

## Case report : The Bisphosphonate-associated Osteonecrosis of the Jaw(BONJ)

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Recently, bisphosphonate-associated osteonecrosis of the jaw(BONJ) is added to the list of diseases of the oromaxillofacial region. BONJ is defined as exposed bone in the jaw that does not heal within 8 weeks after identification, in a patient who has been received to bisphosphonates and has not taken radiation therapy to the craniofacial region. Bisphosphonates bind to bone mineral are concentrated in highly active remodeling site, reside in the skeleton for a long time, and do a role as powerful inhibitors of bone resorption. As the patients receiving bisphosphonates therapy grow in number, the patients of BONJ would go on increasing in Korea. We would like to present two patients who were suspected to BONJ, describe the outline of BONJ, and mention importance of our understanding about BONJ. BONJ is rare disease, but once it develops, its prognosis is very poor. Our adequate understanding of BONJ is necessary to prevent it and cope with it properly.

Key words: Bisphosphonate, Osteomyelitis, Osteonecrosis

### I. INTRODUCTION

There are various diseases in the oromaxillofacial region. However, the similarity of their symptoms and clinical features makes a confusion when the clinicians confirm the diagnosis of the disease. Many imaging techniques and laboratory tests are developed constantly, but there are still limitations. Recently, the other one is added to the list of diseases

of the oromaxillofacial region. That is called bisphosphonate-associated osteonecrosis of the jaw (BONJ). The BONJ is named as different nomenclatures, which are bisphosphonate-related osteonecrosis of the jaw (BRONJ), bisphosphonate-induced osteonecrosis of the jaw (BIONJ), and bisphosphonate-associated osteonecrosis(BON) of the jaw.<sup>1)</sup> BONJ is defined as exposed bone in the jaw that does not heal within 8 weeks after identification by a health care provider, in a patient who is receiving or has received bisphosphonates and has not taken radiation therapy to the craniofacial region. The 8-week duration is consistent with period where oral surgical procedures would have resulted in soft tissue closure, and exposed bone would not exist any longer. Suspected cases of which exposed period cannot fulfil the criteria of BONJ should receive follow-up evaluation to confirm diagnosis.<sup>2)</sup> Bone exposure is

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the precondition of BONJ and other signs and symptoms may or may not be present. But, signs and symptoms may occur before developing detectable osteonecrosis. They include pain, swelling, suppuration, ulceration, mobile teeth, gingival fistula, extraoral fistula and paresthesia. Maxillary sinusitis following osteonecrosis can be found out in maxilla-involved case.

Bisphosphonates bind to bone mineral and are concentrated in highly active remodeling sites, reside in the skeleton for a long time, up to 10 years,<sup>3)</sup> and do a role as powerful inhibitors of bone resorption. Eventually, bisphosphonates increase bone strength by preventing trabecular plate perforation and improving bone mineralization in undermineralized bone.<sup>3)</sup> Oral bisphosphonates prescribed to treat osteoporosis and Paget's disease are etidronate, risedronate, ibandronate, and alendronate. More potent nitrogen-containing bisphosphonates administered intravenously (pamidronate and zoledronate) stabilize metastatic cancer deposits in bone (breast, prostate and lung cancer), and treat the bone resorption of multiple myeloma.<sup>4)</sup>

As the patients receiving bisphosphonates therapy grow in number, the patients of BONJ would go on increasing in Korea. Regardless of administration route, bisphosphonates deposit in entire skeleton of human body. But, osteonecrosis develops uniquely in the jaw bone. This is the reason dental clinicians should pay attention to bisphosphonates. So, we would like to present two patients who were suspected BONJ, describe the outline of BONJ, and mention importance of our understanding about BONJ.

## II. CASE REPORT

### 1. CASE 1

A 65-year-old woman was referred from local dental clinic for two elevated tender lesions on the crest and lingual gingiva of right lower residual ridge on January, 6th, 2009. In the letter of request, her previous dentist said that her extracted wound

discharged pus and didn't respond to any treatment. She complained that the lesion was bited while eating and pressing the lesion made stinging pain. Four months earlier, she had her right lower second premolar and second molar teeth pulled out at local dental clinic. After extraction them, dull pain was followed and extraction wound discharged pus. During four months, repetitive curettage and antibiotics therapy were carried out and symptoms were improved. But wound was not completely healed. Her medical history included hypertension and osteoporosis, she was receiving oral bisphosphonate (alendronate) for five years to manage osteoporosis.

In our hospital, patients underwent panoramic radiograph, computerized tomography (CT) to evaluate of the jaw bone. Although four months have passed after extraction, the shape of extraction sockets have maintained in panoramic radiograph. Also, in the images of CT, we could see the ill-defined trabecular bony destruction with surrounding sclerosis, buccal cortical perforation, and buccolingual periosteal new bone formation of right mandibular posterior body area. We referred the patient to the department of the oromaxillofacial surgery in our hospital. Biopsy for evaluating the bony lesion was performed and the result was osteomyelitis. During two weeks, incision and drainage with systemic antibiotic therapy were performed repeatedly. Pain and swelling relieved gradually, but the wound could not obtain complete healing.



Fig. 1a. Photograph image



Fig. 1b. Panoramic radiograph image

## 2. CASE 2

A 68-year-old woman was referred from local dental clinic for prolonged oral ulcers of tongue and fistula near left labial frenum on March, 26th, 2009. We could find two ulcerated sites on both ventral surface of tongue and could see pus discharge on apical area of left upper central incisor. Left central

incisor was extracted for prosthodontic treatment in the last year(14 months ago). After extraction, the extraction wound didn't heal well and pus discharged constantly. So, in local dental clinic, several times of incision and drainage were performed. Dull pain and intermittent bleeding was followed the one month before. She underwent periodic medical checkup and was prescribed for cerebral infarction, hypertension, benign tumor of thyroid gland and osteoporosis in local medical clinic. For several years, she has taken bisphosphonates to manage osteoporosis. In her early period of treatment, alendronate was prescribed and then, ibadronate was prescribed.

We were planned to refer to the department of oromaxillofacial surgery for managing oral fistula. In the department of oromaxillofacial surgery, they took a periapical film of extracted site(with gutta percha cone tracing) and confirmed that the origin of pus was the extracted site. Bone scan was taken and

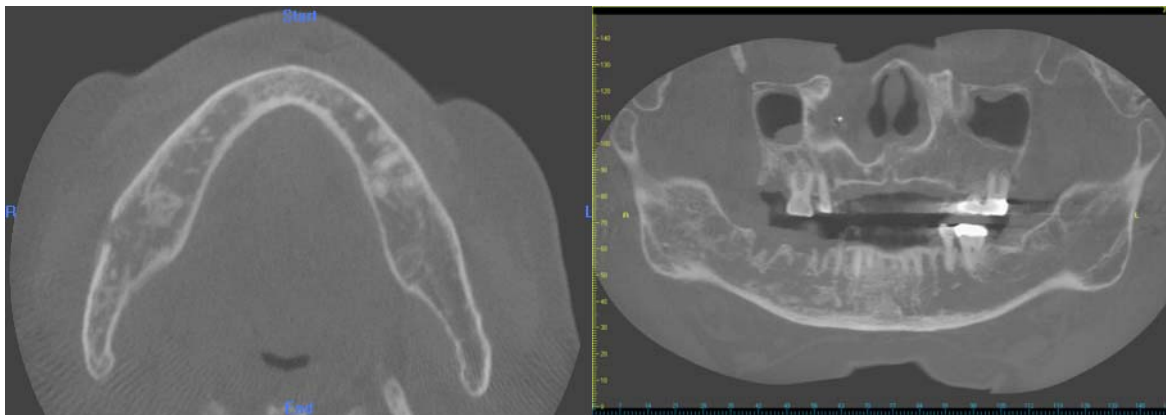


Fig. 1c. Computed tomograph images



Fig. 2a. Photograph images(upper: initial visit, middle: operation, lower: post-operation)



Fig. 2b. Panoramic radiograph image

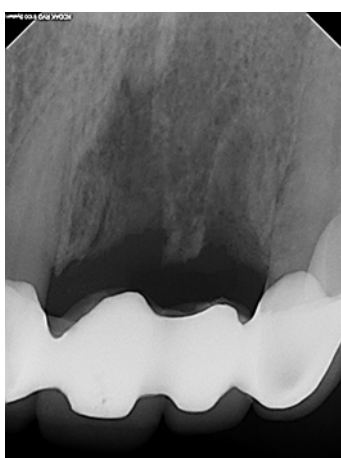


Fig. 2c. Periapical radiograph image

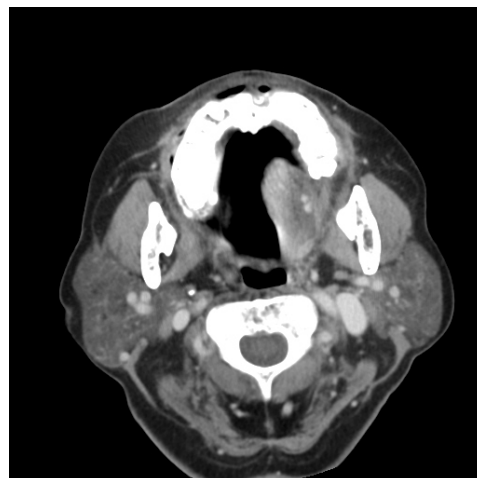


Fig. 2d. Computed tomograph image

revealed some infection in the anterior area of left maxilla. In the CT images of paranasal sinus, bone lysis was found. Systemic antibiotics reduced the amount of pus, but pus discharged constantly. Curettage and histopathological examination of bony lesion was carried out, and the lesions showed the characteristics of osteomyelitis.

### III. DISCUSSION

Common features of two above patients were that extraction wound showed poor healing beyond normal healing period and that oral bisphosphonates were prescribed to manage osteoporosis for several years. They have not taken radiation therapy on craniofacial region. After taking everything into consideration, we could give a diagnosis of BONJ to two cases.



Fig. 2e. Bone scan image

So far, there are no authentic data about incidence of BONJ. The published incidence data of BONJ in patients receiving intravenous bisphosphonates for hypercalcemia and bone metastasis ranges from 0.8% to 12%.<sup>5)</sup> The risk for BONJ in patients treated with oral bisphosphonates for osteoporosis is quite lower than patients treated with intravenous bisphosphonates. In Australian data, the incidence of BONJ for treated with alendronate is 0.01% to 0.04%.<sup>5)</sup> Although oral bisphosphonates are

administered, the medication period over 3 years or existence of medical comorbidities (corticosteroid therapy, diabetes mellitus, systemic chemotherapy, smoking, alcohol use, cancer diagnosis) can increase the risk of BONJ.<sup>6-9)</sup>

Although mechanisms of BONJ have not been well-known, there are several hypotheses. One of the major action mechanisms of bisphosphonates is osteoclastic inhibition, which is supported several mechanisms including inhibition of osteoclast differentiation from monocyte-macrophage precursor, increased osteoclast apoptosis and reduction of osteoclast activity.<sup>10)</sup> In everyday life, mechanical stress are given to normal bone and microcracks occur. The osteocyte detects these microcracks and initiates the bone remodeling cycle to repair the damage. The intense inhibition of osteoclast function cannot repair microcracks from normal mechanical loading or injury.<sup>11)</sup> If bone remodeling is inhibited, bone necrosis can occur eventually. The antiangiogenic property of bisphosphonates is mentioned as a potential contributing factor for the development of osteonecrosis. Bisphosphonates inhibit angiogenesis, decrease capillary tube formation, and inhibit vascular endothelial growth factor both in vitro and animal studies.<sup>12)</sup> However, this theory has been refuted by the fact that more potent antiangiogenic drugs such as thalidomide, alpha-2a interferon, endostatin and angiostatin have not produced osteonecrosis in the jaws.<sup>7)</sup> The other hypothesis is that bisphosphonates accumulated within bone exhibit direct toxic effect on surrounding osteocytes and inhibit proliferation and wound healing capacity of oral mucosa in vitro. It is not clearly known whether the lesion initiates in the bone, or it may originate in the mucosa.<sup>14)</sup> So, it is assumed that bisphosphonates deposits in bone may influence in altering the wound healing of oral mucosa and the initiation of BONJ. Some bisphosphonates are cytotoxic to human intestinal epithelial cells.<sup>15)</sup> The fact suggests that bisphosphonates have a potentially toxic effect on oral mucosa. The case of severe oral ulcerations on the tongue, mouth and oropharynx due

to sucking alendronate tablet was reported.<sup>16)</sup> The patient had no history of aphthous ulcer or any mucosal disorders. Nathaniel et al. reported 5 patients, who had exposed bone lesion resulted from BONJ in the mylohyoid ridge and also had tongue ulcerations which contact directly with the exposed bone.<sup>17)</sup> It suggests the possibility of direct mucosal injury of this drug.

Why does bisphosphonate-induced osteonecrosis develop only in the maxilla and mandible? There are several reasons related to unique environment of the oral cavity. First, jaw bone covered with oral mucosa is exposed and communicates to the external environment. In oral cavity, normal oral microflora always exist and other microorganisms invade frequently. Also, bisphosphonates are preferentially deposited in the active remodeling site, such as the maxilla and mandible. Jaw bones are under occlusal pressure constantly, so active bone remodeling is continued. Frequent dental treatments involved with dentoalveolar bone is another reason.<sup>7,18,19)</sup> They include dental extraction, dental implant placement, periapical surgery and periodontal surgery involving osseous injury. Local anatomy including mandibular tori, mylohyoid ridge and palatal tori is other risk factor. Their covering mucosa is so thin that can get injured easily from denture, dental instrument, toothbrush and so on. And periodontal disease and periapical disease themselves increase the risk of BONJ.<sup>5)</sup>

In evaluating the bony lesion of our patients, we used panoramic and periapical radiographs, CT and bone scan. Besides the imaging techniques we used, magnetic resonance image(MRI) can give additional information. The various radiographic findings of BONJ are sclerosis of bone, thickened lamina dura, persistent extraction socket, bony lysis, sequestration and periosteal new bone formation. Sclerosis and persistent extraction socket is imputed to mineralization resulted from reduced resorption of the bone and marked inhibition of remodeling.<sup>20-22)</sup> Periosteal reaction and sequestration are predominant in advanced stage. Panoramic radiograph is routinely used and easily accessible

imaging method to evaluate the jaw bone. But there are some limitations. As the buccal and lingual cortical bone may cover the internal body of jaw, any internal change is difficult for panoramic radiograph to visualize.<sup>20)</sup> Radiographic changes in panoramic and periapical radiographs are found evidently when there is significant bony involvement, so may not reveal significant changes in the early stage of osteonecrosis. Radiographic findings are similar to periapical pathology, periodontal pathology, bony lesion of multiple myeloma or osteomyelitis, so radiologic differential diagnosis is needed.<sup>18)</sup> Also, the radiographic features resemble osteoradionecrosis, chronic sclerosing osteomyelitis, bony metastasis, and Paget's disease. CT has greater sensitivity in detecting BONJ compared with panoramic radiograph.<sup>23)</sup> Therefore, CT is useful to detect sequestration, periosteal reaction, and extent of osteolysis and shows increased medullary bone sclerosis extending over the limit of the bone exposed in the oral cavity.

BONJ is rare disease, but once it develops, it gives negative impacts the quality of life, causes difficulties with adequate nutritional intake and give harmful effect to maintaining patient's health. Also, it can make medical trouble between patient and clinician. Our adequate understanding of BONJ is necessary to prevent it and cope with it properly. From now on, BONJ should be implicated in differential diagnosis when patients complain pain on maxilla or mandible.

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국문초록

## 증례 보고: 악골에 발생한 비스포스포네이트 관련 골괴사증 (BONJ)

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김균요 · 고유정 · 허윤경 · 최재갑

최근, 골다공증 치료 약물인 비스포스포네이트와 관련된 악골괴사증(BONJ)이 구강악안면 영역에서 발생할 수 있는 새로운 질환의 하나로 떠오르고 있다. 비스포스포네이트와 관련된 악골괴사증은 구강내로 노출된 악골이 관찰된 후 8주가 지나도 완전히 치유되지 않고 지속되는 상태를 말하며, 환자는 구강악안면 영역에 방사선 치료를 받은 병력이 없어야 하며, 비스포스포네이트로 치료 중이거나 치료받은 병력이 있어야 한다. 비스포스포네이트는 골에 결합하는 물질인데, 골개조가 활발히 일어나는 곳에 고농도로 집적되어 장기간 골격 내에 머물면서 골흡수를 강력히 억제하는 효과를 발휘한다. 한국에서도 골다공증이 나 암환자에서 골전을 막기 위해 비스포스포네이트로 치료를 받는 환자가 점차 늘고 있으며, 이는 또한 BONJ의 발생 가능성도 증가함을 의미한다. 우리는 BONJ로 의심되는 환자를 두 증례 소개하고자 하며, 이와 함께 BONJ가 어떤 질환이며, BONJ에 대한 치과의사의 인식의 중요성을 언급하고자 한다. BONJ는 드물게 발생하는 질환이긴 하나, 일단 발생하면 예후가 불량한 경우가 대부분이다. 그래서, BONJ에 대한 충분한 이해가 악골괴사를 예방하고, 치료하는 데 반드시 필요할 것이다.

주제어: 비스포스포네이트, 골괴사증, 골수염

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