Case Report

Post-Herpetic Osteonecrosis of the Jaw in a Patient on Oral Ibandronate Therapy: A Case Report

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Background: Osteonecrosis of the jaw (ONJ) is a rare complication, which can be caused by bisphosphonate administration. Clinical features include bone death with areas of persistent bone exposure. This complication can be triggered by several factors including trauma, dental surgery, and infection.

Case Report: The authors report a rare case of ONJ in a 58-year-old female patient, who is on oral ibandronate therapy for osteopenia and subsequent to an episode of herpes zoster (HZ) infection. The patient presented with unresolved gingival swelling with pus exudate and bone exposure at lower right molar area. Tingling sensation was presented at the right side mandibular skin. Root planning was given and followed by Clindamycin administration, however, the condition still persisted. A definitive diagnosis of ONJ was made after no sign of bone healing over a period of 2 months. Ibandronate was then discontinued after consultation with her doctor. Extraction of symptomatic tooth within exposed bone was then considered since periodontal treatment did not improve the condition. Lower right first molar was extracted followed by antibiotic prescription for 2 weeks. The swelling gingiva and exposed bone healed in 2 weeks, the tingling sensation subsided after 4 months, and the extraction socket was completely filled in 3 years.

Conclusion: Long-term oral bisphosphonate administration and an episode of HZ infection could cause ONJ in this patient. HZ infection may trigger the development of ONJ. This could be due to the impaired healing effect of bisphosphonates.

Keywords: Osteonecrosis of the jaw, Osteopenia, Herpes zoster virus, Bisphosphonate

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Osteoporosis is the most common metabolic bone disorder. It affects approximately 200 million of the population worldwide[1]. If left untreated, the disease can result in serious health issues such as fragility fractures, bone deformities and disability. Furthermore, osteopenia, a condition characterized by low bone mineral density but to the lesser extent than osteoporosis, can also lead to a risk of bone fracture. It has been estimated that osteoporosis led to 1.5 million fractures per year in the US[2].

Thus, prevention and treatment of these conditions are crucial. The therapeutic strategy is to inhibit the resorption of bone by osteoclasts. The most frequent class of drugs prescribed to treat these disorders is bisphosphonates[3]. Among many marketed bisphosphonates, ibandronate (a nitrogen-containing bisphosphonate) has been approved for the prevention and treatment of postmenopausal osteoporosis. It is available both in oral and intravenous formulations. Ibandronate therapy has been proved to effectively stabilize bone loss by reducing bone turnover in postmenopausal osteoporosis[4,5]. A serious adverse effect of bisphosphonate administration is osteonecrosis of the jaw (ONJ), a condition leading to a localized areas of bone death and persistent bone exposure for more than 2 months and with no history of radiation therapy to the jaw bone[6,7].

ONJ can be induced by several etiologic factors[8]. Therapeutic indications and type of medications can affect ONJ frequency[9]. Up to date, intravenous bisphosphonate formulation in patients with advanced malignancies and skeletal metastases remains the major risk factor for ONJ[6,9-12]. Only a small number of cases have been diagnosed with ONJ following oral bisphosphonate route[9,13]. Predisposing factors for the development of ONJ include history of trauma, dental surgery, or dental infection[12-14]. In addition, a few cases of osteonecrosis have been reported in association with herpes zoster (HZ) infection of the trigeminal nerve[15-18].

HZ is a painful vesicular rash presenting in the area innervated by the affected sensory nerve. The lesions are frequently located in the thoracolumbar dermatomes in about half of the cases, followed by the facial dermatomes innervates by the trigeminal nerve[19]. When the maxillary or

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mandibular divisions of the trigeminal nerve are involved, lesions may appear unilaterally either on the face, or the oral mucosa innervated by the nerve. The most common complication of HZ infection involving the trigeminal nerve is a prolonged post-herpetic neuralgia[18,20]. Osseous involvement in HZ infection is a rare phenomenon[21].

Here, the authors present a case of post-herpetic ONJ in a patient on long-term ibandronate therapy for osteopenia.

Case Report

The 58-year-old Thai female patient was diagnosed with osteopenia and had been taking 150 mg of ibandronate (Boniva) once a month orally for 2 years to prevent osteoporosis. In June 2009, she was diagnosed with HZ in the right mandibular area and was prescribed Acyclovir 300 mg every 8 h for 7 days. About 3 weeks after the episode, she presented at Thammasat University Dental Clinic with an abscess at the right lower molar gingiva and complaining of pain in the affected region. The patient also reported tingling sensation at the right mandibular dermatome. She was diagnosed with periodontitis and was treated by subgingival root planning and irrigation with normal saline solution. After 2 weeks, however, pain and abscess were not subsided. The patient was then referred to Thammasat University Oral and Maxillofacial Surgery clinic (OMF clinic) for further evaluation.

In September 2009, the patient presented at the OMF clinic for further examination, diagnosis, and treatment of the sign and symptom. Extraoral examination, on presentation, revealed scars of the right mandibular skin due to HZ infection (Figure 1A). Intraoral examination showed a long span bridge extending from lower right first premolar to lower right second molar. Gingival swelling with pus discharge and exposed bone were seen between lower right first molar and second molar area (Figure 1B). A 9-mm pocket was presented at the distolingual area of lower right first molar. Radiograph show radiopacity of prosthetic bridge. Alveolar bone around the roots of lower right first molar and second molar area was dense and displayed radiating trabecular pattern (Figure 1C).

A swab of pus for culture and sensitivity tests was taken and the patient was prescribed Clindamycin 300 mg 1x3 for 1 week. The culture yielded a growth of *Streptococcus* group D.

Based on American Association of Oral and Maxillofacial Surgeons definition, these signs and symptoms were consistent with ONJ that the patient had current treatment with a bisphosphonate, showed exposed bone in the maxillofacial region persisting for more than 8 weeks, and had no history of radiation therapy to the jaws[7]. Orthopedic surgeon was then consulted, and a decision was made to discontinue ibandronate since then. With regard to the bridge, the joints between lower right second premolar, first molar, and second molar were cut and lower right first molar was extracted. Amoxicillin/clavulanate 1 g 1x2 for 2 weeks and 0.2% chlorhexidine mouth rinse were then prescribed because the patient had rash after taking Clindamycin.

At 1-week follow-up, the patient reported pain relief in the molar area. Healing of alveolar socket was observed. However, tingling sensation at the right mandibular dermatome still persisted. At the four-month follow-up, patient showed a slowly healing socket (Figure 2A) and the itching sensation subsided. Patient education and routine follow-up for oral health care were continuously given to maintain good oral hygiene and prevent ONJ. The extraction socket was completely filled within 3 years (Figure 2B). Lower right second premolar was later retreated (Figure 2B) but had been extracted later. In 2015, all teeth from lower right first premolar to first molar had been replaced with implants (Figure 2C).

Discussion

Oral bisphosphonates are the most widely prescribed antiresorptive drugs used to treat and prevent

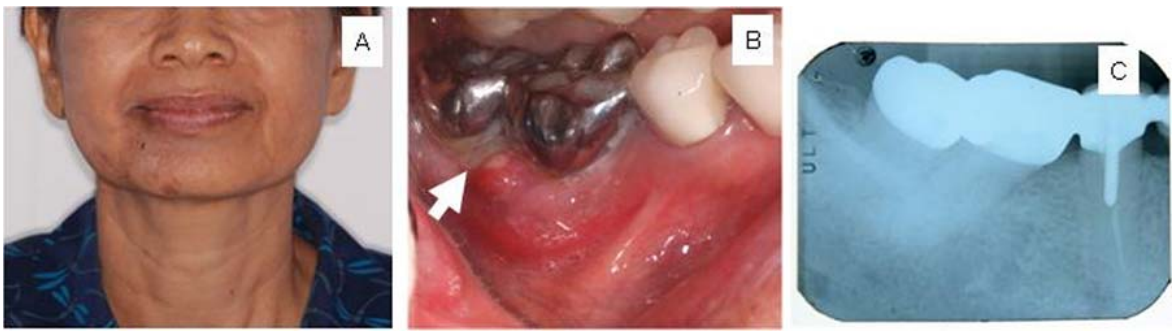

Figure 1. A) Skin lesions of herpes zoster (healing phase) on the right mandibular region (V3 area), (B) Gingival swelling with pus discharge and bone exposure (arrow) seen on interdental papilla between lower right first molar and second molar, (C) Periapical radiograph of lower right second premolar to second molar area.

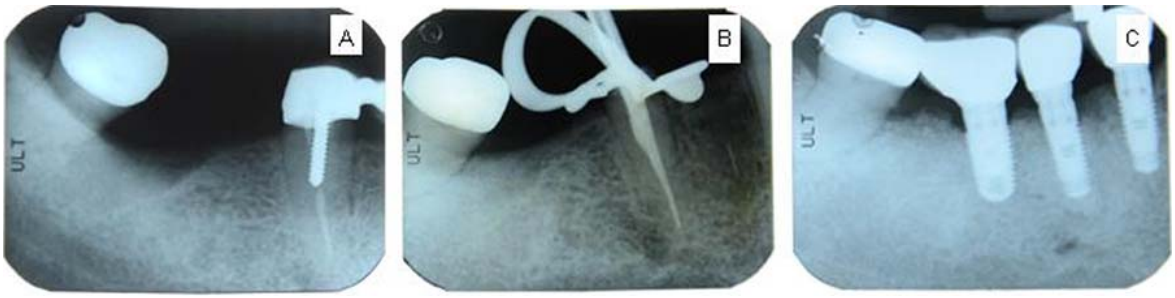

Figure 2. Periapical radiograph of lower right second premolar to second molar area A) 4 months after extraction, B) 3 years after extraction, and C) 6 years after extraction.

osteoporosis. Among the commonly prescribed oral bisphosphonates, ibandronate is one that the dental professionals could come across. Like other bisphosphonates, prolonged use of oral ibandronate has been reported recently to associate with ONJ[13], regardless of its low incidence. There are also reports of association between osteonecrosis and HZ infection although it is a rare phenomenon[18,21-23]. To the best of the authors' knowledge, this paper is the first to report the clinical presentation of a non-oncology patient with ONJ who had received oral ibandronate and experienced an episode of HZ infection.

Ibandronate is a potent and long-acting bisphosphonate that accumulates to bone surface and in intra-osseous for prolonged periods after administration[24,25]. Since the first report of bisphosphonate-related osteonecrosis of the jaw in 2003, a number of reported cases have risen dramatically. However, most case reports were oncology patients receiving long-term intravenous (IV) bisphosphonates[6,11,26]. Among ONJ patients, the occurrence of ONJ are more frequently in patients receiving IV bisphosphonates (94.2%) than in patients receiving oral forms (5.8%). In addition, most patients who developed ONJ had cancer (93.8%)[26]. The risk for ONJ in patients exposed to IV bisphosphonates for cancer therapy is higher than those exposed to oral bisphosphonates (up to 20% vs. 0.07%)[12,27,28]. In Korea, the estimated frequency of ONJ in osteoporotic patients taking oral bisphosphonates has been reported to range from 0.05 to 0.07%[28]. In Australia, the occurrence of ONJ associated with oral alendronate is 0.01 to 0.04%[12]. It has been estimated that the risk of ONJ in osteoporotic patients who receive oral bisphosphonates increases approximately 2.3-fold compared with patients who do not[29]. Most case reports of ONJ associated with oral bisphosphonates had been prescribed with alendronate[12,13,28,30]. Few cases have been reported in association with ibandronate[12,13,28,30]. Despite its low risk, this particular complication should not be overlooked.

Several risk factors contribute to the development of ONJ. The most commonly cited factor is oral surgical procedures, tooth extraction in particular[6,12,13]. It is calculated that tooth extraction increases the frequency of ONJ by 9-fold in patient taking oral bisphosphonate for the treatment of osteoporosis[12]. This suggests that patients taking bisphosphonates have a greater risk of getting ONJ after dentoalveolar surgery. Additionally, ONJ can also be initiated by infection[14,31]. Park et al describes periapical infection and periodontitis as preceding events before the patient are diagnosed with ONJ. These patients had a history of receiving oral bisphosphonates to prevent osteoporosis[31]. Uncommon presentations of ONJ following HZ infection involving trigeminal nerve have also been reported[18, 21-23].

HZ is caused by varicella zoster virus, which remains in the sensory ganglia in a latent state. When the latent virus is reactivated, a cutaneous vesicular eruption and/or alveolar bone necrosis are induced in the area of innervated sensory nerve[18,21-23]. The occurrence of HZ is approximately 0.2 to 0.3% per year and usually occurs in middle-aged and elderly people[23]. The incidence of activation in the trigeminal nerve is 13%, with the ophthalmic nerve most affected, followed by the maxillary and the mandibular nerves, respectively[32]. The complications of osteonecrosis have been reported to occur at the range from 2 to 12 weeks with average of 21.2 days after HZ reactivation[18,22,33,34]. In this case presentation, bone exposure occurred 3 weeks after HZ manifestation.

Physiologic osseous healing requires a series of healing steps and multiple cell types. Ibandronate could interfere with several cellular functions in the bone microenvironment. The primary theory is the suppression of osteoclast and osteoblast activities[35,36], consequently lower the ability of bone repair. Alternatively, the antiangiogenic property of ibandronate may affect local blood supply[37], although patent vessels have been monitored in most histological examinations[38]. Apart from these two common theories, other cell types, i.e. fibroblast and macrophage, are also affected by ibandronate[35,39]. The combined impact of this drug on the above mentioned cells may contribute to impaired wound healing. It is postulated that herpes zoster can cause alveolar bone damage by affecting vascular supply and the terminal branches of trigeminal nerve supplying the periodontium and periosteum[17,20,40].

Ibandronate and HZ have been both reported separately to cause osteonecrosis, however this case reported two factors contributing to the development of ONJ. The

association of ibandronate and herpes zoster induced bone necrosis is not clear. Here, we proposed that ibandronate affected the bone repair processes by reducing resident bone cell functions. A varicellar zoster virus infection might accelerate the rate of periodontal breakdown and could favor the growth of subgingival periodontopathic bacteria[17]. Because alveolar bone is separated from the oral cavity by a thin lining periodontium and chronically exposed to the outside environment and oral microbiota, it may be more susceptible to damage by ibandronate accumulation in the bone. When trauma and/or infection of the jaw bones incite the pre-existing ibandronate-impaired alveolar bone, the healing capacity of such bone and surrounding soft tissues may be doubly impaired.

Conclusion

There is no conclusive relationship between oral bisphosphonate and HZ infection and the risk of developing ONJ. This report serves to alert dental and medical professionals to the importance of a thorough medical history, including the concurrent drug therapy. Proper guidance, comprehensive dental assessment and preventive dental regimen should be provided to patients. Many questions concerning the underlying pathogenesis of ONJ still remain. Further research is needed to elucidate the precise relationship between bisphosphonates, risk factors, trigger events and ONJ.

What is already known on this topic?

Oral bisphosphonates can cause ONJ but this condition occurs at a very low rate. Common risk factors for inducing ONJ include surgical procedures such as tooth extraction, and infection.

What this study adds?

The present study reported the first case of ONJ in a patient who received oral bisphosphonate and experienced an episode of HZ infection.

Potential conflicts of interest

The authors declare no conflict of interest.

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ภาวะกระดูกขากรรไกรตายภายหลังจากติดเชื้อไวรัสงูสวัดในผู้ป่วยที่ได้รับยาไอแบนโดรเนต: รายงานผู้ป่วย

สมหญิง พัฒน์ธีรพงศ์, จักรพงศ์ เตชนันท์, ปาริฉัตร ลิ้มสุวรรณ

ภูมิหลัง: ภาวะกระดูกขากรรไกรตาย เป็นภาวะแทรกซ้อนที่พบได้ยาก สามารถเกิดขึ้นได้จากการได้รับยากลุ่มบิสฟอสโฟเนต อาการแสดงทางคลินิกที่สำคัญคือมีตำแหน่งกระดูกตายเผยผึ่งไม่มีเนื้อเยื่ออ่อนปกคลุม ภาวะนี้อาจถูกกระตุ้นได้จากหลายปัจจัย เช่น การบาดเจ็บ การผ่าตัดในช่องปาก และการติดเชื้อ

รายงานผู้ป่วย: ผู้ป่วยหญิง อายุ 58 ปี ได้รับยาไอแบนโดรเนตชนิดรับประทานเพื่อรักษาภาวะกระดูกบางและมีอาการของการติดเชื้อไวรัสงูสวัด ได้รับการวินิจฉัยว่ามีภาวะกระดูกขากรรไกรตาย มารับการรักษาด้วยอาการเหงือกบวมมีหนอง และมีกระดูกเผยผึ่งที่บริเวณกระดูกขากรรไกรล่างด้านขวาบริเวณฟันกราม นอกจากนี้ผู้ป่วยมีความรู้สึกเหมือนโดนของแหลมทิ่มแทงบริเวณผิวหนังด้านนอกของขากรรไกรล่างขวา ผู้ป่วยได้รับการเกลารากฟันและยาคลินดามันซิน แต่อย่างไรก็ตามอาการเหงือกบวมมีหนองและมีกระดูกเผยผึ่งยังคงอยู่ ให้การวินิจฉัยเป็นภาวะกระดูกขากรรไกรตายหลังจากที่ไม่พบการหายของกระดูกที่เผยผึ่งเป็นระยะเวลา 2 เดือน ภายหลังปรึกษาแพทย์เพื่อหยุดยาไอแบนโดรเนต การถอนฟันที่มีอาการในบริเวณที่มีกระดูกเผยผึ่งได้รับการพิจารณา เนื่องจากการรักษาด้วยการเกลารากฟันไม่ได้ผล ผู้ป่วยได้รับการถอนฟันกรามซี่ที่หนึ่งล่างขวาร่วมกับให้ยาปฏิชีวนะเป็นเวลา 2 อาทิตย์ พบว่าเหงือกยุบบวม กระดูกที่เผยผึ่งมีเนื้อเยื่ออ่อนปกคลุมภายใน 2 อาทิตย์ ความรู้สึกเหมือนโดนของแหลมทิ่มแทงลดลงภายหลังจาก 4 เดือน และหลุมเบ้าฟันที่ถูกถอนไปตื้นขึ้นในเวลา 3 ปี

สรุป: การได้รับยาไอแบนโดรเนตเป็นระยะเวลานานร่วมกับการติดเชื้อไวรัสงูสวัด อาจส่งผลให้เกิดภาวะกระดูกขากรรไกรตายในผู้ป่วยรายนี้ การติดเชื้อไวรัสงูสวัดอาจกระตุ้นให้เกิดภาวะกระดูกขากรรไกรตาย เนื่องมาจากผลของบิสฟอสโฟเนตต่อการหายของแผล