Fatal Bleeding in Conjunction with Mandibular Medication-related Osteonecrosis of the Jaw (MRONJ)

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Received 13 December, 2016/Accepted for publication 22 February, 2017

Abstract

Here, we report a case of fatal bleeding in conjunction with mandibular medication-related osteonecrosis of the jaw (MRONJ). A 75-year-old Japanese man was referred to our department with osteonecrosis of the jaw due to bisphosphonate (BP) for multiple bone metastases from prostate cancer. Aggressive surgical intervention was ruled out due to a poor prognosis in terms of life expectancy. Death occurred due to hemorrhagic shock resulting from massive oral bleeding caused by necrosis of the mandible. Numerous reports have suggested that jaw necrosis is induced not only by BP, but also RANKL antibody, steroids, and molecularly-targeted agents. This suggests that the number of cases of MRONJ is likely to increase among elderly patients in whom general health is already poor. The American Association of Oral and Maxillofacial Surgery recommends aggressive treatment only in cases of stage 3 disease. Therefore, such a therapeutic strategy may only be available for cases of jaw necrosis in which the general health status of the patient is otherwise good. To prevent a life-threatening outcome in cases of MRONJ, physicians, who are responsible for determining the drug strategy, should cooperate with oral surgeons in determining the best therapeutic strategy.

Key words: Medication-related osteonecrosis of the jaw —
Bisphosphonate (BP)-related osteonecrosis of the jaw —
Anti-cancer treatment — Complications

Introduction

The role of bisphosphonate (BP) in the development of osteonecrosis of the jaw (ONJ) is now well known among doctors, who are responsible for prescribing this type of

medication, dentists, oral surgeons, and even patients. This is due to the publication of a position paper on BP-related ONJ (BRONJ)³²⁾.

Recent studies have suggested that ONJ is induced not only by oral BP, but also by RANKL monoclonal antibody drugs^{11,23)}, ste-

roids, non-oral BP drugs, and molecularly-targeted agents^{14,15,18,22)}.

Hospitals are now seeing an increase in the number of cases of non-BP related ONJ. In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) acknowledged the scope of this change in our understanding of the etiology of this condition by changing its name to medication-related osteonecrosis of the jaw (MRONJ)²⁵⁾. In the AAOMS position paper²⁵⁾, symptomatic treatment, mouth rinse, and pain control are recommended as the main methods of management up until stage 2 disease; scraping is limited to only soft tissue; and aggressive surgical procedures are not recommended, except in stage-3 patients. We believe that adherence to this strategy is likely to result in an increase in the number of cases of uncontrolled ONJ.

Here, we report an elderly patient who died of hemorrhagic shock due to massive oral bleeding as a result of lower jaw necrosis. At the time, the patient was on BP for treatment of bone metastasis from prostate cancer. The patient, who was followed up over a long period of time, received no aggressive surgical intervention due to a poor prognosis for life expectancy.

Further investigation of the diagnosis and a new therapeutic strategy will be discussed.

Case Presentation

Patient: A 75-year-old man.

Medical history: The patient had had heart failure and prostate cancer, and had received hormone therapy and zoledronic acid for approximately 1 year after being diagnosed with multiple bone metastases. The cancer was unresponsive to hormone therapy, however. Therefore, concurrent hormone therapy and docetaxel administration were selected, which is the standard treatment in castration-resistant cases (Fig. 1, Table 1).

Chief complaint: Pain in the tooth due to an apical lesion in the mandibular left molar.

Fig. 1 Bone scintigraphy

Accumulation of R1 in cervical vertebrae, spinal column, and pelvis; diagnosed as multiple bone metastases of prostate cancer.

Clinical Procedures and Outcomes

At the time of the patient's first visit to his local dentist, he had already been on luteinizing hormone releasing hormone (LH-RH) therapy and monthly zoledronic acid for 7 months. Zoledronic acid was administered 7 times at doses of 28 mg. Three months later, he visited our department for extraction of the tooth which was giving him pain. No extraction was performed, however, due to concern that it might result in ONJ, and cleaning and medication with an antibacterial agent were selected instead.

Four months later, the patient was still undergoing chemotherapy and the pain in his tooth had become intolerable. Therefore, the mandibular molars were extracted with the agreement of the patient and urology

Table 1 Treatment course

Aug. XX00	First medical examination at Department of Urology. PSA 2,242 ng/ml. Palpation revealed stone-like hardness.
Sept. XX00	Biopsy: Gleason score 5 + 4. Bone scintigraphy showed bone metastasis (Fig. 1). [Diagnosis] Prostate cancer-prone bone metastasis.
Nov. XX00	Commencement of LH-RH hormone therapy and zoledronic acid administration.
Sept. XX01	First visit to our department with chief complaint comprising request for extraction of mandibular left molar. Was referred to us from local dental clinic. No extraction performed due to risk of ONJ.
Jan. XX02	Torpidity of left nervus mentalis region appeared. Discharge of pus and exacerbation of pain in mandibular left first molar. Mandibular left first molar tooth extraction was performed, as chemotherapy could not be continued due to pain in jawbone. Subsequent epithelization of socket was good, and torpidity of left nervus mentalis disappeared.
Aug. XX02	ONJ developed around maxillary left premolar (Fig. 2 A, B).
Feb. XX03	ONJ expanded around maxillary left premolar (Fig. 2 C, D).
Aug. XX03	Torpidity of left nervus mentalis region showed relapse; ONJ developed in mandibular left molar region (Fig. 2 E–H).
Jan. XX04	ONJ expanded further around maxillary left premolar; maxillary left canine became detached (Fig. 3 A–C).
Dec. XX04	ONJ expanded in left maxilla and mandible (Fig. 3 D–G).
Jan. XX05	Left jaw position shifted. CT image showed pathological fracture of left mandible (Fig. 4 A, B).
May. XX05	Abscess and fistula formation developed in left sub-mandible (Fig. 4 C, D).
Jun. XX05	Bleeding from mandibular ONJ region and impaired consciousness necessitated emergency hospitalization. At 6 days after hospitalization. Bleeding from mandibular ONJ region occurred 3 times within short period; patient died of hemorrhagic shock.

department doctors. Zoledronic acid administration had reached a total dose of 48 mg at this point, with the last dose being given 3 months earlier. An ampicillin drip was selected as the preoperative antibacterial agent. The surface of the bone of the extraction socket was dry. Re-epithelialization was good in the wound of the extracted teeth, and progress was considered to be good. After a while, chemotherapy was resumed.

Seven months later, the patient complained of sudden onset pain in the region of the left maxillary molars. A follow-up examination revealed that the alveolar bone of the maxilla was exposed, and mobility was evident in the surrounding teeth (Fig. 2). Treatment for this comprised cleaning and administration of antibiotics. Spontaneous tooth loss continued to occur, however, together with clear evidence of ONJ on a large scale. Therefore, in addition to administration of antibiotics and

analgesics, occlusal adjustment was performed and necrotic tissue excised together with any remaining sharp-edged bone.

Recurrent pain from the ONJ of the maxilla worsened as the course of chemotherapy progressed, but slightly ameliorated during washout periods. At this point, tegafur-uracil, enzalutamide, flutamide, estramustine, cabazitaxel, and abiraterone acetic ester were being administered as adjunct therapies for the prostate cancer.

At 12 months after the onset of ONJ of the maxilla, torpor of the left mental nerve region was also evident, in addition to pain and bone exposure around the left mandibular molars (Fig. 3).

Cleaning was subsequently performed and antibiotics administered, but bone exposure continued to expand, accompanied by repeated infection. The ONJ gradually progressed and, at 17 months, the patient com-

Fig. 2 Osteonecrosis of jaw (ONJ) images and oral cavity findings

A, C: Simple X-ray images; E, G: Computed tomography images; B, D, F: Progress in upper jaw ONJ; H: Mandibular ONJ

A, B: ONJ had developed around maxillary left premolar.

C, D: ONJ had expanded around maxillary left premolar.

E, F, G, and H: Torpidity of left nervus mentalis region showed relapse; ONJ had developed in mandibular left molar region.

Fig. 3 Images of osteonecrosis of jaw (ONJ), enlargement, and oral cavity findings

A, B, C: ONJ showed more expansion around maxillary left premolar; maxillary left canine was detached.

D, E, F and G: ONJ showed expansion in left maxilla and mandible.

plained of jaw deviation. Subsequent examination revealed a pathological fracture (Fig. 4).

At this point, 5 years had passed since the patient was first admitted. Pain control had become difficult, and mandible detachment and jaw position reconstruction were dis-

cussed. Several days later, there was a hemorrhage from the portion of the jaw affected by ONJ, and the patient showed impaired consciousness. The patient was then admitted to hospital as an emergency case. At this time, radical treatment of the ONJ was considered necessary to control the bleeding, and a plan

Fig. 4 Photographs of pathological fracture within and outside oral cavity
 A, B: Left jaw position showed shift. CT image showed pathological fracture of left mandible.
 C, D: Abscess and fistula formation at left submandibular.

was made for embolization based on the assumption that the patient's general condition would stabilize. The plan now was to detach and reconstruct the portion of the mandible affected to bring about a temporary arrest of hemorrhage. Early in the morning of the 6th day after hospitalization, hemorrhaging from the necrotic portion of left mandible occurred, and measures were taken to stop the bleeding with styptics and sutures. Nonetheless, after several hours, a large amount of bleeding involving the inferior alveolar artery occurred again from the same lesion and the patient fell into a state of shock. His family did not desire procedures to prolong life, and the patient died of hemorrhagic shock.

Discussion

Approximately 42,000 patients are diagnosed with prostate cancer in Japan each year. In 2020, it is expected that the yearly mortality rate will increase to 21,000 patients^(7,20). With prostate cancer, there is an extremely high 10-year survival rate if the diagnosis is made early⁽¹⁰⁾. In advanced cases, such as those involving distant metastases, the standard

strategy is the application of hormone treatment in conjunction with docetaxel combination therapy.

Hormone therapy is effective in at least 90% of such patients. Over half of highly advanced cases with distant metastases become insensitive to hormone therapy after several years, however. Therefore, it is predicted that the number of highly advanced cases in which anti-bone resorptive agents have to be used will increase, and this is especially likely to be associated with elderly patients whose general health status is already poor due to the rapid aging of the Japanese population.

In the AAOMS position paper⁽²⁵⁾, the risk of occurrence of ONJ was found to be between 0.7% and 6.7% in patients treated with zoledronic acid, as opposed to between 0% and 0.019% in placebo groups^(9,21,24,27). Similarly, in a systematic review of randomized control studies^(9,21,23,24), the risk of ONJ occurrence was indicated to be 1% with treatment as opposed to between 50 and 100 times greater than that if left untreated. Additionally, outcomes in groups treated with denosumab, a RANKL monoclonal antibody drug, were comparable with those in patients treated with zoledronic

acid^{24,26)}.

Concurrent use of bevacizumab, a multikinase inhibitor, with zoledronic acid increases risk of ONJ to 0.9%^{14,15,18,23)}. Risk has also been reported to increase with concurrent use of sunitinib, a tyrosine kinase inhibitor, and zoledronic acid^{1-6,8,15,17,29)}. These findings suggest the need to consider carefully the synergistic effects of concurrent chemotherapy in diagnosing MRONJ.

The AAOMS position paper²⁵⁾ recommends symptomatic treatment, mouth rinse, and pain control as the main methods of management in treating cases of MRONJ up until stage 2 disease. It also recommends debridement only as a means of relieving soft tissue irritation and achieving infection control.

Furthermore, aggressive surgical procedures, such as surgical debridement or resection for longer-term palliation of infection and pain, is only recommended in cases of stage 3 disease^{9,19,26,28,31)}.

Good results have been reported with aggressive surgical treatment such as reconstructive surgery following mandible detachment when no neovascularization was present^{12,13,28)}. Furthermore, some studies from Japan^{1,2,16,30)} have reported that it is possible to control ONJ by aggressive surgery or prompt reconstructive surgery in breast cancer patients on BP drugs. They also note that mandible detachment of the area affected or up to its borders may be necessary in some cancer patients, as long as the general health condition otherwise allows.

In determining whether to select aggressive surgical treatment, the oral surgeon must take into account a number of factors, including a poor prognosis in terms of life expectancy and its potential effect on the patient's QOL. This will be a difficult decision in patients already under palliative care.

In the present case, the patient had castration-resistant prostate cancer with a poor prognosis. The patient had survived for a long period of 6 years, however, owing to successful medication with hormone therapy and docetaxel. Moreover, this patient had stage-3 MRONJ and was undergoing long-term pallia-

tive treatment for infection and pain. Therefore, mandible resection was considered. It was difficult to determine the optimal timing for surgical treatment, however, due to the worsening general health of the patient as a side effect of chemotherapy. Consultations were carried out with radiologists regarding embolization of the inferior alveolar artery in the mandible due to pathological fracture. Surgical intervention would have been appropriate earlier, perhaps at stage 2, where we may have been able to halt the necrotic progress and subsequent fatal bleeding.

In the future, as the prevalence of cancer increases with the aging of the population, we believe that the prevalence of ONJ among the elderly will probably increase, and the scenario is likely to be further complicated by the development of various drugs, such as molecularly-targeted therapies. We believe that the present case could be taken as representative of the kind of problems that are likely to be encountered in elderly patients in poor general health and with stage-3 disease.

We believe that the oral surgeon will need to consider the feasibility of surgical treatment at stage 2 with ONJ, while the patient is still in good general health and capable of undergoing such treatment. An increase in the rate of surgical treatment of MRONJ at stage 2 would lead to a change in the therapeutic strategy for stage-3 disease.

Conclusion

Here, we have summarized our experience of a case involving hemorrhage due to osteonecrosis of the jaw resulting from ONJ caused by BP drugs for bone metastasis from prostate cancer.

Acknowledgements

We would like to express our gratitude to the doctors of the Urology Department of the Hachioji Hospital of Tokai University who provided special assistance and guidance.

Conflicts of Interest

There are no conflicts of interest that need to be disclosed with regard to this paper.

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