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Hyperbaric oxygen therapy as a conservative approach for osteoradionecrosis of the jaw in an osteoporotic patient receiving oral bisphosphonate therapy: a case report

Atsushi Shudo[1,2*]

Abstract

Background: Osteoradionecrosis of the jaw (ORNJ) is a well-known chronic side effect of radiotherapy (RT) for head and neck malignancies. Osteonecrosis of the jaw (ONJ), similar pathology to ORNJ, may be induced by bisphosphonate (BP) therapy and is known as BP-related ONJ (BRONJ). Although differences exist between ORNJ and BRONJ in terms of clinical features and management methods, ONJ in a patient with history of both RT and BP therapy is categorized as ORNJ in the diagnostic criteria, despite the possibility that the ONJ may be affected by BP considering the pharmacology and mechanism of action. To date, management of ORNJ with a history of BP therapy has been scarcely discussed.

Case presentation: We report here our experience of serious ORNJ in an 82-year-old osteoporotic woman receiving oral BP therapy. She had undergone partial maxillectomy to treat left maxillary gingival cancer and had received RT of 60 Gy as postoperative treatment. She had a history of osteoporosis, for which she had been administered BP for 8 years and 5 months. A bony sequestrum 45 × 25 mm in size was found at the site of the mandibular ramus, and the clinical diagnosis was ORNJ. We administered hyperbaric oxygen therapy (HBOT), scheduled for 3–5 days per week in 2 courses, 35 times. After HBOT, we performed sequestrectomy avoiding invasive surgery such as mandibulectomy. After the surgical procedure the wound healed completely. Bone regeneration was confirmed by computed tomography postoperatively. There have been no signs of recurrence as of 4 years after the operation.

Conclusions: We undertook a multimodality approach with HBOT and conservative surgery and achieved a satisfactory outcome. HBOT may be worthy of consideration as a conservative approach for ORNJ in patients receiving BP therapy, leading to the possibility of avoiding invasive surgery such as mandibulectomy.

Keyword: Hyperbaric oxygen therapy, Osteoradionecrosis of the jaw, Bisphosphonate therapy, BRONJ, Case report

Background

Osteoradionecrosis of the jaw (ORNJ) is a well-known chronic side effect of radiotherapy (RT) for head and neck malignancies. ORNJ is defined as exposed irradiated bone that fails to heal over a period of 3 months without any evidence of persisting or recurrent tumor (Marx 1983; Epstein et al. 1987). It may progress irreversibly once it develops and reduces the quality of life of the patient to a great extent. When osteonecrosis of the jaw (ONJ), similar in nature to ORNJ, is induced by bisphosphonate (BP) therapy, it is known as BP-related ONJ (BRONJ). BRONJ is a chronic condition of the oral cavity resulting in mucosal ulceration and exposure of underlying necrotic bone and the following secondary complications, for which several diagnostic criteria exist (Ruggiero

*Correspondence: atsushi.shudo@tokushukai.jp
[1] Department of Oral and Maxillofacial Surgery, Kishiwada Tokushukai Hospital, Kishiwada, Osaka, Japan
Full list of author information is available at the end of the article

et al. 2014; Khan et al. 2015). While according to these criteria ONJ in a patient with a history of both RT and BP therapy is diagnosed clinically as ORNJ, the possibility that the ONJ may be affected by BP is not considered in the diagnosis.

Hyperbaric oxygen therapy (HBOT) has been recommended and used in a wide variety of medical conditions, including osteoradionecrosis and refractory osteomyelitis (Tibbles and Edelsberg 1996; Leach et al. 1998). Recent studies have suggested the possibility of using HBOT in the treatment of BRONJ (Khan et al. 2015; Freiberger et al. 2012), but these recommendations are not supported by definitive evidence and have been debated (Ruggiero et al. 2014; Nadella et al. 2015; Ceponis et al. 2017). There are few reports of ORNJ in patients who have been treated with BP and few discussions on their management. We report a case of ORNJ in an osteoporotic patient receiving oral BP therapy, which was successfully treated by a multimodality approach with HBOT and conservative surgery.

Case presentation

An 82-year-old woman was referred to our outpatient clinic for consultation on conservative treatment of ORNJ. She had undergone partial maxillectomy to treat left maxillary gingival cancer (diagnosed as squamous cell carcinoma histologically) and had received RT of 60 Gy as postoperative treatment. She had a history of osteoporosis, for which she had been administered alendronate for 8 years and minodronate for 5 months. BP therapy had been discontinued at the time of the surgery for maxillary gingival cancer.

The first clinical examination revealed redness of the facial skin around the mandibular angle and severe trismus (< 1 mm, < 1 finger) caused by markedly indurated buccal mucosa. Intraoral examination showed exposed necrotic bone on the left mandible and discharge of pus (Fig. 1). Imaging examination including panoramic radiography and computed tomography (CT) showed a bony sequestrum 45 × 25 mm in size, which was not separated completely from normal bone, at the site of the mandibular ramus (Fig. 2). Results of bacterial examination identified anaerobic bacteria (*Propionibacterium* species) in addition to *Klebsiella pneumoniae* and *Streptococcus viridans*, which were commensal oral bacteria. The clinical diagnosis was ORNJ.

The patient's previous oral and maxillofacial surgeon had suggested left hemimandibulectomy including left condylotomy and reconstruction surgery, which she refused given the potential cosmetic and functional postoperative complications. Therefore, we proposed a treatment plan involving a multimodality approach as follows: no invasive surgery requiring mandibulectomy or reconstruction; conservative treatment with antibiotics and HBOT; and sequestrectomy when sequestrum was completely separated from normal bone. The patient gave her consent to our proposal.

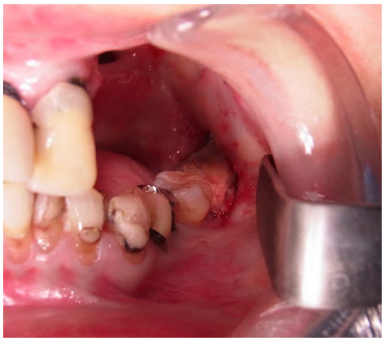

Fig. 1 Clinical presentation, intraoral view. Exposed necrotic bone was found on the left mandible

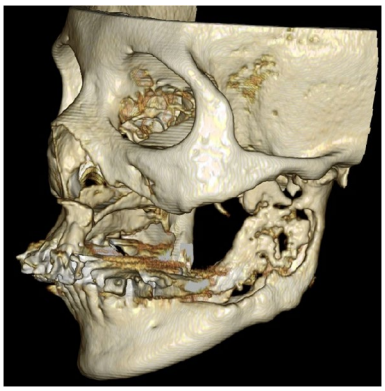

Fig. 2 Three-dimensional (3D) computed tomography (CT) imaging findings at the first examination. CT showed a bony sequestrum 45 × 25 mm in size at the site of the mandibular ramus

We administered HBOT, scheduled for 3–5 days per week in 2 courses, 35 times. HBOT was administered for 60 min in a monoplace (single occupancy) hyperbaric chamber (BARA-MED; Koike Medical, Tokyo, Japan), which was pressurized at about 2.0 ATA (atmospheres absolute) with 100% oxygen. As an antibiotic administration method in parallel with HBOT, amoxicillin or clarithromycin was used when we found a large amount of pus, and was discontinued when pus discharge disappeared. Anaerobic bacteria were not detected in the bacterial examination after HBOT. In accordance with the patient's request, we conducted careful follow-up rather than performing the operation immediately after HBOT. Six months after the end of HBOT, when CT revealed completely separated sequestrum and pathological hairline fractures (Fig. 3), we performed sequestrectomy

Fig. 3 Preoperative 3D CT imaging findings. CT revealed completely separated sequestrum and pathological hairline fractures

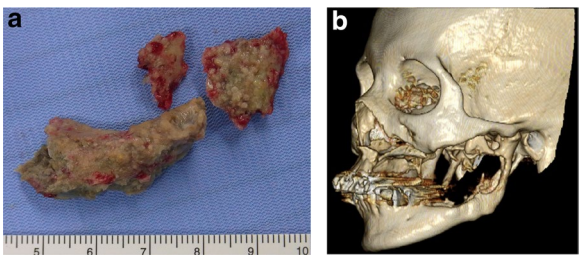

Fig. 4 **a** Surgical specimen. The specimen was diagnosed histologically as sequestrum. **b** 3D CT imaging findings on the first postoperative day

Fig. 5 3D CT imaging findings at 6 months postoperatively

with the patient's consent (Fig. 4). The operation was performed under intravenous sedation with midazolam, since intubation was difficult because of severe trismus and the risk of complete fracture of the mandibular ramus. After the surgical procedure the wound healed completely. Bone regeneration was evaluated by CT at 6 and 12 months postoperatively (Figs. 5, 6). The subsequent clinical course was uneventful, and there have been

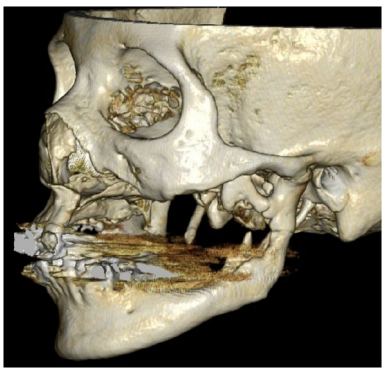

Fig. 6 3D CT imaging findings at 12 months postoperatively. Mandibular bone had grown over time

no signs of recurrence as of 4 years after the operation. The patient was pleased with the outcome.

Discussion

ORNJ is defined as a serious complication of RT, especially for head and neck cancer, and is a long-known disease. In 1983 Marx proposed the pathophysiological theory for ORNJ, as follows: (1) radiation, (2) hypoxic-hypocellular-hypovascular tissue, (3) tissue breakdown, and (4) chronic non-healing wound (Marx 1983). These criteria formed the cornerstone for HBOT in the treatment of ORNJ. Alternatively, ONJ may develop in association with BP administration. The first case reports to describe the relationship between high-dose intravenous BP and the incidence of ONJ in cancer patients were published in 2003 (Marx 2003). In 2004, Ruggiero et al. reported the relationship between oral BP in osteoporotic patients and the incidence of refractory osteomyelitis (Ruggiero et al. 2004). These two conditions (ONJ and refractory osteomyelitis) were considered to be the same BP-associated disease, which was termed BRONJ. The pathophysiology of BRONJ has not been fully elucidated, but several etiological hypotheses are proposed such as direct toxicity to the bone, altered bone remodeling or oversuppression of bone resorption, angiogenesis inhibition, and soft tissue toxicity, all of which may be induced by BP (Russell et al. 2008).

There are several diagnostic criteria for BRONJ (Ruggiero et al. 2014; Khan et al. 2015), which prescribe as a provision no previous treatment with radiation to the oral-maxillofacial region (e.g., "no history of radiation therapy to the jaws" by the American Association of Oral and Maxillofacial Surgeons (Ruggiero et al. 2014), and "no history of radiation therapy to the craniofacial region" by the International Task Force on ONJ (Khan et al. 2015)). In both of these guidelines, ONJ in a patient

with a history of both RT and BP therapy is diagnosed clinically as ORNJ.

ORNJ and BRONJ clearly differ in etiology. In recent years it has been reported that some differences also exist in clinical features and treatment methods (Grisar et al. 2016; Obinata et al. 2017). In our case, the patient presented with pathological fracture and no periosteal reaction. These features are common in ORNJ rather than BRONJ and are consistent with ORNJ as the clinical diagnosis. However, our patient had received long-term oral BP administration over 8 years and 5 months, raising concern that ORNJ might be affected by BP as a deteriorating factor, considering the pharmacology and mechanism of action (Russell et al. 2008). Recent reports suggest that the use of BP may contribute to earlier development of ORNJ (Miniello et al. 2019). Otherwise, BRONJ might have developed in the region affected by mandibular ONJ.

It is difficult to accurately distinguish causes between RT and BP when osteomyelitis has progressed and the bone has completely necrotized. Mitsimponas et al. reported that ORNJ was dominated by fibrosis and hyperexpression of Collagen I, a feature not seen in BRONJ specimens (Mitsimponas et al. 2014). Additionally they suggested that BRONJ was characterized by deviation from the normal bone architecture. From such pathophysiological findings, it might be possible to determine whether the etiology is RT or BP. However, the differences could not be judged from the usual histopathological examination and also could not be distinguished in our case.

We performed HBOT because it has been suggested that this approach may be therapeutically effective for both ORNJ and BRONJ (Ruggiero et al. 2014; Khan et al. 2015; Tibbles and Edelsberg 1996; Leach et al. 1998; Bennett et al. 2016). According to the most recent classification of ORNJ proposed by Lyons et al. (Lyons et al. 2014), our case was a serious one classified as stage 4, meaning essentially that mandibulectomy was necessary. Although some studies have reported that HBOT is invalid for advanced ORNJ (Dieleman et al. 2017), it was effective in our patient with severe ORNJ who had a history of BP administration. It is unclear how much HBOT contributed in the multimodality approach, but anaerobic bacteria disappeared after HBOT. HBOT as a conservative treatment in such cases may therefore be worthy of consideration.

The present study had some limitations. We cannot make definitive conclusions because our study was a case report; additionally, ORNJ with a history of BP therapy was complicated in pathogenesis. Although it definitely will be time-consuming, a larger cohort of patients has to be collected.

Recently, new understanding of the pathophysiology of ORNJ has been proposed by the radiation-induced fibroatrophy (RIF) theory, which suggests that the progression of ORNJ is induced by deregulation of fibroblastic activity in atrophic tissue caused by previous radiotherapy (Lyons and Ghazali 2008). On the basis of this theory, the usefulness of vascular-directed therapy using pentoxifylline and antioxidant therapy using α-tocopherol (vitamin E) (PENTO) has been reported (Kahenasa et al. 2012; McLeod et al. 2012). The PENTOCLO regimen, a combination of PENTO and clodronate, is also reported as an effective treatment for refractory ORNJ (Delanian et al. 2011). Clodronate is an antiresorptive agent classified in BP, but few reports mention the risk of BRONJ under PENTOCLO therapy (McLeod et al. 2012). It is reported that the incidence of BRONJ is 0.01–0.1% in osteoporotic patients and 1.1–6.7% in cancer patients (Ruggiero et al. 2014; Khan et al. 2015). Therefore, given the low incidence it may not be necessary to seriously consider BP administration. However, clodronate is one of the first-generation non-nitrogen-containing BPs, which originally carried a low risk for BRONJ (McLeod et al. 2012; Crépin et al. 2010). Thus, it is important to consider PENTOCLO as a new treatment for RIF or refractory ORNJ.

We employed a multimodality approach with HBOT and conservative surgery and achieved a satisfactory outcome. Even ORNJ with a history of BP administration may suitable for conservative treatment. Further study of the relationship between ORNJ/ BRONJ and HBOT is also warranted.

Conclusions

Our results suggested that ORNJ with a history of BP administration may be responsive to conservative treatment. By employing HBOT, it may be possible to avoid invasive surgery such as mandibulectomy and still obtain good results.

Abbreviations

BP: Bisphosphonate; BRONJ: Bisphosphonate-related osteonecrosis of the jaw; CT: Computed tomography; HBOT: Hyperbaric oxygen therapy; ONJ: Osteonecrosis of the jaw; ORNJ: Osteoradionecrosis of the jaw; RIF: Radiation-induced fibroatrophy; RT: Radiotherapy.

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Author contributions

AS contributed to the design and implementation of the research, to the analysis of the results, to the writing of the manuscript, and read and approved the final manuscript.

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Availability of data and materials
All data used for this report are included in the text.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Competing interests
The author declares no competing interests.

Author details
[1]Department of Oral and Maxillofacial Surgery, Kishiwada Tokushukai Hospital, Kishiwada, Osaka, Japan. [2]Department of Oral and Maxillofacial Surgery, Hyogo College of Medicine, Hyogo, Japan.

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