Abstract: We report a case of osteonecrosis of the jaw (ONJ) associated with denosumab therapy in a 62-year-old female patient being treated for bone metastases from breast cancer. Upon initial presentation at the Department of Oral Medicine, Hokkaido University Hospital, the patient's mandibular molar teeth were extracted because of severe periodontal disease. Two months later, epithelialization of the sockets was observed and treatment with antiresorptive drugs was started for bone metastases. One year after tooth extraction, bone exposure in the right lower first molar region was observed, and stage 2 medication-related ONJ (MRONJ) was diagnosed. Up to this time, the patient had received zoledronic acid twice and denosumab 22 times. Denosumab was discontinued by the oncologist, and oral antibiotics with rinsing of the exposed bone area were prescribed. By 36 weeks after discontinuation of denosumab, a sequestrum in the posterior part of the mandible was naturally shed, and the site was healed.

Introduction
Antiresorptive drug-related osteonecrosis of the jaw (ONJ) has been related to reduced bone turnover due to osteoclast inhibition. Many reported cases of medication-related ONJ have been associated with bisphosphonates, as these drugs induce apoptosis in osteoclasts. Recently, however, denosumab and bevacizumab have also been associated with ONJ (1,2).

Given that bisphosphonates and denosumab both block osteoclast function, it may be possible that strong blockade of osteoclast function may cause ONJ. Denosumab-related osteonecrosis of the jaw (DRONJ) has also been reported in patients with osteoporosis (3-6). However, there are some reports of ONJ in cancer patients treated with denosumab for bone metastases; information and results of treatment for these patients are still scarce, however. In present report, we document successful conservative treatment of ONJ with denosumab, following discontinuation of the drug, in a female patient being treated for multiple bone metastases from breast cancer.

Case Report
The patient was a 62-year-old woman undergoing chemotherapy for breast cancer, multiple lung metastases, right pleural dissemination, mediastinal lymph node metast-
tasis, and multiple liver metastases. She complained of lower back pain, and computed tomographic scans revealed sacral metastases. Multiple bone metastases were diagnosed, and the patient was scheduled to receive zoledronic acid.

In February 2012, the patient was referred to our hospital from the Department of Breast Surgery, Hokkaido University Hospital, for a detailed oral examination and treatment before receiving zoledronic acid. The initial examination demonstrated severe periodontal disease in the left upper first molar and the left and right lower second molars. The patient’s medical history included diabetes and hypertension, which were being controlled. Panoramic X-ray findings at the initial examination revealed severe alveolar bone resorption in the region of the right lower second molars (Fig. 1a). In February 2012, both lower second molars were extracted because of severe periodontal disease. Approximately 2 months later, epithelialization of the sockets was observed, and zoledronic acid treatment was started in May 2012. Based on the judgment of a breast surgeon, zoledronic acid was administered twice before the treatment was changed to denosumab in July 2012. The patient received 120 mg of denosumab once per month, and denosumab was administered 10 times up to April 2013. The breast cancer primary lesion and the bone metastases were controlled, and the patient received continuous periodontal treatment from a periodontist.

In April 2013, exposure of 3 mm of alveolar bone in the right lower first molar region was observed, with redness, swelling, and pain in the surrounding mucosa (Fig. 1b, c). On the basis of the clinical course, the patient was diagnosed as having stage 2 bone modifying agent-derived spontaneous medication-related ONJ. A conservative

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**Fig. 1**

a. Initial panoramic X-ray examination revealed severe alveolar bone resorption in the region of the right lower second molars. 
b. After extraction of the right lower second molar, the patient received 120 mg of denosumab once per month. Denosumab was administered 10 times up to April 2013. A 3-mm rectangular area of exposed bone was evident in the mandibular posterior space (mirror image) in April 2013. 
c. Panoramic X-ray findings in April 2013.

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**Fig. 2**

a. In January 2015, 9 months after withdrawal of medication, a sequestrum in the posterior part of the mandible was shed naturally. 
b. Panoramic image showed no extensive area of osteolysis without a sequestrum in January 2015. 
c. The mandibular sequestrum site is no longer visible in this panoramic image obtained in January 2015. 
d. The mandibular sequestrum site healed and became epithelialized in February 2015.
approach with antibiotic agents, local cleaning, and benzethonium chloride gargling was chosen, with careful observation of the patient’s progress. Because the extent of jaw osteonecrosis had expanded by April 2014, denosumab treatment was discontinued based on the judgment of the patient’s attending breast surgeon, but the remaining chemotherapy was continued. Up to this point, the patient had received zoledronic acid twice and denosumab 22 times. Although the exposed bone site in the right lower jaw was found to have expanded in August 2014, the patient progressed with no acute symptoms. In January 2015, 9 months after the cessation of medication, the right lower second premolar was shed naturally, and in February, a sequestrum that had been observed in the right lower molar area became detached (Fig. 2a-c). In February 2015, the sequestrum segregation site had become epithelialized and healed (Fig. 2d). In March 2015, examination at the Department of Breast Surgery revealed further exacerbation of multiple bone metastases and hypercalcemia; therefore, the breast surgeon considered readministration of denosumab. After consultations between our department and the Department of Breast Surgery, denosumab was readministered. Subsequently, the patient showed good progress, with no bone exposure at the sites where ONJ had been observed.

**Discussion**

In the present case of DRONJ, the good response to conservative management was due to early diagnosis and discontinuation of denosumab for 9 months prior to splitting of the sequestrum. It seems that the cause of jaw necrosis in the present case was a denture-related ulcer in the lower jaw.

Although in this case bisphosphonate (4 mg) was used 2 times and denosumab (120 mg) 22 times, when the dosing period was taken into consideration, the main cause of ONJ was considered to be denosumab. Some patients with ONJ may have used bisphosphonates before administration of denosumab, which makes it difficult to determine the true influence of each individual drug (1,3). For diagnosis of ONJ, dentists should differentiate patients who have received only one drug from those who have received both. Furthermore, careful examination of the dosage and time of administration of each drug is essential for making a diagnosis of MRONJ.

Denosumab is a human monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand (RANKL) (1,3). It reduces bone turnover, decreases bone resorption, increases bone density, and inhibits the formation, differentiation, and function of osteoclasts (1,5). Denosumab has also been used for the treatment of osteoporosis and skeletal-related events in patients with cancer (2,4,7). Because of their different mechanisms of action, bisphosphonate is deposited in bone tissue, whereas denosumab functions extracellularly and circulates in the blood, and is not deposited in bone tissue (1-3). Some studies have indicated that denosumab is more effective than bisphosphonate in inhibiting osteoclast function and bone remodeling (8). Unlike bisphosphonate, denosumab shows nonlinear dose-related activity (6). Denosumab is absorbed rapidly, and the serum concentration peak is achieved at approximately 10 days with a serum half-life of 25-29 days. Bone turnover normalizes a few months after denosumab administration (6). The effect of denosumab on bone remodeling is reversed shortly after discontinuation of the drug.

Since the first report of DRONJ by Taylor (7), further cases have been documented (Table 1). However, details

| Author | Sex | Age | Primary diseases | Dose (mg) | Duration period (months) | Site of ONJ | Treatment | Duration to sequestrum segregation (months) | Year |
|--------|-----|-----|-----------------|----------|-------------------------|------------|----------|-------------------------------------------|------|
| 1 Taylar | M | 60 | Prostate cancer | UNK | UNK | Mandible posterior | ABT | 15 | 2010 |
| 2 Aghalllo | F | 65 | Sacral giant cell | 120mg/month | 24 | Mandible posterior | ABT | UNK | 2010 |
| 3 Malan | M | 67 | Prostate cancer | 120mg/month | 26 | Mandible posterior | ABT+SURG | 18 | 2012 |
| 4 Diz | M | 73 | Prostate cancer | 120mg/month | 18 | Mandible posterior | ABT+SURG | 18 | 2012 |
| 5 Ohga | F | 64 | Cololectal cancer | 120mg/month | 7 | Mandible anterior and posterior | ABT+SURG | 7 | 2015 |
| 6 You | F | 56 | Prostate cancer | 120mg/month | 18 | Mandible posterior | ABT+SURG | 6 | 2016 |
| 7 Souza | M | 58 | Prostate cancer | 120mg/month | 49 | Mandible canine | ABT+SURG | 5 | 2016 |
| 8 Ohga | F | 61 | Breast cancer | 120mg/month | 22 | Mandible posterior | ABT | 9 | 2016 |

ABT: antibiotics, ABT+SURG: antibiotics + surgery, UNK: unknown.
of the duration and dose of denosumab and bisphosphonate in relation to clinical factors have not always been fully reported (9). Some clinical studies have documented spontaneous segregation of a bone sequestrum after discontinuation of denosumab (6,9), the sequestrum having been shed naturally at 7 months after denosumab withdrawal (6). In common with bisphosphonate related osteonecrosis of the jaw (BRONJ), the posterior mandible is one of the most common sites for DRONJ (6,9). Although the clinical presentation of DRONJ is very similar to that of BRONJ, denosumab is a soluble protein that does not need to be internalized by osteoclasts. Denosumab and bisphosphonates exert different mechanisms of action on bone tissue.

Although discontinuation of denosumab in patients with DRONJ may lead to an improvement of oral health-related quality of life (QOL), there is a possibility that bone metastasis may worsen in those with cancer. Therefore, it is necessary to weigh the advantages and disadvantages of denosumab discontinuation in DRONJ patients while considering their overall QOL (6,9). The international consensus for DRONJ treatment includes conservative measures initially, followed by surgical therapy if no effect is observed. The incomplete healing of DRONJ that may occur after conservative surgical treatment has prompted increased interest in more extensive surgery for this condition. However, it is important for dentists to consider conservative surgical treatment for ONJ. Decisions about discontinuation of bone-modifying agents should be made with the cooperation of an oncologist, and QOL should be maintained by considering the overall condition of individual patients, their cancer stage, and life expectancy (6,9). In order to confirm the effect of denosumab discontinuation in ONJ patients, more clinical studies and further accumulation of ONJ cases will be required.

The present patient gave informed consent for publication of her case details.

This case report was presented at an invited special workshop session of MRONJ at the Japanese Society of Oral Diagnosis/Oral Medicine in September 2016.

Conflict of interest
The authors have no conflict of interest or research funding to declare.

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