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CASE REPORT

Medication-related osteonecrosis of the jaws caused lethal sepsis in an edentulous patient with multiple systemic factors

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Key Clinical Message

Medication-related osteonecrosis of the jaw (MRONJ) is developed even in the patients who are edentulous and treated with short-term bisphosphonate therapy and oral administration. It sometimes causes lethal sepsis in patients who have multiple health problems such as diabetes, cirrhosis, steroid use for interstitial pneumonia, sepsis, and spinal disk herniation.

Keywords

Antiangiogenic medications, antiresorptive agents, bisphosphonate, bisphosphonate-related osteonecrosis of the jaw, medication-related osteonecrosis of the jaw, systemic factors.

Introduction

Bisphosphonates are the most commonly prescribed drugs for osteoporosis treatment [1]. They are also used to treat multiple myeloma, bone metastases, and calcium disorders [2]. These patients reportedly often develop bisphosphonate-related osteonecrosis of the jaw (BRONJ) that is caused by subsequent dental surgery [3, 4]. In general, it is thought that nitrogen-containing bisphosphonates are much high risk of osteonecrosis than nitrogen not-containing bisphosphonates. It is also thought that intravenous bisphosphonates are much high risk than oral bisphosphonates. Thus, medications for cancer, such as Zoledronate (Zometa®), are thought to have much high risk of osteonecrosis than medications for osteoporosis, such as Alendronate (Bonalon®) [5]. In addition, it is considered that long-term bisphosphonates therapy tends to cause osteonecrosis. Besides bisphosphonates, other antiresorptive agents such as denosumab and antiangiogenic medications also cause osteonecrosis [6]. Thus, the American Association of Oral and Maxillofacial Surgeons position paper published in 2014 and the committee recommended changing the nomenclature of BRONJ to the term "medication-related osteonecrosis of the jaw" (MRONJ) to accommodate the growing number of jaw osteonecrosis cases associated with other antiresorptive and antiangiogenic therapies [7]. According to the position paper, there are three categories of risk factors for MRONJ: (1) medication-related risk factors (e.g., bisphosphonate use), (2) local factors (e.g., dental surgery), and (3) demographic and systemic factors and other medication factors.

In this case report, the patient developed MRONJ and died of sepsis, although he received short-term oral bisphosphonate therapy and had not received any dental surgical treatment because he was completely edentulous. However, he had many systemic factors such as diabetes, cirrhosis, and steroid use for interstitial pneumonia. The presence of multiple systemic factors can be a very high risk for MRONJ, even though there are few medication-related factors and local factors [8–10].

Case Report

The patient was a 59-year-old man with a history of smoking and drinking, insulin use for diabetes, cirrhosis associated with chronic hepatitis C, steroid use for interstitial pneumonia, sepsis, and spinal disk herniation. This study was conducted according to the guidelines of Hiroshima City Hiroshima Citizens Hospital, and a written informed consent was obtained from this patient. He was suddenly hospitalized with interstitial pneumonia. At that time of admission, white blood cell count (WBC) was 7800/μL and C-reactive protein (CRP) level was 15.523 mg/L. He was treated for 2 months before developing MRONJ. During the treatment period, he was treated with intravenous steroids (i.e., methylprednisolone sodium succinate 1000 mg/day for 3 days, prednisolone sodium succinate 20 mg twice daily for 4 days, and methylprednisolone sodium succinate 1000 mg/day for 3 days). This regimen was followed by oral steroids (i.e., prednisolone 60 mg/day for 2 months). To prevent steroid-induced osteoporosis, he was treated with oral bisphosphonate (i.e., alendronate 35 mg/week for 7 weeks). However, the administration of these drugs was stopped because of a right buccal space infection. A physician consulted us and referred the patient to our department. The patient had severe swelling from the right buccal area to the infraorbital region, hypesthesia, and tenderness, but no spontaneous pain (Fig. 1A). He was edentulous and usually used complete dentures. There were ulcerations and exposed bone on the alveolar part of the right incisor and molar (Fig. 1B and C). A pus discharge was observed in that area. The orthopantomogram did not show any bone resorption on the right mandible (Fig. 2A). Computer tomography (CT) scanning with a radio-contrast agent showed swelling in the right buccal area, but showed no mandibular bone resorption (Fig. 2B). Magnetic resonance imaging (MRI) demonstrated an abnormal signal (e.g., low signal on T1-weighted [T1W1] MRI and high signal on T2-weighted [T2W1] MRI) in the bone marrow of the right mandibular angle (Fig. 2C), which suggested the presence of osteomyelitis in that area. Multiple-drug-resistant *Enterococcus faecalis* was detected by bacteriological identification (Table 1). Based on these results, the patient was diagnosed as having right mandibular cellulitis, sepsis, and disseminated intravascular coagulation (DIC). Treatment was started. We administered intravenous antibiotic treatment and irrigated part of the exposed bone with povidone–iodine every weekday. At 3 days after the first visit, sequestrectomy and drainage were administered

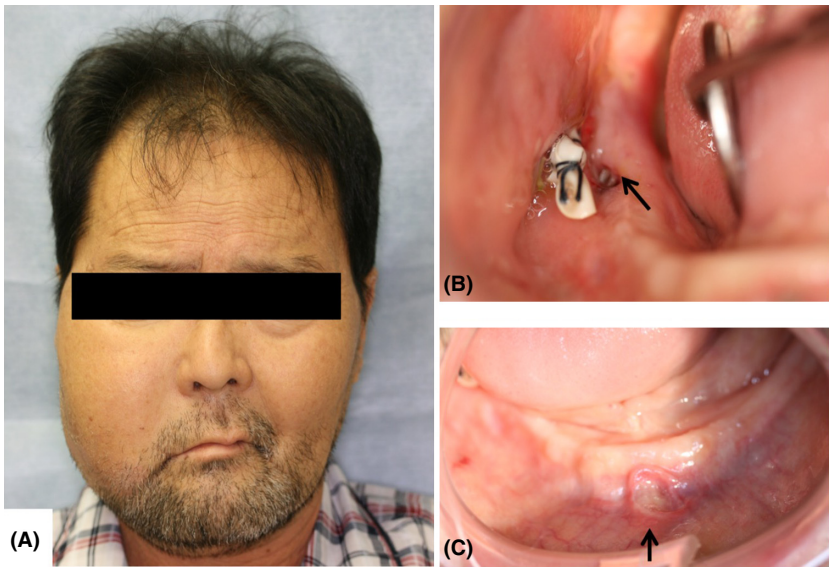

Figure 1. (A) Severe swelling from the right buccal area to the infraorbital region. (B) Bisphosphonate-related exposed necrotic bone in the right posterior mandibular (during drainage). (C) Exposed bone on the alveolar part of the right incisor.

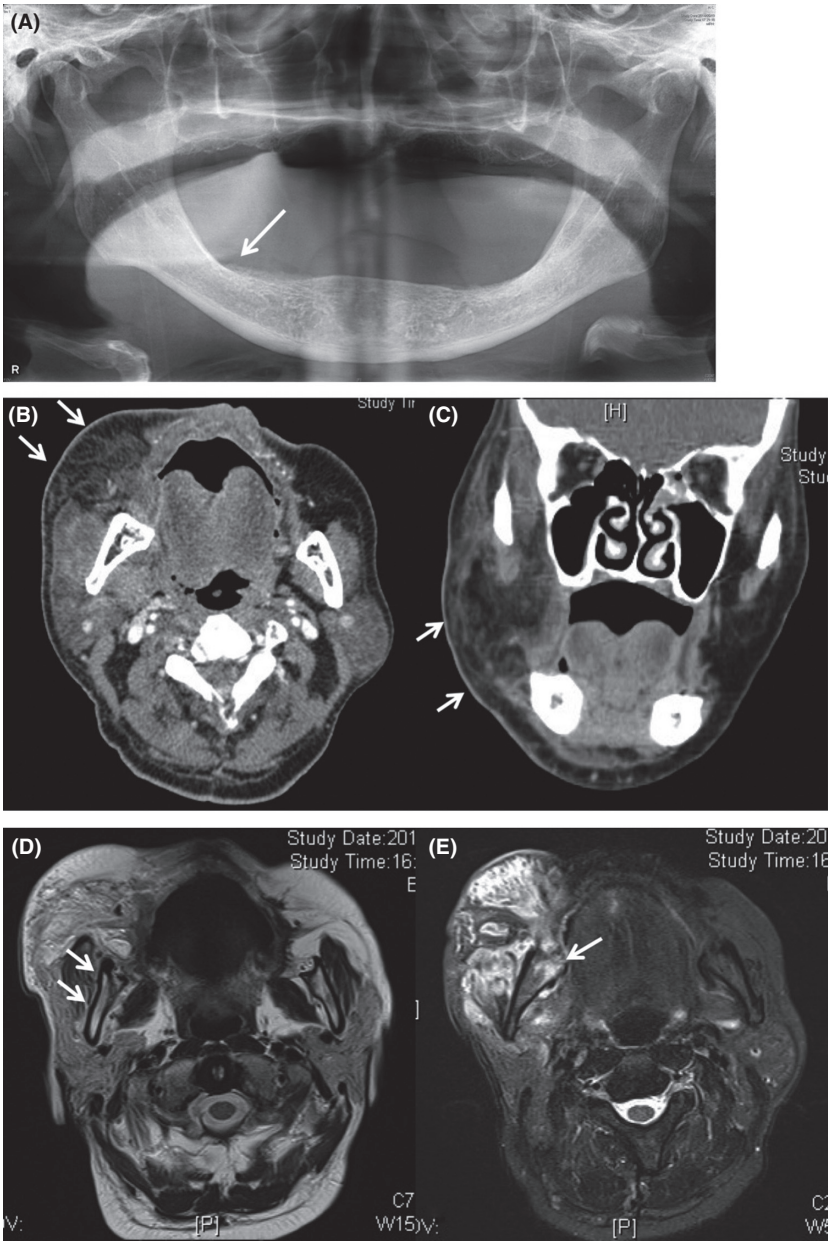

Figure 2. (A) No bone resorption is present on the right part of the mandibula in orthopantomogram analysis. (B, C) Right buccal swelling is apparent, but there is no bone resorption of the mandibula, based on computer tomography (CT) analysis. (D, E) Abnormal signal (i.e., a low signal on T1-weighted imaging [TIWI] and a high signal on T2-weighted imaging [T2W1]) of the bone marrow on the right angle part of the mandibula.

(Fig. 1B). The pathologic findings showed extracted bone-like sequestrum. During the treatment, the patient developed acute inflammation. Therefore, we changed the antibiotics from meropenem hydrate (Meropen; Sumitomo Dainippon Pharma Co., Ltd., Osaka, Japan) alone to meropenem hydrate and ampicillin/sulbactam (Unasyn S; Pfizer Inc., New York, USA) (Fig. 3). One month after the first visit, swelling from right buccal area had nearly disappeared (Fig. 4A) and there was fistulation in the right region (Fig. 4B). Exposed bone remained on the alveolar portion of the right mandibular molar and pus discharge was present (Fig. 4C and D). Antibiotic-resistant bacteria (Gram-positive bacilli) were detected at that time (Table 1). Therefore, we changed the antibiotics to

Table 1. Bacterial identification and microbial sensitivity test.

Bacterial identification	First visit Enterococcus faecalis	18 days from first visit Gram-positive Bacillus
Antibiotic Reagents (trade name)	MIC	MIC
Aminobenzyl Penicillin (Viccillin)	2	>8
Sulbactam/Ampicillin Unasyn S	<8	>16
Amoxicillin/Clavulanate (Augmentin)	<2	>4
Benzylpenicillin (Penicillin G)	2	>8
Cefditoren pivoxil (Meiact)	>2	>2
Cefazolin (Cefamezin)	2	>2
Cefpirome (Broact)	16	>16
Cefotiam (Pansporin)	>16	>16
Cefozopran (Firstein)	16	>16
Flomoxef (Flumarin)	>16	>16
Imipenem/Cilastatin (Tienam)	<1	>8
Meropenem (Meropen)	2	>8
Gentamicin (Gentacin)	8>	8
Clarithromycin	–	4
Erythromycin (Erythrosine)	4	>4
Minocycline (Minomycin)	<1	8
Levofloxacin (Cravit)	2	>4
Clindamycin (Dalacin)	>2	>2
Fosfomycin (Fosmicin)	16	>16
Sulfamethoxazole/ Trimethoprim (Baktar)	<0.5	2

sitafloxacin (Gracevit; Daiichi Sankyo, Tokyo, Japan) (Fig. 3). Seven weeks after the first visit, his condition had taken a turn for the worse. We treated him with ceftriaxone (Rocephin; Hoffman–La Roche, Basel, Switzerland) (Fig. 3). Eight weeks after the first visit, he died of multiorgan failure. Finally, we diagnosed this patient as MRONJ. His multiple systematic factors and MRONJ caused lethal sepsis because it fulfilled the diagnostic criteria: previous treatment with bisphosphonate, exposed bone in the maxillofacial region that has persisted for 8 weeks and no history of radiation therapy to the jaws.

Discussion

In recently years, there have been many reports on osteonecrosis of the jaw (ONJ) caused by bisphosphonates and by other antiresorptive and antiangiogenic therapies [6, 11, 12]. The investigators of these reports accordingly recommended changing the term of this disease from "bisphosphonate-related osteonecrosis of the jaw" to "medication-related osteonecrosis of the jaw" [7]. Denosumab, a RANK ligand inhibitor, is an antiresorptive agent and used to treat osteoporosis, multiple myeloma, and giant cell tumor [13]. This agent inhibits bone resorption by a different mechanism than that of bisphosphonate. The manufacturer reports that the frequency of ONJ with denosumab is nearly the same as the frequency with zoledronic acid treatment [14]. Thus, it may be that the development of ONJ is associated with the inhibition of bone resorption, rather than the use of a certain type of drug. However, it is considered that careful attention is required for the use of bisphosphonates in the present case due to the frequent use for the treatment of osteoporosis, osteopenia, and other diseases.

Many reports indicate that the incidence of ONJ is significantly higher with the use of intravenous (IV) bisphosphonates such as zoledronic acid (Zometa; Novartis, Basel,

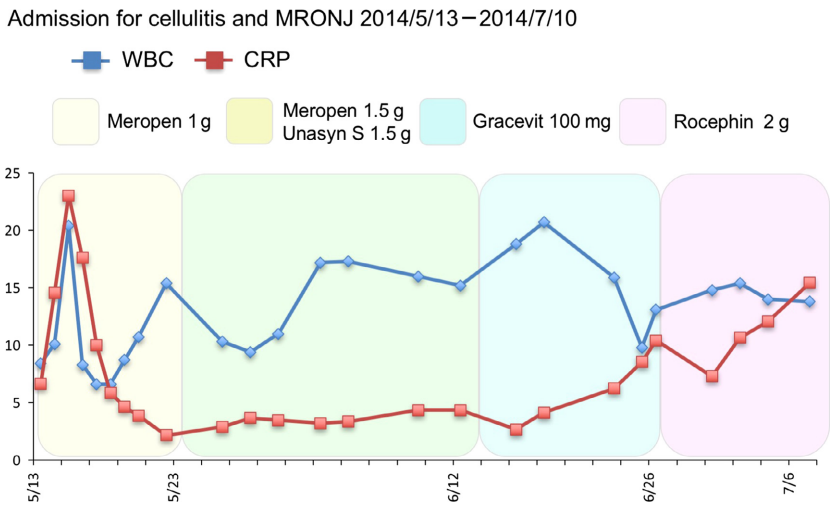

Figure 3. The transition in the laboratory test values for the white blood cell count (WBC) and the C-reactive protein (CRP) level, and the use of several antibiotics for cellulitis and medication-related osteonecrosis of the jaws (MRONJ).

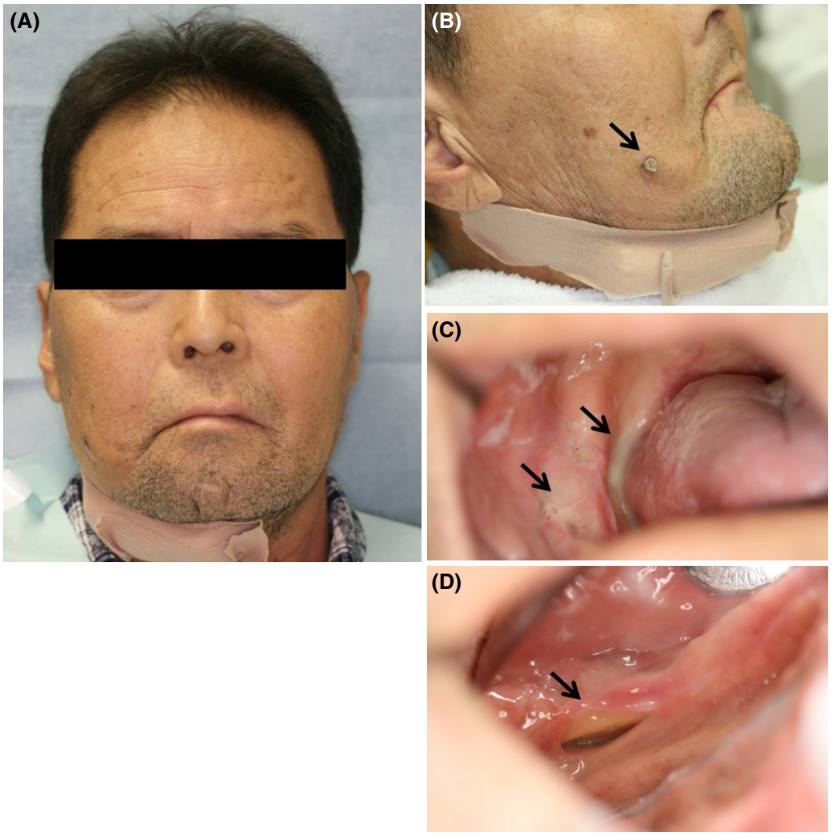

Figure 4. (A) Disappearance of swelling from the right buccal area to the infraorbital region. (B) Fistulation in the right region. (C) Discharge of pus by exposed bone on the alveolar part of the right mandibular molar. (D) Exposed bone on the alveolar part of the mandibular right molar.

Switzerland) than by the use of oral bisphosphonate [3, 15]. The incidence of ONJ because of the use oral bisphosphonates was higher in Japan than in Europe and America [16]. The period of drug use is also important, and long-term use is considered a high risk for the development of ONJ.

In our patient, the period of oral bisphosphonates use was only 7 weeks, but it caused severe symptoms. It may be that these symptoms were because of his multiple systemic factors. In this case, bisphosphonate was used as preventive administration for steroidal osteoporosis. Thus, it is thought that there were another option not to use bisphosphonate for such a high-risk patient or at least before administration we had to perform a risk assessment for MRONJ enough.

Glucocorticoides are associated with an increased risk for MRONJ [17]. He received steroid pulse therapies and oral steroids for interstitial pneumonia. Diabetes is also a risk factor for MRONJ [8]. His glycemic control was extremely poor. In addition, the presence of comorbid condition such as obesity, alcohol use, and smoking was a risk factor for MRONJ [9].

Local factors are also important in the development of MRONJ. Dentoalveolar surgery such as tooth extraction is a major risk factor. Poor oral hygiene and oral infection such as periodontal disease are also risk factors [18, 19]. The patient did not receive any dental surgery or radiation therapy. However, there were some ulcerations caused by the use of ill-fitting dentures. The dentures were possibly contaminated with oral bacteria. In this case, we do not know whether the dentures were ill-fitting and there were denture-related traumatic ulcers because he already had ulcerations and exposed bone when we first saw him. However, we think denture-related traumatic ulcers might have promoted a MRONJ. Osteonecrosis of the jaw has also been reported in patients with no history of surgery or in edentulous regions of the jaw [20]. Physicians have to be careful with the use of bisphosphonates or other bone resorption inhibitors in patients, regardless of the presence or absence of teeth or surgical history.

The most important thing to prevent MRONJ is to perform a risk assessment enough before drug administration. It required cooperation among physicians, nurses, dentists, dental hygienists, pharmacists, and other medical staff [7]. Physicians who prescribe bisphosphonates or other bone resorption inhibitors have to provide a

detailed explanation to patients of the risk of MRONJ and consult dentists if a patient has even a small risk factor. To prevent MRONJ, dentists and dental hygienists have to explain sufficiently to patients the importance of oral hygiene, and perform oral care and dental treatments before patients use these drugs.

Conclusion

There is a tendency to believe that MRONJ is caused by long-term bisphosphonate use (especially intravenous bisphosphonate) and dental surgery. We found that multiple systemic factors can be a worse risk factor for MRONJ because it may cause lethal disease such as sepsis.

Physicians have to be careful when administering bisphosphonate, other antiresorptive agents, and antiangiogenic medications for patients with multiple systemic factors, even if the patients seem to have no problems in the oral cavity.

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Conflict of Interest

The authors have no conflict of interests to disclose.

Authorship

KY: involved in study conception, design, and drafting manuscript; AS: involved in study conception, design, and is the chief doctor for the patient; FO: is one of the main doctors for the patient and performed data acquisition; MN: is supervisor and main doctor for the patient; KS and EY: performed analysis and interpretation of data; YH: is one of the main doctors for the patient and performed data acquisition; SI: made critical revision for this report; ST: made critical revision and is the corresponding author.

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