

## Bisphosphonate related osteonecrosis of the jaws: report of two cases

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### ABSTRACT

Bisphosphonates are compounds used to treat osteoporosis and malignant bone metastasis. Despite the benefits related to the use of these medications, osteonecrosis of the jaws is a significant complication in a subset of patients receiving these drugs. This complication occurs either spontaneously or after a simple dento-alveolar surgery. Recently there were two patients who showed the features of bisphosphonate related osteonecrosis of the jaws (BRONJ) in Gangneung-Wonju National University Dental Hospital. The patients revealed the clinical and radiological features of classical osteomyelitis. This report presents two cases of BRONJ which were examined by plain radiography and computed tomography. (*Imaging Sci Dent 2011; 41 : 129-34*)

**KEY WORDS** : Bisphosphonate; Osteonecrosis; Tomography, X-ray Computed; Osteoporosis

Bisphosphonates are agents used to treat or prevent osteoporosis and treat malignant bone lesion. These agents have been increasingly recommended for use in patients with osteoporosis, Paget's disease of bone, osteolytic bone metastases, and so on.<sup>1-4</sup> Also, these agents reduce skeletal complications such as pain, pathologic bony fracture, and size of osteolytic lesion.<sup>1-3</sup> Oral bisphosphonates such as alendronate (Fosamax) and risedronate (Actonel) are used for the treatment of postmenopausal osteoporosis. These medications are usually prescribed once a week (alendronate 70 mg, risedronate 35 mg).<sup>1</sup>

Despite the benefits related to the use of these medications, osteonecrosis of the jaws is a significant complication in a subset of patients receiving these drugs.<sup>1,2,5,6</sup> It appears that the pathogenesis of this process is most consistent with a defect in the jaw bone physiologic remodeling or wound healing. The negative impact of bisphosphonate is the inhibition of osteoclast function.<sup>1-3,5</sup> Once deposited on the surface of bone, bisphosphonates are internal-

ized by osteoclast, causing disruption of osteoclast-mediated bone turnover and resorption.<sup>2-4</sup>

This complication usually presents after dento-alveolar trauma, elective dental surgery or tooth extraction.<sup>5-8</sup> However, a subset of edentulous and dentate patients have developed necrotic bone spontaneously.<sup>2</sup> There is an increasing concern that the oral bisphosphonates are implicated in osteonecrosis of the jaws.<sup>8</sup>

Recently there were patients showing the features of bisphosphonate related osteonecrosis of the jaws (BRONJ). This report demonstrates 2 cases of BRONJ examined using plain radiography and computed tomography (CT).

### Case Report

#### Case 1

A 74-year-old woman had a complaint of bony exposure on the left posterior maxilla after spontaneous loss of the left maxillary first and second molars 3 months ago. She had been taking oral risedronate (Actonel), a kind of bisphosphonates, 35 mg once weekly for 4 years because of osteoporosis. The intraoral examination revealed the bony exposure on the left maxillary alveolar region, pus discharge, and bleeding on the same site as well as sequestrum

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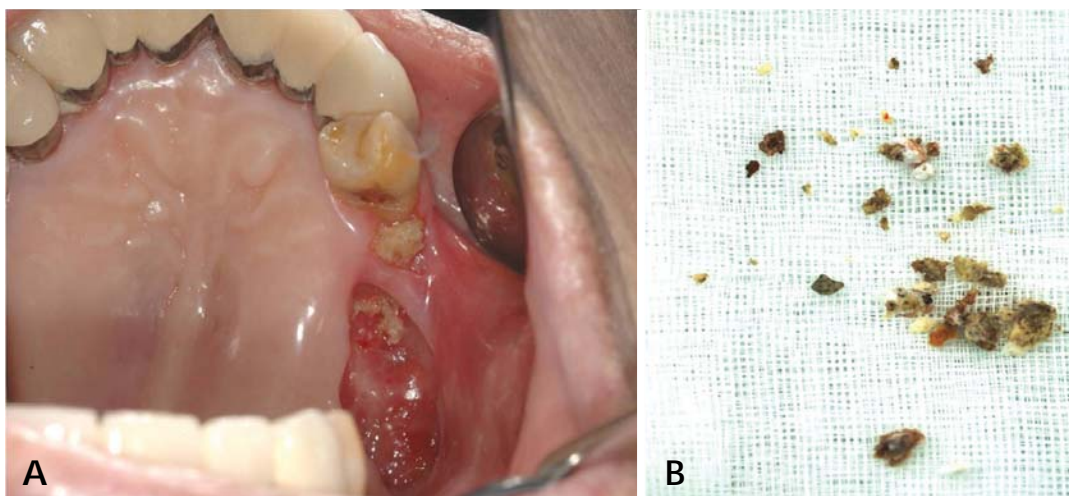


Fig. 1. Intraoral examination reveals alveolar bone exposure (A) and detached sequestrum (B) on left maxillary area of case 1.



Fig. 2. Panoramic radiograph shows a large osseous crater on left maxillary edentulous area.

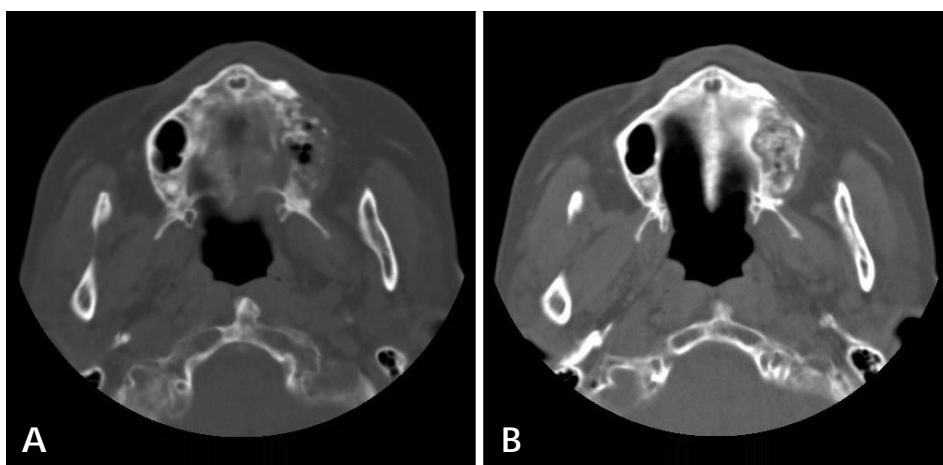


Fig. 3. A. Axial CT image reveals cortical bone destruction, sclerotic change of adjacent trabecular bone. B. Axial CT image reveals numerous bony fragments that is considered as sequestrum.

detached from the area (Fig. 1).

The patient took a panoramic radiograph and CT. On the panoramic radiograph, a large osseous crater and cor-

tical bone destruction were found on the left maxillary edentulous area (Fig. 2). CT images demonstrated cortical bone destruction on the left maxillary edentulous area and

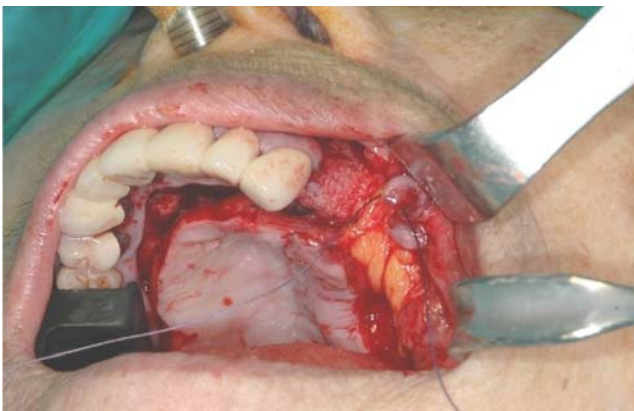
maxillary sinus wall. Adjacent trabecular bone showed sclerotic change. The lesion extended to the maxillary sinus floor and mucositis were observed on the sinus floor. Also there were scattered sequestra on the left maxilla and sinus floor (Fig. 3).

The patient was diagnosed with BRONJ from the clinical and radiological examinations. Treatment began with the cessation of bisphosphonates therapy and removal of the left maxillary first premolar. Saucerization and decortication were performed on that area with sequestrectomy (Fig. 4).

Biopsy from the lesion of bone demonstrated sequestrum infiltrated with chronic inflammatory cells. There was not vivid osteocyte in the lacunae (Fig. 5). Through the histopathologic feature, this case was confirmed as BRONJ. During 6 months follow-up period, there was no sign of recurrence (Fig. 6).

## Case 2

A 72-year-old woman had a chief complaint of swelling

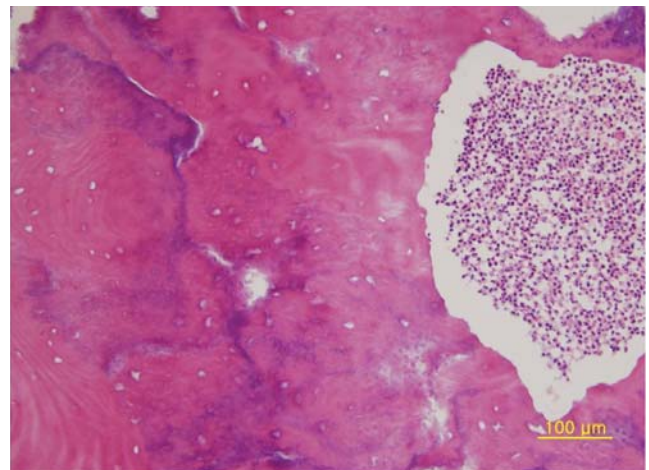


**Fig. 4.** Saucerization and decortication are performed on that area with sequestrectomy.

on the left maxillary canine area after extraction of the left maxillary canine 2 months ago. She had been taking oral risedronate (Actonel), a kind of bisphosphonates, 35 mg once weekly for 3 years and 5 months because of osteoporosis. The intraoral examination showed a necrotic bone exposure on the left maxillary edentulous area with a swelling and pus discharge through a fistula.

The patient took the intraoral and panoramic radiographs, and CT. Plain radiological examination showed a sequestrum of bony fragment with trabeculation at the socket area (Fig. 7). CT images demonstrated the separated lamina dura from the extraction socket of the canine and mild mucositis on the left maxillary sinus (Fig. 8). The patient was diagnosed with osteomyelitis from the clinical and radiological examinations. The treatment was performed with saucerization, fistulorraphy, and sequestrectomy.

The patient revisited 1 year and 6 months later. The chief



**Fig. 5.** Photomicrograph of specimen of biopsy shows infiltration of chronic inflammatory cell and no vivid osteocyte in the lacunae (H&E stain,  $\times 200$ ).



**Fig. 6.** Panoramic radiograph shows bone remodeling on the 6 months follow-up period in case 1. There is no sign of recurrence on left maxillary area.





Fig. 7. A. Intraoral radiograph of case 2 reveals bony fragment with trabeculation on socket of left maxillary canine. B. Panoramic radiograph shows separated lamina dura on socket of left maxillary canine.

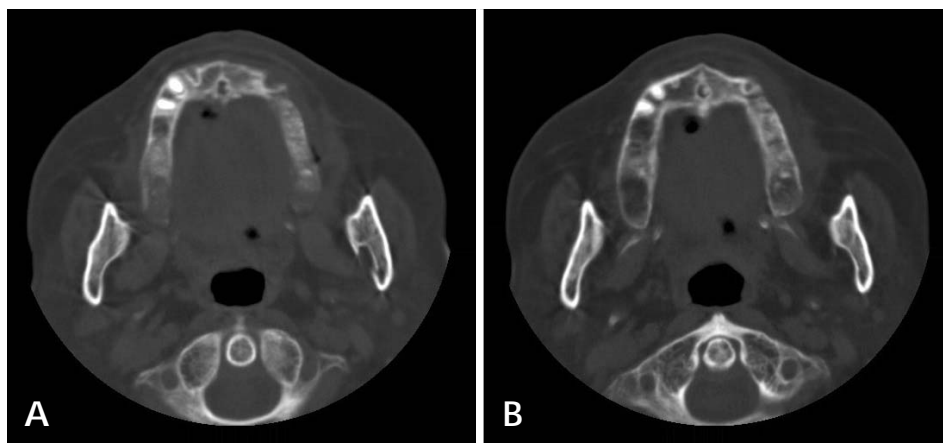


Fig. 8. A. Axial CT image reveals separated lamina dura on socket of left maxillary canine. B. Axial CT image shows mild buccal soft tissue swelling.



Fig. 9. Intraoral examination of case 2 reveals recurrence sign of alveolar bone exposure and pus discharge on right mandibular edentulous area.

complaint was bony exposure on the right mandibular edentulous area with pus discharge (Fig. 9). Plain radiographic

examination showed the decrease in bone density on the right mandibular alveolar process, resorptive area with irregular shape, and sequestrum on the crestal area (Fig. 10). The patient was diagnosed with BRONJ from the clinical and radiological examinations. Treatment began with the cessation of bisphosphonates therapy. And then, saucerization and decortication were performed on that area with sequestrectomy. Biopsy from the bony lesion demonstrated sequestrum infiltrated with chronic inflammatory cell as well as bacterial flora (Fig. 11). Histopathologic findings confirmed the diagnosis of BRONJ. During 3 months follow-up period, there was no recurrence sign.

## Discussion

Bisphosphonates inhibit osteoclast-mediated bone turnover and endothelial cell function. Cells treated with bisphosphonates demonstrate decreased proliferation, incre-

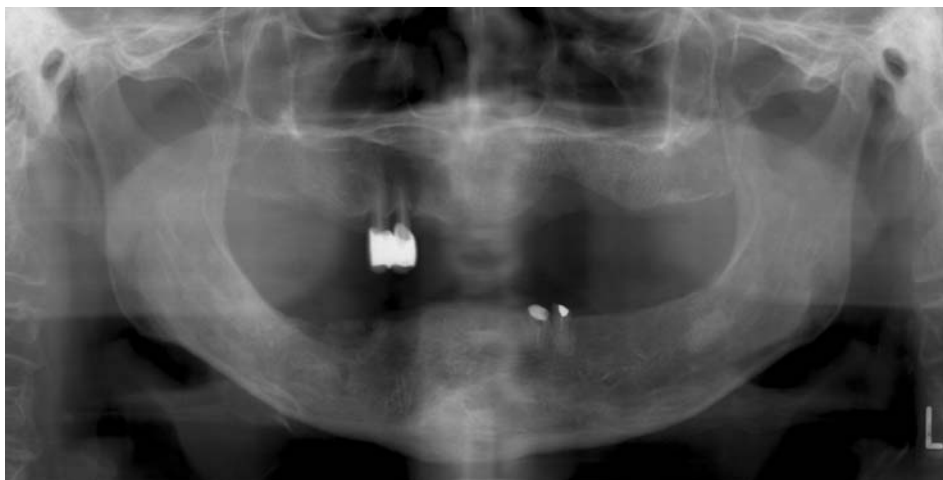


Fig. 10. Panoramic radiograph shows decreased bone density and sequestrum on right mandibular area.

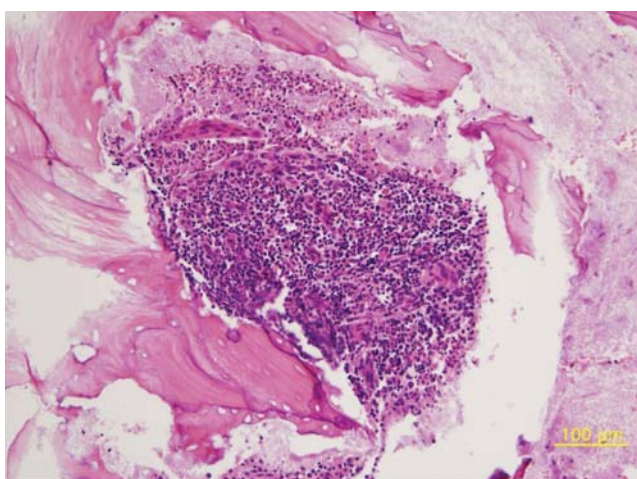


Fig. 11. Photomicrograph of sequestrum shows heavy infiltration of chronic inflammatory cell and bacterial flora (H&E stain,  $\times 200$ ).

ased rate of apoptosis, and a decrease in capillary-tube formation.<sup>1,4</sup> Bisphosphonates also demonstrate antiangiogenic properties owing to their ability to significantly decrease circulating levels of vascular endothelial growth factor (VEGF).<sup>1,8</sup>

BRONJ was first reported in 2003, recognized a few years after bisphosphonates approval for use.<sup>9</sup> There was a growing number of BRONJ in patients receiving oral bisphosphonates therapy. Ortega et al reported that the incidence of BRONJ varied from 0.15% to 12% of patients receiving bisphosphonates for treatment of osteoporosis.<sup>10</sup>

There is an increasing concern that oral bisphosphonates are implicated in osteonecrosis of the jaws, albeit less commonly than that observed with the more potent intravenously administered bisphosphonates. Recent retrospective clinical studies have identified several potential risk factors associated with the development of BRONJ. These include

a history of dento-alveolar trauma, duration of bisphosphonates exposure, and the type of bisphosphonates.<sup>3,7,9-12</sup> In the majority of BRONJ cases reported to date, recent dento-alveolar trauma was the most prevalent and consistent risk factor.<sup>3</sup>

The lesion related with BRONJ is most frequently symptomatic when surrounding tissues become inflamed or there is a clinical evidence of infection. Signs and symptoms include pain, tooth mobility, mucosal swelling, erythema, and ulceration.<sup>2-8</sup> Some patients may also present with complaints of altered sensation in the affected area.<sup>2</sup> These cases showed the clinical features such as pain, bone exposure, pus discharge, bleeding, and swelling. The patients had been taking oral risedronate (Actonel), a kind of bisphosphonates 35 mg, once weekly for treatment of osteoporosis for 4 years and 3 years 5 months, respectively. In both cases, there were loss of teeth that could be regarded as the causative factor of dento-alveolar trauma and subsequent osteonecrosis of the jaws.

Radiographic changes are not evident until there is significant bone involvement. Therefore, panoramic and periapical radiographs may not reveal significant changes in the early stages of osteonecrosis.<sup>1-3</sup> Early or late radiographic changes may mimic classic periapical pathology or osteomyelitis. In the cases presented, plain radiographs and CT images were taken, which showed signs of bone destruction with sequestrum and mucositis on the adjacent maxillary sinus. These features were not differed from classic osteomyelitis.

Magopoulos et al<sup>3</sup> reported that cessation of bisphosphonates therapy combined with surgical debridement and long term antibiotic therapy was the treatment of choice in BRONJ patients. In case 1, the patient was treated with saucerization, decortications, and sequestrectomy on the

problematic area with the cessation of bisphosphonates therapy. During the follow-up period of 6 months, there was no recurrence sign. In case 2, the patient was treated with saucerization, fistulorraphy, and sequestrectomy without cessation of medication. However, there was recurrence of osteonecrosis on the mandible after 1 year 6 months. Treatment was performed again on the recurrent area. Saucerization, decortications, and sequestrectomy were performed with the cessation of bisphosphonates therapy. During the follow-up period of 3 months, there was no sign of recurrence after the retreatment.

It is critical that the dentist should be aware of this significant complication which can occur spontaneously or after any dento-alveolar procedure in the population receiving bisphosphonates. Because the oral examination and review of the patient's medical history are currently the most effective and sensitive means of detecting BRONJ, dental professionals are in a unique position to identify and diagnose this disease process early in its course.

This report serves to alert dentists about the potential complication of bone necrosis in patients receiving bisphosphonates therapy. For the treatment of BRONJ, dentists need to consider ceasing the use of bisphosphonates.

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