



Case Report

Bisphosphonate-related osteonecrosis of the jaw complicated by Ludwig's angina

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Abstract

Ludwig's angina is a life-threatening cellulitis that involves the submandibular and sublingual spaces. It often occurs after an infection of the roots of the teeth. However, modern dental care and use of antibiotics for oral infections have made Ludwig's angina rare. We present here a cancer patient exhibiting the sequential features of bisphosphonate related osteonecrosis of the jaw on bone scan complicating with Ludwig's angina. This report highlights the need for medical practitioners to be alert to these rare combinations in the compromised patient after bisphosphonate therapy. To the best of our knowledge, no case of Ludwig's angina secondary to osteonecrosis of the jaw has been reported. Copyright © 2014 Elsevier Taiwan LLC and the Chinese Medical Association. All rights reserved.

Keywords: bisphosphonate; bone scan; jaw; Ludwig's angina; osteonecrosis

1. Introduction

Ludwig's angina is an infection of the submandibular and sublingual spaces. It can potentially lead to a fatal airway obstruction. It often occurs after an infection of the mandible. We present here a cancer patient exhibiting the sequential features of bisphosphonate-related osteonecrosis of the jaw (BRONJ) on bone scan and complicating with Ludwig's angina. This report highlights that practitioners should be alert to these rare combinations in the compromised patient after bisphosphonate therapy.

2. Case Report

An 83-year-old man, who had been diagnosed 2 years earlier with prostate cancer, presented with submandibular

swelling and inability to swallow saliva for 1 week. With preliminary assessment as Ludwig's angina at a local hospital, and patient had undergone antibiotic prophylaxis and to abscess drainage prior to the referral. He was nonfebrile and not in respiratory distress. Computed tomography of his neck showed a significant inflammation with abscess and fistula formation in the left submandibular space. Presence of periosteal reaction, osteolytic and osteoblastic change, bone sequestration, and destruction of the mandible were noted (Fig. 1).

Tc-99m methylene diphosphonate bone scan (Fig. 2) exhibited intense bone lesion in the lower jaw (black arrow) and evidence of distant bone metastasis (open arrows). He was admitted to the dental ward for airway observation and further treatment in September 2010. The aerobic and anaerobic cultures of his blood yielded negative results. Empirical use of 1200 mg augmentin and 500 mg metronidazole intravenously q. 8 hours was given. Subsequently the patient received sequestectomy of the mandible and oral mucosa flap reconstruction. During the operation, an open wound over the left

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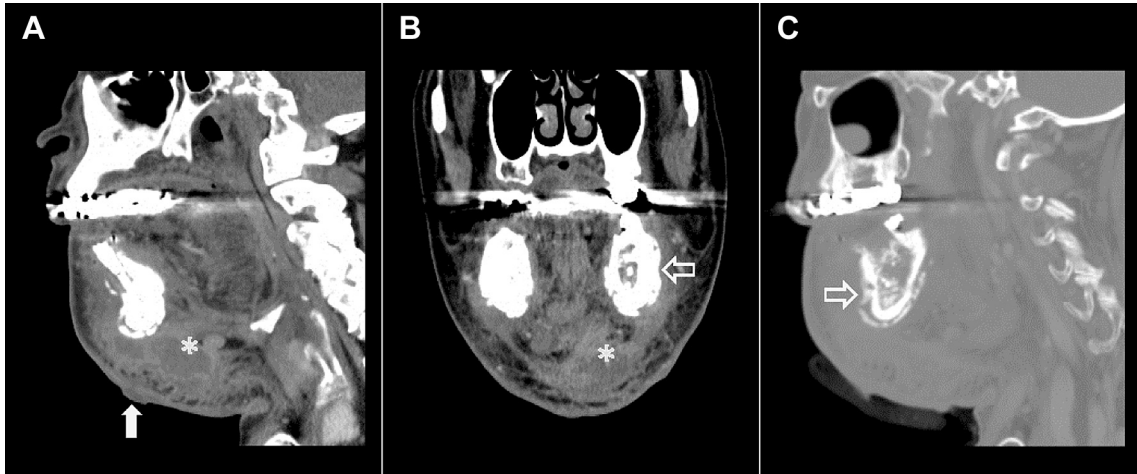


Fig. 1. Contrast-enhanced computed tomography (A, sagittal; B, coronal-reformatted) images show extensive subcutaneous swelling, abscess (asterisk) in the submandibular space and a fistula (arrow) noted. The airway is patent. (C) Bone window image revealing periosteal reaction, osteolytic and osteoblastic changes, and intramedullary sequestra within the mandibular body (open arrow). The computed tomography findings are consistent with osteonecrosis of the jaw.

chin, deep caries, and sequestrum formation in left mandible were found. Histologically, inflammatory cell infiltration, and granulation of soft-tissue were observed. Bone sequestration, necrosis, and ingrowth of squamous epithelium in the mandible were also noted (Fig. 3). A diagnosis of Stage 2

BRONJ, distinguished by bone exposure with soft-tissue and mandible infection, was confirmed. His pus culture yielded no bacterial growth due to the recent antibiotics exposure. The patient was then switched to 1 g augmentin tablet twice daily. Subsequent follow-up at 2 weeks and 3 months at the

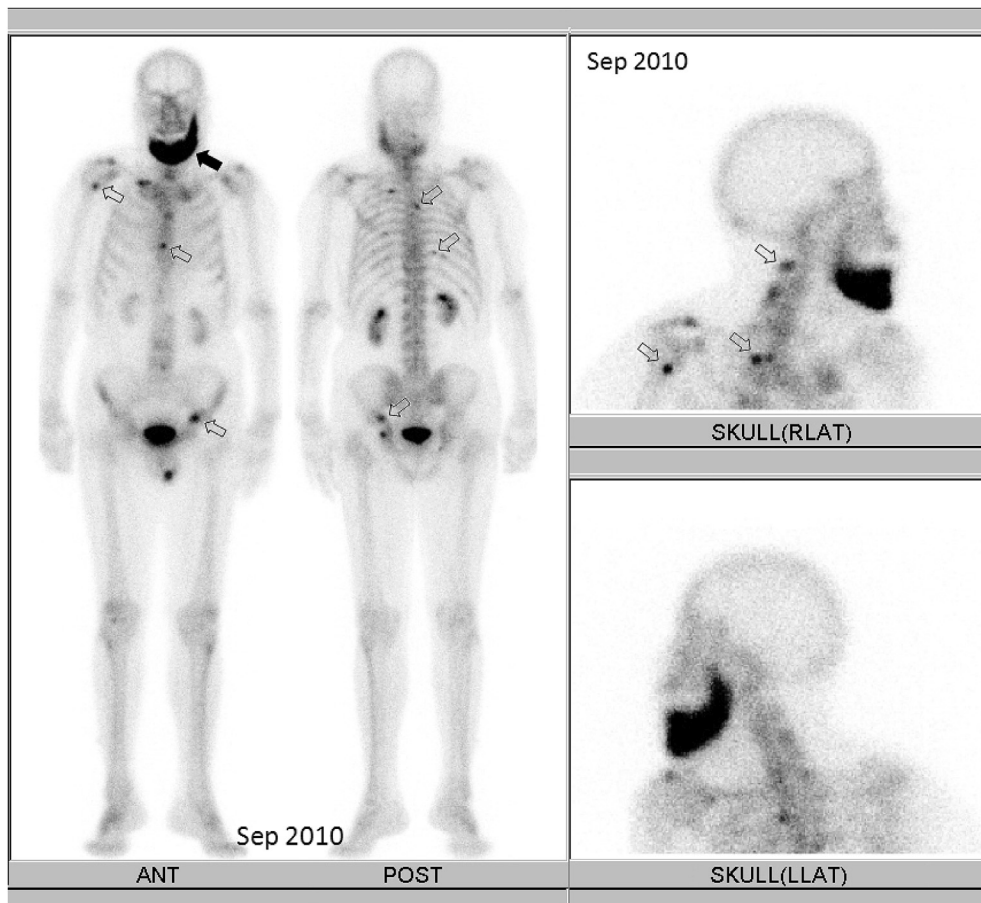


Fig. 2. Tc-99m methylene diphosphonate bone scan exhibited intense bone lesion in the lower jaw (black arrow) and evidence of distant bone metastasis (open arrows).

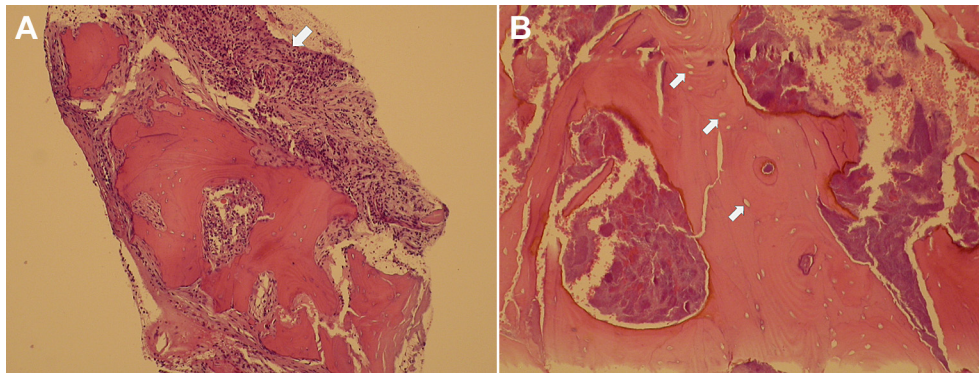


Fig. 3. (A) Low power ($\times 100$) hematoxylin and eosin histology demonstrating infiltration of inflammatory cells (arrow) in the mandibular bone. (B) Osteonecrosis. Dead bone with empty lacunae (arrows) noted. The histology is consistent with necrosis of the bone.

outpatient clinic showed a progressive resolution of soft-tissue swelling. Thereafter, our service had no further contact with the patient.

Regarding his past medical history (Fig. 4), the patient had prostate cancer (Gleason score 4 + 3) with urinary bladder invasion and distant skeletal spreading that was treated with palliative prostatectomy in October 2008, and intravenous zoledronic acid monthly thereafter. With partial response of metastatic disease after 1 year of the therapy, the patient sought dental care for a nonhealing tooth socket in the left lower jaw. He underwent several courses of antibiotics therapy with no significant improvement. In June 2010, an area of infected and exposed necrotic bone in the left mandible was noted, consistent with Stage 2 BRONJ according to the American Association of Oral and Maxillofacial Surgeons criteria. Zoledronic acid was then discontinued and hormone therapy was provided.

3. Discussion

Bisphosphonates are inhibitors of osteoclastic bone resorption, indicated for the treatment of an array of bone

disorders. Suppressed bone turnover by bisphosphonates adds to microdamage accumulation and danger of infections. BRONJ, which was first described in 2003,¹ is a rare but serious side effect of treatment with bisphosphonates. About 95% of cases occurred among cancer patients receiving high-dose intravenous bisphosphonates.²

The working definitions of BRONJ have been proposed as the development of necrotic bone in the oral cavity of a patient who is receiving bisphosphonate treatment, despite adequate treatment for 8 weeks, without malignancy and no prior radiotherapy to the head and neck.³ Patients with BRONJ are categorized into three stages according to the clinical signs and symptoms. Briefly, patients with Stage 1 disease have exposed bone but are asymptomatic. Stage 2 disease is characterized by exposed bone with regional soft-tissue infection. Patients exhibiting exposed bone associated with soft-tissue infection, and accompanied by pathologic fracture, oral-cutaneous fistula, or osteolysis extending to the inferior border are considered Stage 3. The underlying etiology and the predilection of BRONJ remain unclear. Estilo et al⁴ reported that *Actinomyces* colonization was found in all 310 biopsy cases. Other authors have described that biofilms could be

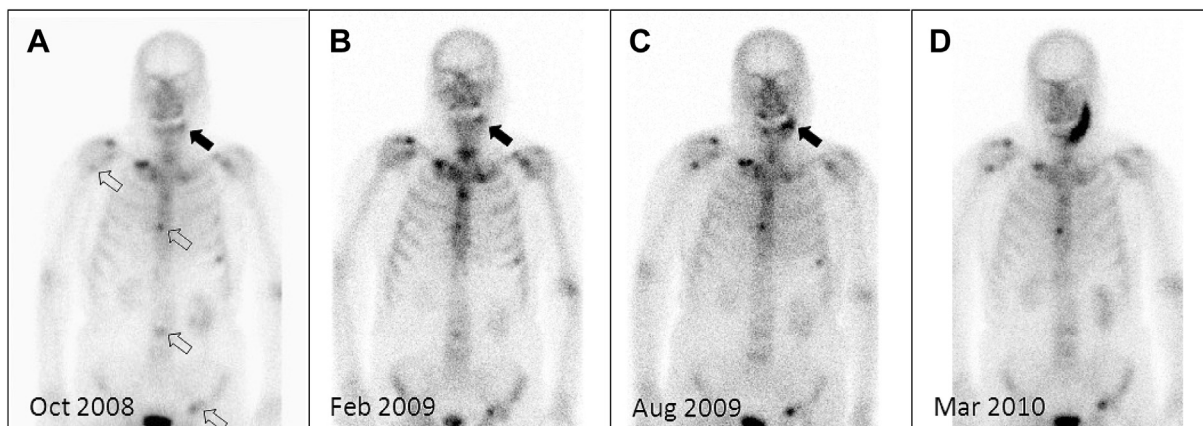


Fig. 4. Sequential changes of the osteonecrosis of the jaw on Tc-99m methylene diphosphonate scanning. In October 2008, the patient took monthly zoledronic acid to treat distant bone metastases (open arrows). After 1 year of therapy with partial response of metastatic disease, the patient sought dental treatment for a non-healing tooth socket in the left mandible (black arrow). In June 2010, a necrotic bone in the left mandible was noted clinically, consistent with the criteria of bisphosphonate-related osteonecrosis of the jaw (black arrow). Hormone therapy was given instead of zoledronic acid. Ludwig's angina developed in September 2010 (Fig. 2).

identified on the bone/tooth and mucosal surfaces around BRONJ that are composed of *Actinomyces* and other organisms.^{4,5} However, it is unclear if bisphosphonates causes direct toxicity to the bone and/or soft tissues, which is infected secondarily,^{6,7} or if infection is the immediate cause exacerbated by the use of bisphosphonates. Nevertheless, necrotic bone may be the infectious source in the oral cavity, especially in immunocompromised patients who are under chemotherapy. Furthermore, the lesion may progress to cause a serious complication, as was the case in our patient.

BRONJ appears to be time-dependent with higher risk after long-term use of bisphosphonate.⁸ Our patient had been treated with zoledronic acid for >1 year. Although he was followed-up by appropriate dental care, the presence of osteonecrosis was not noticeable initially. However, a small focus had been seen in the lower jaw about 19 months before the patient's surgeon was aware of his problems and took intervention (Fig. 4). It is not clear whether the radiotracer deposits in BRONJ bone or the surrounding reactive bone.⁴ Nevertheless, increased uptake on bone scintigraphy is noted in a majority of BRONJ cases, varying from 60% to >90%.^{4,9} Dore et al¹⁰ described the high sensitivity of bone scanning in identifying BRONJ in the early stage, especially with single-photon emission computed tomography/computed tomography. Generally speaking, bone scintigraphy appears to be a sensitive but not specific modality in this setting and is considered valuable in delineating early BRONJ in most cases.

Ludwig's angina, characterized as a rapidly progressive gangrenous cellulitis of the mouth floor, is an ear, nose, and throat emergency. It can lead to lethal consequences due to airway obstruction. Most cases of Ludwig's angina are odontogenic in etiology, primarily resulting from infections of the second and third molars, where BRONJ happens to occur most readily. Once infection develops, it spreads contiguously to the sublingual space and may spread to the deep neck space.

Although no similar case has been reported, the authors suggest that BRONJ may be a risk factor of submandibular and sublingual infection, and when a cancer patient is treated with zoledronic acid, Tc-99m methylene diphosphonate bone scintigraphy is considered as a reasonably effective diagnostic tool to identify BRONJ in the early stage.

References

1. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;**61**:1115–7.
2. Favus MJ. Diabetes and the risk of osteonecrosis of the jaw [editorial]. *J Clin Endocrinol Metab* 2007;**92**:817–8.
3. Advisory Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *J Oral Maxillofac Surg* 2007;**65**:369–76.
4. Estilo CL, Van Poznak CH, Williams T, Bohle GC, Lwin PT, Zhou Q, et al. Osteonecrosis of the maxilla and mandible in patients with advanced cancer treated with bisphosphonate therapy. *Oncologist* 2008;**13**:911–20.
5. Hansen T, Kunkel M, Weber A, Kirk J, Patrick C. Osteonecrosis of the jaws in patients treated with bisphosphonates—histomorphologic analysis in comparison with infected osteoradionecrosis. *J Oral Pathol Med* 2006;**35**:155–60.
6. Reid IR, Bolland MJ, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? *Bone* 2007;**41**:318–20.
7. Scheper MA, Badros A, Chaisuparat R, Cullen KJ, Meiller TF. Effect of zoledronic acid on oral fibroblasts and epithelial cells: a potential mechanism of bisphosphonate-associated osteonecrosis. *Br J Haematol* 2009;**144**:667–76.
8. Saifeldeen K, Evans R. Ludwig's angina. *Emerg Med J* 2004;**21**:242–3.
9. Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y. “Bis-phossoy jaws”: high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. *J Craniomaxillofac Surg* 2008;**36**:95–103.
10. Dore F, Filippi L, Biasotto M, Chiandussi S, Cavalli F, Di Lenarda R. Bone scintigraphy and SPECT/CT of bisphosphonate-induced osteonecrosis of the jaw. *J Nucl Med* 2009;**50**:30–5.