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Author(s)	Moritani, Yasuhito; Donen, Masaki; Fujimori, Masaki et al.
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CASE REPORT

Extensive oral bisphosphonate related osteonecrosis of the maxilla: utilization of bone scintigraphy for detection of lesion and the combination of HBO therapy and surgery: case report and hypothesis

Yasuhito Moritani[a, b*)], Masaki Donen[c)], Masaki Fujimori[d)], Kanchu Tei[b, e)] and Yoichi Ohiro[b)]

ABSTRACT : We report a case of extensive oral bisphosphonate-related osteonecrosis of the maxilla with oral alendronate in an 86-year-old female being treated for osteoporosis. The patient fell down while walking and hit her right face on the guard rail before 6 months from first visit to our hospital. However, the patient hadn't visited any hospital and get any treatment.

The patient experienced agitation of the right maxillary molar and referred to our hospital from dental clinic. In the initial our examination, localized swelling of bilateral mucous membrane of the palate and fistulas of lateral alveolar mucosa were observed. CT revealed a wide range of sequestrum in the right maxilla. The patient was diagnosed with Stage 3 MRONJ. The patient had been taking oral alendronate 35 mg/week for 6 years and 1 month. Antibiotics administration, local irrigation, and hyperbaric oxygen therapy (HBO) performed before operation. The recent addition of single photon emission computed tomography (SPECT)/CT increased the accurate detection of disease extent in MRONJ. SPECT/CT imaging was performed before surgery in present case for detection of lesion. The combination of surgery and HBO therapy was effectively performed in MRONJ. Patients achieved a good healing course.

Key Words : MRONJ, HBO, Bone SPECT/CT

INTRODUCTION

Bisphosphonates (BPs) are drugs that are widely used in the treatment of osteoporosis and bone metastasis of solid tumors. As BPs effectively decrease skeletal events, they are used as therapy for the treatment of the osteoporosis. Although the therapeutic advantage of BPs exists, BPs or antiangiogenic agents are related with medication-related osteonecrosis of the jaw (MRONJ).[1-5)] Regarding treatment, several patients cannot be effectively managed with conservative therapy alone[5, 6)] and surgery is ultimately required. Furthermore, adjuvant therapy such as hyperbaric oxygen therapy (HBO) is also considered for refractory MRONJ cases.[7)]

Bone single-photon emission computed to1mography/computed tomography (SPECT/CT) increased the accurate detection of disease extent in MRONJ.[8, 9)] Herein, we report a case of extensive medication-related osteonecrosis of the maxilla by oral bisphosphonate, which might have been triggered by facial trauma caused by a fall.

CASE REPORT

The patient was an 86-year-old woman with a chief complaint of right maxillary molar movement.

a) Department of Dentistry and Oral Surgery, Sapporo City General Hospital, Sapporo, Japan
b) Department of Oral and Maxillofacial Surgery, Division of Oral Pathobiological Science, Faculty of Dental Medicine and Qradnate School of Dental Medicine, Hokkaido University, Sapporo, Japan
c) Department of Dentistry and Oral Surgery, Kushiro Red Cross Hospital, Kushiro, Japan
d) Department of Oral and Maxillofacial Surgery, Kushiro Rosai Hospital, Kushiro, Japan
e) Department of Dentistry and Oral Surgery, Obihiro Kyoritsu Hospital, Obihiro, Japan

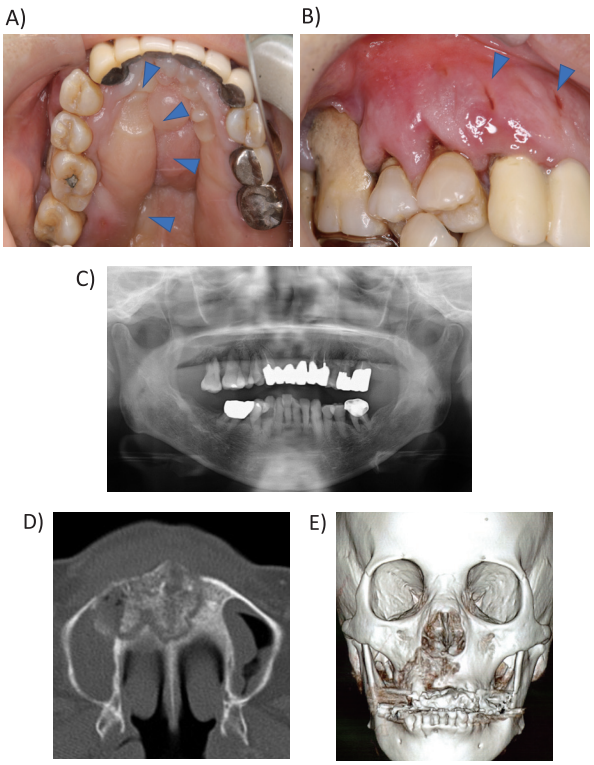

FIGURE 1
(A, B) Intraoral photograph showing obvious swelling of palate and gingival fistulas in #12 and #13 (blue arrowhead).
(C) Dental panoramic radiography showing bone resorption around #16 and #17.
(D, E) Axial section of CT image showing the large sequestrum at maxilla. 3D-CT image showing clear sequestrum formation at right maxilla.

Current Medical History: In October 20XX, the patient fell down while walking and hit her right face on the guard rail. The patient did not seek medical help and was not treated. In December 20XX, the patient experienced agitation of the right maxillary molar. The patient had been referred to our hospital from her private clinic in March 20XX+1. Her medical history included osteoporosis, hypertension, and diabetes mellitus (DM). The patient had been taking oral alendronate 35 mg/week (total dose: 10, 290 mg) for 6 years and 1 month.

Intraoral findings: Pulsation was assessed in right palate (Figs. 1A). Pus was draining from the fistula of the lateral alveolar mucosa of around #12, 13 (Fig. 1B), and the bone was palpated with probe. Panoramic radiography revealed bone permeability around #17, 16 (Fig. 1C). CT revealed a partial sequestrum formation in the right maxilla (Fig. 1D, E). The clinical diagnosis was MRONJ stage 3. We decided on surgery to remove sequestrum and HBO therapy before and after surgery.

During hospitalization, #14, 15, 16, and 17 extractions

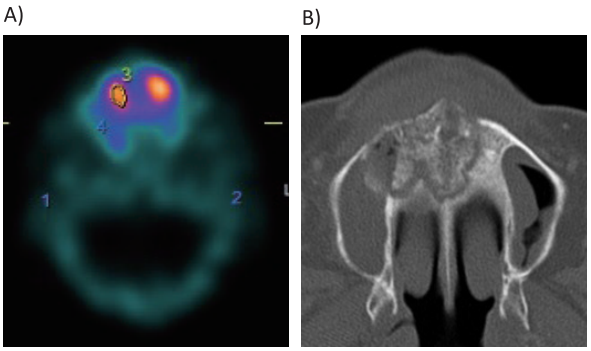

FIGURE 2
(A, B) Bone SPECT/CT imaging in maxilla before surgery for MRONJ.

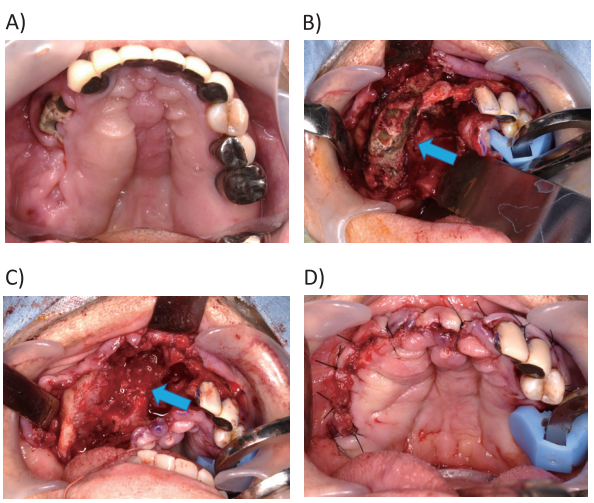

FIGURE 3
(A) Intraoral photograph just before the operation.
(B) Removing a large sequestrum (blue arrow)
(C) There is no oroantral communication with removing the sequestrum (blue arrow).
(D) Closing the wound by suture.

were performed. Administration of oral alendronate was discontinued based on her physician's discretion. Bone SPECT/CT of the bone was conducted, and the standardized uptake value (SUV) peak of the central lesion was 4.28 (Fig. 2A, B). Bone SPECT/CT was useful in the identification of the extent of MRONJ lesions. The patient underwent 20 sessions of HBO therapy prior to surgery. After 20 HBO treatments, maxillary pain was significantly improved. Then, the patient underwent surgery under general anesthesia in June 2018 (Fig.3.A-C). The separated sequestrum was removed as en bloc, and the wound was closed by suture completely (Fig.3D). The removal bone was match with range of the bone SPECT/CT. Postoperatively, the patient underwent 10 sessions of HBO therapy. One and a half months after surgery, the

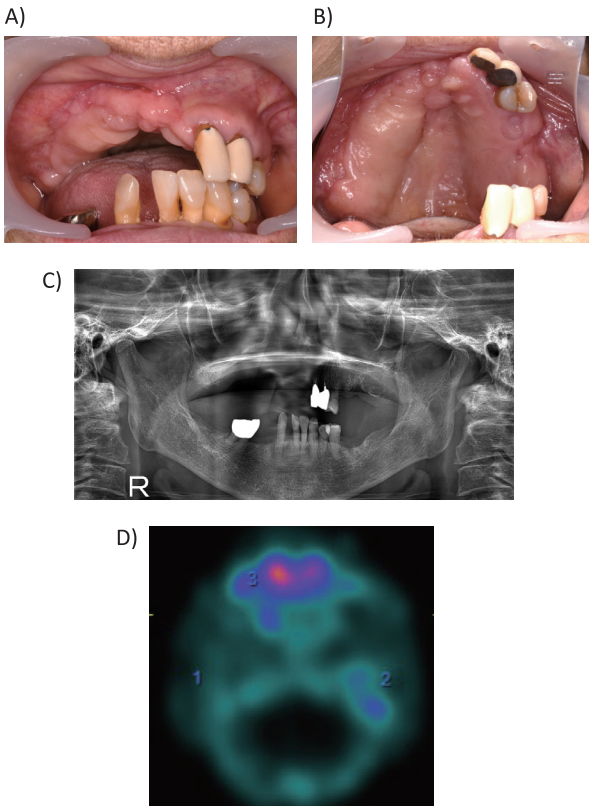

FIGURE 4
(A, B) Intraoral pictures 1.5 month after surgery. The wound epithelialized without infection. (C) Panoramic radiography 3 months after surgery for MRONJ.
(D) Bone SPECT/CT imaging in maxilla 3.5 months after the operation.

wound epithelialized without infection and the pain has disappeared. (Fig. 4A, B). On panoramic radiography, no pathological findings were observed after removal of the sequestrum (Fig.4C). SPECT/CT confirmed that there were no inflammatory activity of osteomyelitis at the bone margin after removal of the sequestrum at 3.5 months after the surgery (Fig.4D).

DISCUSSION

In this case, the patient appeared to have an extensive MRONJ. Moreover, the patient was on long-term oral BP treatment. We hypothesized that MRONJ, which had been asymptomatic, was triggered by facial trauma and the subjective symptoms appeared. With the advent of super-aging society, the incidence of facial injuries due to falls among elderly people is increasing.[10-12] Therefore, in the treatment of MRONJ among elderly individuals, a history of facial trauma should be considered during diagnosis and treatment.

Osteonecrosis of the Jaw Study Committee Position Paper 2016 suggests that withdrawal of antiresorptive agent (ARA) is preferable in case of confirmed diagnosis of MRONJ development until MRONJ treatment is completed.[13] We think that a therapeutic withdrawal of ARA in patients with MRONJ allow restoration of bone metabolism is a means that could be considered. However, Osteonecrosis of the Jaw Study Committee Position Paper 2023 comments that withdrawal of ARA in the treatment of MRONJ and its efficacy is controversial.[14]

In relation to the extent of surgical resection, it is standard to decide the extent of bone resection by taking a safety margin from the border of the sequestrum.[5,6,15-17] After we cut the bone intraoperatively, we made a final decision by confirming the state of bleeding in the bone segment.[5, 15, 17] We utilized bone SPECT/CT to establish the extent of MRONJ resection. Fluorescence-guided surgery is applied in some facilities.[18]

Bone SPECT/CT has very high sensitivity for the detection of MRONJ.[8, 9] SUV has been previously applied to the bone SPECT to treat some cancer patients with bone metastases.[19, 20] Recently, it has been utilized for the evaluation of osteomyelitis, and it can facilitate a semi-quantitative assessment of osteomyelitis using SUV.[8, 9] Bone SPECT/CT has a clinical effect on the evaluation of anti-inflammatory action of HBO for the various types of osteomyelitis of jaw.[7] However, compared to MRI, bone SPECT/CT captures inflammatory units more acutely, but it also has more false positives, we should be careful.

In our department's MRONJ surgery cases, bone SPECT/CT is routinely performed, which provides useful information for the surgery. In the preoperative, there is almost but not completely separation of the sequestrum (Fig.1D). It is thought that there was a certain amount of blood flow in the jawbone and surrounding tissues. It has been reported that acellular bone and sequestrum formation with osteoclastic activity surrounded by inflammatory cellular infiltration is found, and that a vasculature exists in/around MRONJ lesion.[17, 23] In our case, the maxillary sequestrum was almost separated from the surrounding bone following lesion progression, the radioactive tracer had reached in/around the lesion. SPECT/CT is useful in assessing the activity of osteomyelitis. We can understand the extent of inflammatory lesions and physiological changes in the lesion prior to surgery, and we believe that bone SPECT / CT is meaningful.

There are many reports that bone SPECT/CT imaging

is useful even when the boundaries are unclear.[21, 22] According to these paper, the mean SUVmax values for stage 0 (n=21), 1 (n=13), 2 (n=25), and 3 (n=10) patients with unclear boundaries were 5.82 ± 3.20, 5.46 ± 3.79, 8.16 ± 3.93, and 10.57 ± 8.43, respectively.[23] Furthermore, SUVmax , SUVpeak, and SUVmean were significantly different between the clinical stages. ($p = 0.024$, $p = 0.027$, $p = 0.039$, respectively). We think that SUV values derived from quantitative bone SPECT/CT results are useful not only for staging MRONJ patients, but also for detecting areas where the boundary with sequestrum is unclear, as they are objective and reliable indicators even at different stages of MRONJ, including areas of unclear boundaries.[22]

We performed HBO to improve the environment and clinical symptoms of the MRONJ lesion in the maxilla before surgery, and to increase the success rate of the surgery.[7, 24] We have also reported several cases in which preoperative HBO reduced SUVpeak and improved clinical symptoms before surgery.[7, 24] As a pre-surgical treatment, HBO has successfully treated MRONJ lesions, thereby: improving the quality of life of afflicted patients, increasing wound healing, and reducing edema, inflammation and pain.[7, 24-28]

SPECT/CT can evaluate the activity of inflammation in the entire jawbone and is useful for preoperative assessment of the extent of surgery, but it is difficult to identify the boundary between healthy bone and squestrum in real time. Fluorescence-guided surgery using the VELscope provides the ability to observe autofluorescing healthy bone, which is useful for identifying the boundary between healthy bone and decayed bone in real time.[29] However, in the operative field with heavy bleeding, the hemoglobin in the blood absorbs the green luminescence, making evaluation difficult and dependent on the surgeon's experience. In addition, it cannot be used for preoperative prediction of the extent of surgery. Preoperative confirmation of the inflammatory activity of osteomyelitis contributed to a more accurate determination of the extent of surgery.

The HBO will gain more clinical significance for MRONJ therapy in the future.[7, 25, 30] In our case, treatment protocol involves performing HBO 20 times preoperatively. Postoperatively, the patient underwent 10 sessions of HBO therapy. In Japan, HBO is limited to 30 times due to insurance claims. We have modified the MARX report to perform HBO 20 times preoperatively and 10 times postoperatively.[31] This therapy pattern also showed improvement in SUV values on FDG-PET in MRONJ lesions after HBO, and we believe that it was expected to have a sufficient anti-inflammatory effect.[24] There are mechanisms of action for HBO against inflammation.[7, 25] Pressure in a high-pressure environment indicate that oxygen dissolves in the blood regardless of the presence of hemoglobin, which in turn dramatically promotes blood circulation. Breathing of 100% oxygen can only achieve about 6-fold normal oxygen partial pressure. Under HBO, the partial oxygen pressure is approximately 14-fold of that during the normal times.[7] In regards to the chemical effects, oxidative killing action of macrophages and neutrophils is augmented by improving the oxygen partial pressure in tissues.[7, 25] In addition, the reactive oxygen combined with nitrogen species that are produced lead to positive intracellular modulation related with bone turnover.[20] Spiegelberg et.al have reported that HBO can improve bone activity and health, including osteoclast.[32] We need to uncover pathophysiology of HBO, as well as to the underlying biology of normal bone turn over in the future.

Although there are many papers that show the benefits of performing HBO before surgery, we recognize that there may be some controversy regarding the evidence of HBO.[24-28, 32] Watanabe et al analyzed patients (206 patients of stage 2 and 46 patients of stage 3) at single center.[17] They reported that extensive surgery is highly effective against ARONJ regardless of disease stage if clinical and imaging findings indicated a sequestrum separation, whereas HBO therapy before and after surgical approach can be effective. They performed treatment with a combination of surgery and HBO preoperatively and postoperatively in 86 stage 2 and 23 stage 3 patients. In stage 2 , the treatment outcome was healed (70 cases) or improved (12cases) or stable (4 cases). In stage3 , the treatment outcome was healed (20 cases) or improved (3 cases).[17] In contrast, more than 46 sessions of HBO therapy was less associated with healing than was non-HBO therapy. More frequent HBO does not seem to lead to improved treatment outcomes. It was difficult to determine whether HBO therapy is superior to the placebo due to the absence of high-level evidence in the literature.[17, 30] Unfortunately, we have not been able to compare this case with placebo without HBO therapy. There is a possibility of overtreatment in some cases, and we would like to carefully consider the use of HBO in the future on a case-by-case basis.

CONCLUSION

We report a case of extensive medication-related osteonecrosis of the maxilla by oral bisphosphonate. Bone SPECT/CT imaging was useful in the identification of the extent of MRONJ lesions. The patient received surgery combined with HBO for extensive MRONJ of maxilla and achieved a good healing course.

CONFLICT OF INTEREST

The authors declare no competing interest.

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INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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