontal disease, surgery, trauma, and poor oral hygiene[20]. Nevertheless, risks predisposing patients to complicating infections of the surrounding tissues of the jaw remain unclear. The present case was associated with the risks of developing MRONJ (i.e., cancer-bearing status and radiation therapy, and no dental consultation at the time of the administration of bisphosphonate); however, there were no apparent risks of complicating serious infection, except for a short-term (1 week) administration of steroids. In this case, a dental consultation before bisphosphonate and steroid-administration was imperative. It is essential to prevent ONJ by collaborating with dentists even before administering bisphosphonate. Although the risk of developing infectious diseases does not increase in

patients with a daily dose of <10 mg or a cumulative dose of <700 mg of prednisone[21], it is possible that 30 mg/day steroid may increase the risk of infection for patients with ONJ. Even if drug-induced pneumonia is suspected and if the patient's respiratory status has been maintained, a careful follow-up without steroids could be considered. Even if steroid administration is necessary, it should be done cautiously and only after a dental referral. Therefore, it is necessary to recognize the possibility of infection in all cases of MRONJ. Early diagnosis, appropriate management, and careful follow-up are necessary and should be conducted in cooperation with dentists.

Although MRONJ has not been described in association with epidermal growth factor receptor (EGFR) kinase inhibitors, Chandra et al. reported that EGFR signaling is critical for osteoprogenitor maintenance and new bone formation[22]. Furthermore, a case report has highlighted the possible association of osimertinib treatment with MRONJ[23]. We cannot prove the involvement of osimertinib in the exacerbation of MRONJ in the present case, because steroids were also administered to the patient. Therefore, more such cases need to be investigated to evaluate the potential risk of EGFR tyrosine kinase inhibitors, including osimertinib, causing exacerbations and infections in patients with MRONJ.

IV. Conclusions

In conclusion, even with proper management of MRONJ, complicating infections can progress rapidly and be life-threatening. However, lifesaving is possible if appropriate multidisciplinary treatments, including dental intervention, are implemented. Therefore, increased vigilance for early detection and treatment is required, even after appropriate dental intervention. Patients must also be educated to seek appropriate medical care for early detection.

Contributors

IO, KS, HK contributed to the conception of

study design, analysis of case, data interpretation, and the writing of the manuscript. KK contributed to the conception of analysis of case and data interpretation. TK, AK, SI, and TS contributed to acquisition of data. HT and KT contributed to the conception of the study design and data interpretation. All authors read and approved the final manuscript.

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Conflicts of interest

The authors report no conflicts of interest.

Ethical approval

Informed consent was obtained from patient's family. This is not human research. This is not animal research.

Data availability

No additional data.

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