

Special Article - Dental Public Health

Conservative Management of Medication-related Osteonecrosis of the Jaw *via* Cooperation between the Regional Dental Association and a Hospital without Dentists: A Case Report

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Abstract

Osteonecrosis of the jaw is a rare but severe adverse reaction to treatment in cancer patients. Because this disorder is associated with antiresorptive therapy and exposure to antiangiogenic agents, the comprehensive term Medication-Related Osteonecrosis of the Jaw (MRONJ) has been recently introduced. Here, we report a case of MRONJ caused by the concomitant use of bevacizumab and bisphosphonate, where this side effect was successfully controlled *via* a cooperative system established with the regional dental associations. As the patient exhibited an asymptomatic exposed bone, conservative management was chosen by the community dentist. Oral hygiene instruction, denture adjustment, oral rinse, and oral care using hinokitiol were performed. After complete resolution of MRONJ, antiangiogenic agent-targeted chemotherapy was resumed, which resulted in a partial response of both the primary lesion and lung metastases. The electronic medical record viewing system, known as "Nagoya Memorial Net," was very useful for sharing information between the medical oncologist and the community dentist.

Keywords: Medication-related osteonecrosis of the jaws; Bisphosphonate; Antiangiogenic agents; Hinokitiol; Medical and dental cooperation; Electronic medical record viewing system

Abbreviations

BRONJ: Bisphosphonate-Related Osteonecrosis of the Jaw; MRONJ: Medication-Related Osteonecrosis of the Jaw; IPsec: security architecture for Internet Protocol, VPN: Virtual Private Network

Case Presentation

A 66-year-old man complained of knee pain and was referred to the Department of Orthopedic Surgery in Nagoya Memorial Hospital. He was diagnosed with a metastatic bone tumor in the left tibia (Figure 1). Further examinations were performed, which revealed that he had advanced rectal cancer with multiple metastases in the lung (Figure 2) along with the metastatic bone lesion. The patient was a heavy smoker (60 cigarettes /day; 46 years) and did not drink an alcohol. Prior to undergoing cancer treatment, he consulted with a community dentist to review his oral hygiene conditions. Periodontal disease was noted, and his tongue was thickly coated. His oral mucosa was reddish and edematous; his partial dentures were ill-fitted within both the maxilla and mandible. At first, he was instructed to abstain from smoking and keep the oral mucosa clean with rinsing; then, full dentures were newly made to reduce his risk of Medication-Related Osteonecrosis of the Jaw (MRONJ) before cancer treatment. In combination with intravenous administration of zoledronate, chemotherapy was initiated using bevacizumab. After the 5th administration of bisphosphonates, two areas of the exposed bone were visible on his right hemimandible (Figure 3). On

T2-weighted magnetic resonance imaging, a high-signal-intensity area was identified (Figure 4), corresponding to focal osteonecrosis. Because the patient did not complain of pain, he was diagnosed with stage 1 MRONJ. Microbiological analysis revealed a mixed normal oral flora, including Streptococcus and Neisseria species. Treatment with bevacizumab and zoledronate was discontinued and conservative management was initiated *via* a cooperative partnership between the regional dental associations and Nagoya Memorial Hospital using fax technology and a Virtual Private Network (VPN) (known as "Nagoya Memorial Net"). Rather than chemotherapy, radiation therapy was applied to the bone metastasis (36 Gy; 12 fractions). The importance of oral hygiene was thoroughly explained to the patient by the community dentists; he was again instructed to stop smoking and gargle using azulene sulfonic acid after each meal. The patient began adjusting his dentures and rinsing them with disinfectants. In addition, hinokitiol-containing gel [1] was used for daily mouth cleaning. Professional dental hygiene treatments were applied at regular intervals, with monthly professional dental examinations. The patient remained asymptomatic and a bone sequestrum was excreted 3 months later; the exposed areas of necrotic bone were completely covered by oral mucosa 4 months after the initiation of conservative management. Antiangiogenic agent-targeted chemotherapy was then resumed, which resulted in a partial response of both the primary lesion and the lung metastasis (Figure 2). Written consent was obtained from the patient for publication of this report and the related photos.

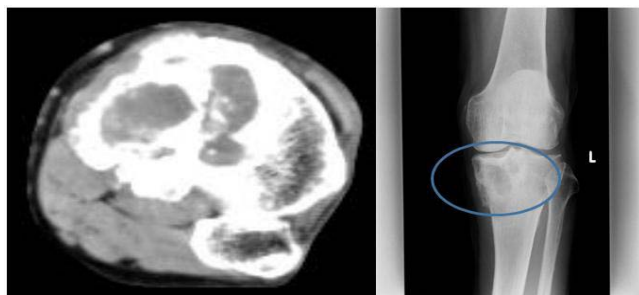


Figure 1: Bone tumor in the left tibia.



Figure 2: Computed tomography showing the rectal primary lesion and pulmonary metastasis, before and after six cycles of chemotherapy.

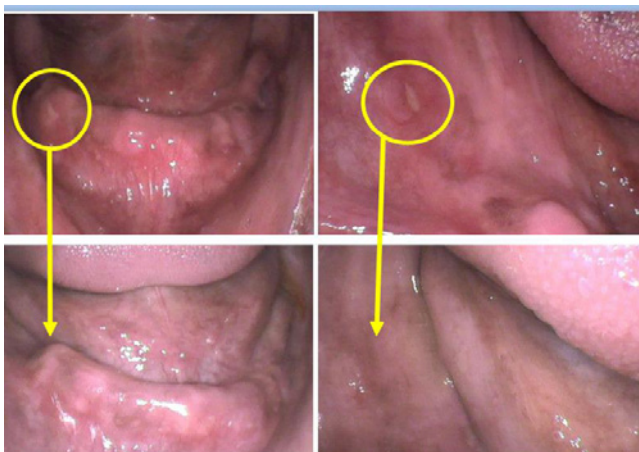


Figure 3: Clinical appearance of medication-related osteonecrosis of the jaw. Two areas of the exposed bone were visible on the patient's right hemimandible, as indicated by the circles.

Discussion/Conclusion

A perioperative oral management fee has been established for the treatment of malignancy in Japan since 2012, as prophylactic intervention is useful for alleviating the oral complications associated with cancer surgery, radiotherapy, and chemotherapy [2,3]. Nagoya Memorial Hospital has neither a department of dentistry nor a department of oral surgery; therefore, we have collaborated with

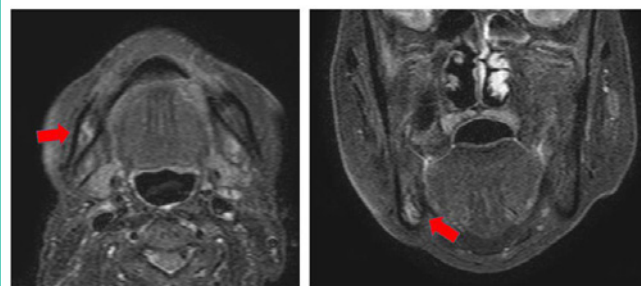


Figure 4: Magnetic resonance imaging. Fat suppression T2 enhancement image showing a hyperintense area in the right mandible, corresponding to focal osteonecrosis.

the regional dental associations near the hospital for 4 years [4]. Among the recorded oral complications, osteonecrosis of the jaw is a rare, but severe, adverse reaction to multiple drugs used for the cancer treatment [5,6]. As this side effect is associated with the use of bisphosphonates, denosumab, and antiangiogenic agents, the comprehensive term MRONJ has been recently introduced [7]. MRONJ may have a devastating impact on cancer patients' quality of life; thus, prophylactic treatment and proper oral management should be well-timed. Intimate cooperation between the patient's medical oncologist and a community dentist is essential for controlling this condition. We utilized the electronic medical record viewing system, so-called "Nagoya Memorial Net," to share the patient's information, including laboratory data and imaging findings, at once. In this report, we described a patient with metastatic rectal cancer whose MRONJ was successfully managed *via* cooperation with a community dentist.

MRONJ, which can affect in 1-20% of cancer patients, is a significant oral complication [6,8]. Marks et al. were the first to report the occurrence of Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) in 2003 [9]. Treatment with bisphosphonates is known to delay bone metastasis development and reduce the risk of skeletal-related events and bone pain in patients with malignancy. The American Association of Oral and Maxillofacial Surgeons has suggested changing the term BRONJ to MRONJ [7], as there have been many reports regarding osteonecrosis of the jaw caused by various drugs, including antiresorptive medications and antiangiogenic agents (e.g., bevacizumab [10], aflibercept [11], sunitinib [12], and evelorimus [13]). MRONJ can be defined as the exposure of the necrotic bone in the maxillofacial region for >8 weeks without remission, and occurs in patients with a history of usage of the above drugs and no history of radiotherapy to the jaws [7,14]. The management of MRONJ is determined based on the stage of the disease; conservative treatment is preferred in the early stages without symptoms, while necrotic bone elimination is indicated in the cases of bone exposure with symptoms [7,15]. Thus, a multidisciplinary team is required to define the management of the lesions, in which the dentist should play a significant role.

However, in a hospital without dentists, it is very difficult to arrange direct discussions, regarding the oral complications of cancer patients, with the professional dental staff. Since the perioperative oral management fee was established in Japan, a cooperative partnership with regional dental associations adjacent to our hospital has been developed, thus enabling a good relationship with our community

dentists [4]. First, the lists of the community dentists were assembled based on the results of a survey of their skill levels, consultation hours of their dental clinics, and their accommodations (e.g., stairway and parking lots, designed for easy accessibility to facilitate patients' consultations). Next, lectures regarding cancer epidemiology and treatment were organized for the community dentists. In 2017, VPN with security architecture for Internet Protocol (IPsec) was introduced into the system of medical and dental cooperation to enhance information sharing with the community dentists. At present, 146 community dentists are registered with our hospital and 256 cancer patients have been enrolled in this cooperation system.

In the present case, concomitant use of bisphosphonate and bevacizumab was suspected to impair wound healing and cause the exposed necrotic jawbone, as the anti-angiogenic properties may compromise microvascular integrity [10,13]. The patient was asymptomatic at the onset of MRONJ and the community dentist chose the conservative management; adjustment of dentures, as well as oral care using local disinfectant rinses. A hinokitiol-containing gel was also used [1] for the prevention of periodontal disease and oral *Candida* infection, because these disorders are the risk factors for MRONJ, as are ill-fitting dentures and invasive dental procedures [16]. Hinokitiol, a component of the essential oils isolated from the Formosan cypress, shows antibacterial activity against various oral microorganisms including fungi [1,17]. The anti-inflammatory actions of this component have also been demonstrated by *in vitro* and *in vivo* studies [18]. While the precise causative mechanism of MRONJ remains unknown, the possible hypotheses include impaired bone repair, suppression of osteoclast activity, infection and inflammation, impaired angiogenesis or vascular repair, and comorbid conditions, such as diabetes and anemia [16,19]. Sharing this patient information amid an intense cooperation between the physician and community dentist is critical for the management of MRONJ. Mutual communication was markedly enhanced by the usage of VPN with IPsec, which enabled our patient to receive the proper oral care and be cured of MRONJ. Antiangiogenic agent-targeted chemotherapy was resumed after the complete resolution of MRONJ, which consequently resulted in a good response to antineoplastic agents without any recurrence of MRONJ.

In conclusion, to control oral complications, such as MRONJ, medical and dental cooperation must be intimate. The electronic medical record viewing system is very useful for the multidisciplinary team, as it enables information sharing in a very rapid and efficient manner.

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