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Original Research

BISPHOSPHONATE INDUCED OSTEONECROSIS OF THE JAWS

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ABSTRACT: Bisphosphonate (BP) is a group of drugs used to treat osteoporosis, multiple myeloma, skeletal metastasis cancer. BP's mechanism of action is to reduce bone resorption by inhibiting the osteoclasts activity. Therefore, the indication of BP is increasingly widespread and becomes the first class of drugs in the treatment of osteoporosis. At Frienship Hospital, over the past five years, we have encountered 12 cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) at various stages. The key message we wish to convey in this report is to kindly encourage close collaboration between internal medicine specialists and oral maxillofacial surgeons during bisphosphonate therapy, in order to minimize the risk of BRONJ complications for patients.

Keywords: Bisphosphonate, bisphosphonate induced osteonecrosis of the jaws (BIONJ)

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1. INTRODUCTION

Bisphosphonates have long been regarded as the preferred therapeutic agents for reducing the risk of vertebral and femoral neck fractures in both men and women with osteoporosis, whether age-related or glucocorticoid-induced. Through the inhibition of osteoclast-mediated bone resorption, bisphosphonates effectively prevent bone loss and preserve skeletal architecture. Their fracture risk–reducing efficacy has been well demonstrated in individuals at high risk of fracture. Furthermore, bisphosphonates are widely utilized in the management of multiple myeloma and bone metastases [1]...

However, in 2003, Marx was the first to report a clinical case of BRONJ. Since then, an increasing number of BRONJ cases have been documented in association with long-term BP therapy [2].

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a severe condition characterized by necrosis of the jawbone in patients undergoing bisphosphonate (BP) therapy. The underlying diseases are often metastatic malignancies (such as multiple myeloma, breast cancer, and prostate cancer), as well as osteoporosis. Several studies have indicated that tooth extraction and infection are strongly associated with the development of BRONJ (Ikebe, 2013) [3].

At Huu Nghi Hospital, the majority of patients are elderly individuals with multiple chronic systemic conditions. Cases of osteoporosis and bone metastases are frequently encountered. Despite this, there remains a lack of effective coordination between internists and oral and maxillofacial surgeons in preventing complications associated with BP use.

This article summarizes cases of jaw osteonecrosis that have been monitored at the Department of Odonto – Stomatology. These cases highlight the importance of obtaining a comprehensive medical history in dental and maxillofacial evaluations and underscore the need for close collaboration between dental specialists and physicians in the management of patients undergoing long-term BP therapy.

2. BACKGROUND

2.1. Mechanism of action of bisphosphonates and pathogenesis of BRONJ

Bisphosphonates (BPs) are synthetic analogues of inorganic pyrophosphate, characterized by limited gastrointestinal absorption and renal excretion without metabolic transformation. BPs exhibit a high affinity for hydroxyapatite crystals in bone and are incorporated at the bone surface. Approximately half of an intravenous dose is absorbed by the skeletal system, where it is retained for extended periods, with a half-life of up to 11 years. Among skeletal sites, the mandible demonstrates a higher bone turnover rate than long bones, and this remodeling activity is even more pronounced in the alveolar bone. Consequently, BPs tend to accumulate selectively in the jawbone. The therapeutic action of BPs is achieved through inhibition of osteoclastic activity, thereby reducing bone resorption and stabilizing bone mass. Moreover, BPs downregulate vascular endothelial growth factor (VEGF), leading to decreased angiogenesis within bone tissue. The dual effects of suppressing osteoclast activity and reducing angiogenesis are believed to contribute to the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ), by impairing the normally rapid bone turnover of the alveolar bone. However, recent evidence suggests that bone remodeling is not necessarily diminished in BRONJ [4–6].

Scanning electron microscopy studies have consistently demonstrated the presence of abundant and diverse bacterial biofilms on the surface of bone affected by BRONJ. One hypothesis posits that bone containing BPs may facilitate bacterial adhesion, as the positive charge generated by the amine groups of BPs interacts favorably with the negative surface charge of bacteria. Osteoclasts are subsequently recruited to these colonized sites, resulting in bone resorption. In vitro experiments further indicate that BP solutions exert cytotoxic effects on multiple cell types; when bone resorption occurs, BPs are released and manifest their cytotoxicity on surrounding cells, thereby contributing to the pathogenesis of BRONJ [4].

2.2. Epidemiology

Evidence from previous studies indicates that the risk of developing BRONJ depends on several factors, including the type of bisphosphonate administered, duration and cumulative dose of exposure, oral health status, and the anatomical site involved.

BRONJ has been reported most frequently in association with nitrogen-containing bisphosphonates of higher potency, such as zoledronic acid and pamidronate. The incidence is notably higher with zoledronic acid, which produces a greater reduction in type I collagen degradation products (N-telopeptides), resulting in more pronounced antiresorptive activity and, consequently, a more substantial suppression of bone remodeling [7].

The incidence of BRONJ is closely associated with both cumulative dose and duration of bisphosphonate therapy, with risk increasing at higher doses and with longer treatment periods [10–14]. Several studies have emphasized the need for caution when zoledronic acid and pamidronate are administered beyond two years. The risk of developing BRONJ during bisphosphonate therapy ranges from over 1% after 12 months to 11% after four years; with zoledronic acid alone, the risk increases from approximately 1% in the first year to 21% after three years. Because orally administered bisphosphonates accumulate more slowly, both the incidence and severity of BRONJ rise progressively with each additional year of use [8–10].

According to existing studies, the incidence of BRONJ among patients with osteoporosis is very low, ranging from 0.15% to less than 0.001% per patient-year of exposure. In contrast, the incidence is considerably higher in cancer patients with bone metastases, owing to more potent suppression of osteoclast activity, with osteonecrosis occurring primarily in those receiving high-dose intravenous bisphosphonates. Wang and colleagues conducted a 5-year retrospective study involving 292 patients treated with intravenous bisphosphonates and reported BRONJ in 3–8% of patients with multiple myeloma, 2–5% of patients with breast cancer, and 2.9% of patients with advanced prostate cancer [11].

BRONJ occurs more frequently in the mandible than in the maxilla and almost invariably originates in the alveolar bone, owing to its higher rate of bone turnover. This phenomenon reflects the greater dependence of the alveolar bone on osteoclast-mediated remodeling in response to occlusal loading, denture pressure, and mechanical strain [12].

Oral infectious foci such as periapical abscesses, periodontitis, and poor oral hygiene, as well as invasive dental procedures including tooth extraction, periodontal surgery, apicoectomy, and dental implant placement, have all been shown to significantly increase the risk of developing BRONJ [13].

2.3. Diagnosis

In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed the diagnostic criteria for bisphosphonate-related osteonecrosis of the jaw (BRONJ), which include the following conditions: [5]

- Exposed bone in the maxillofacial region that has persisted for more than 8 weeks
- Current or previous use of bisphosphonates
- No history of radiation therapy to the craniofacial region

The AAOMS also classified BRONJ into different clinical stages and provided corresponding management guidelines:

Table 1. Stage of BIONJ

BRONJ Stage	Management Recommendations
At Risk: No clinical evidence of necrotic bone in patients receiving BPs	No treatment indicated; patient education
Stage 0: No exposed bone, but nonspecific clinical or radiographic findings	Systemic management including pain control and antibiotics if indicated

Stage 1: Exposed and necrotic bone or fistula probing to bone, asymptomatic and no signs of infection	Antibacterial mouth rinses (0.12% chlorhexidine), clinical follow-up every 3 months, patient education, reassess continued BP use
Stage 2: Exposed bone with signs of infection, such as erythema or purulent discharge	Oral antibiotics, antibacterial mouth rinses, pain control, local debridement to relieve soft tissue irritation and prevent secondary infection
Stage 3: Exposed necrotic bone with pain and one or more of the following: extension beyond the alveolar bone (e.g., mandibular inferior border, ramus, maxillary sinus, or zygoma), pathological fracture, extraoral fistula, oral-antral or oral-nasal communication	Antibacterial mouth rinses, pain control, systemic antibiotics, surgical debridement or resection to control infection and relieve pain

2.4. Treatment

The primary objectives in the management of BRONJ are pain relief, infection control, and stabilization of the affected bone. In this context, invasive interventions that may exacerbate necrosis should be minimized whenever possible.

Therapeutic strategies for BRONJ can be broadly categorized as follows [15]:

Table 2. Management and treatment strategies

Treatment Strategy	Details
Conservative treatment	Antiseptic mouth rinses + analgesics
Non-surgical treatment	Antibiotic and antifungal therapy
Surgical treatment	
Local procedures	Without flap elevation With flap elevation
Extensive procedures	Marginal resection Segmental resection
Adjunctive therapies	Hyperbaric oxygen therapy Parathyroid hormone Platelet-rich plasma (PRP) Ozone laser therapy |

3. MATERIALS AND METHODS

3.1. Materials

The study population consisted of patients receiving treatment for osteoporosis, multiple myeloma, or bone metastases with bisphosphonates at Huu Nghi Hospital. These patients were referred for department of Odonto- Stomatology to diagnose and treat.

3.2. Methods

This study was conducted as a prospective study. **The patients have been followed for five years from 2020 to the present and are still under ongoing surveillance.**

4. RESULTS

At Huu Nghi Hospital, most patients prescribed bisphosphonate therapy undergo pre-treatment dental examinations, counseling, and dental care. Over the past five years, we have conducted a study and follow-up of patients treated with bisphosphonates for various indications, including osteoporosis, prostate cancer, and breast cancer. Our findings are as follows:

A total of 12 patients were diagnosed with BRONJ at various stages, all of whom were female. Two patients had been taking oral bisphosphonates continuously for more than four years, while the remaining patients had received intravenous bisphosphonate therapy.

Three patients were diagnosed with stage 3 BRONJ, with exposed necrotic bone extending beyond the alveolar bone. One of these cases underwent surgical intervention for fistula debridement, while the other two were managed with conservative local treatment.

The remaining patients were diagnosed with stage 0, 1, or 2 BRONJ. Most of them

had been receiving IV bisphosphonates for over three years and presented with poor oral hygiene, multiple carious teeth, and untreated infections at the time of presentation.

In this report, we present one clinical case of stage 3 BRONJ that was managed surgically.

Casereport: An 86-year-old female patient was diagnosed with osteoporosis in November 2013 and began treatment with Fosamax Plus (one tablet per week) for two months, followed by a four-month break, and then another two-month course. From December 2014 to May 2019, she resumed weekly Fosamax Plus continuously for 4.5 years.

During bisphosphonate therapy, she had regular dental check-ups every six months. One year after starting treatment, she developed a crown fracture in the first premolar region, followed by a series of dental procedures including root canal treatment, root fractures, and extractions of infected teeth.

The first signs of BRONJ appeared in August 2018, approximately four years into therapy, when pus discharge was noted in the gingival sulcus near tooth 25. Following extraction of tooth 24 and tooth 25, the extraction site failed to heal after three months, and exposed bone was noted in the alveolar ridge. The patient was treated with antibiotics (Spiramycin + Metronidazole) and 0.12% chlorhexidine mouthwash.

Follow-up was conducted every three months. By May 2019 (after 4.5 years of BP therapy), the patient developed complete exposure of the maxillary alveolar bone. She was advised to discontinue bisphosphonates, continue antibiotic therapy (Spiramycin + Metronidazole), perform regular oral rinses with 0.12% chlorhexidine, take analgesics as needed, and return for regular 3-month follow-ups to extract any remaining infected maxillary roots.

In August 2020, the patient returned with a fistula in the chin area, purulent discharge, redness and swelling of the skin, and exposed mandibular bone. She was diagnosed with stage 3 of BRONJ.

Management: The patient underwent surgical intervention, including extraction of mandibular teeth, removal of necrotic bone, and fistula curettage.

The patient has since been followed up every three months, with stable post-operative recovery.

Preoperative Images

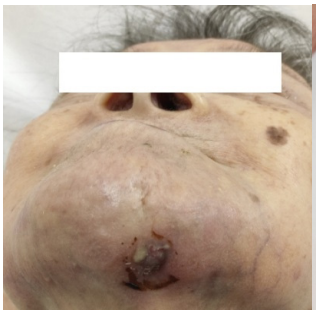

Figure 1a.

Cutaneous fistula in the chin region with spontaneous purulent discharge

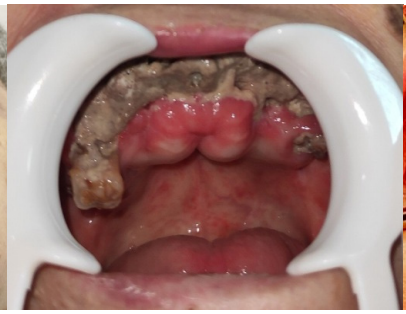

Figure 1b.

Complete exposure of the maxillary alveolar bone

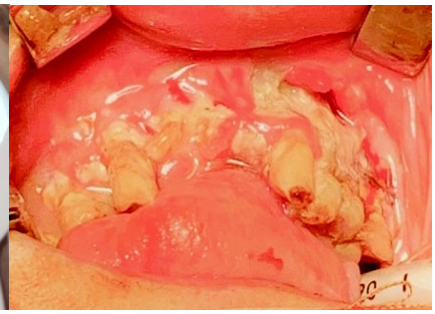

Figure 1c.

Partial exposure of mandibular alveolar bone with lesion extending to the vestibular sulcus

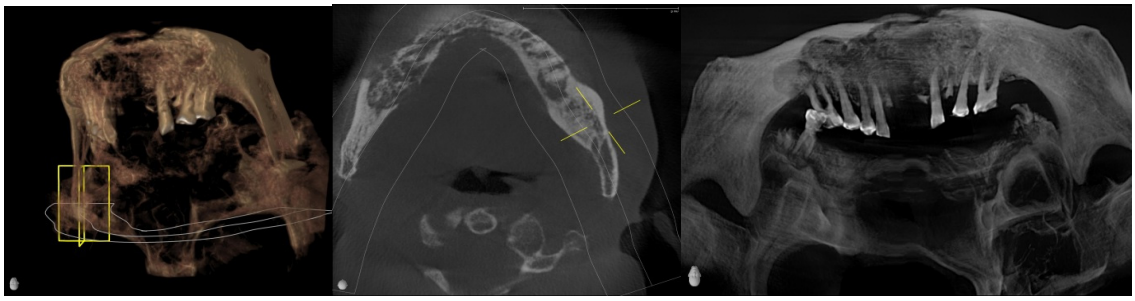

Figure 2. Cone-beam CT image showing extensive necrotic lesion of the mandible with discontinuity of the mandibular basal border

Intraoperative and Postoperative (Day 1) Images

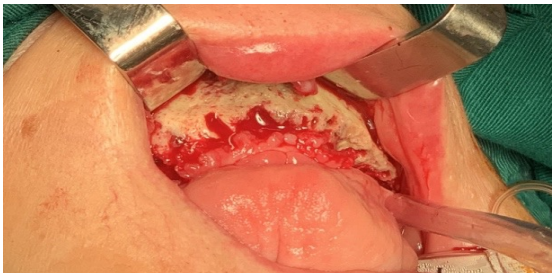

Figure 3. Intraoperative view: extraction of mandibular teeth, removal of necrotic bone, and debridement of the fistulous tract

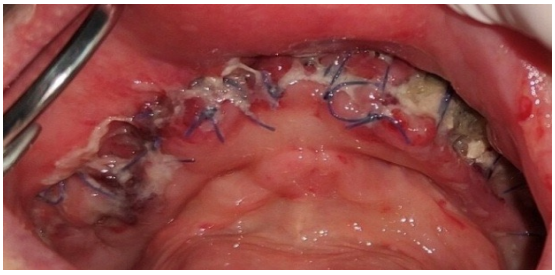

Figure 4. One day post-operation: mild swelling at the surgical site

Postoperative Day 4 Images

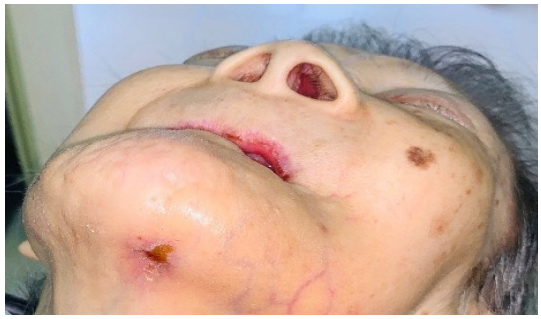

Figure 5a. Closure of the chin fistula

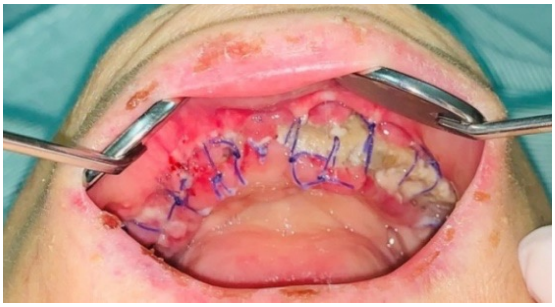

Figure 5b. Clean surgical site with no signs of infection

Follow-Up at 2 and 4 Years Post-Surgery

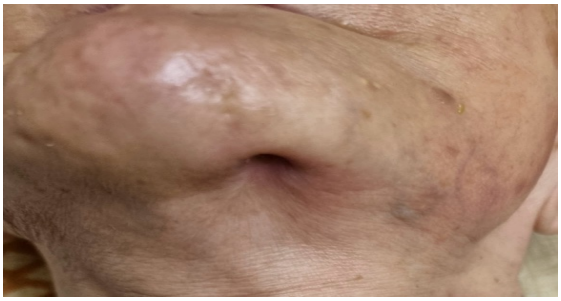

Figure 6a. Two years post-op: fistula remains closed and dry

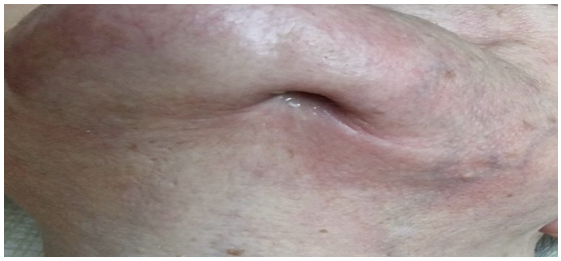

Figure 6b. Four years post-op: slight serous discharge from the fistula site

5. DISCUSSION

This clinical case fully meets the diagnostic criteria for BRONJ as defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS): exposed maxillary bone persisting for more than eight weeks, a history of continuous bisphosphonate use for 4.5 years, and no history of head or neck radiation. The patient initially presented with clinical signs consistent with stage 2 BRONJ, including a fistula with purulent discharge at the gingival sulcus of tooth 25 and prolonged non-healing after extraction of tooth 24 and tooth 25, resulting in exposed alveolar bone. Our initial management approach—discontinuing bisphosphonates, prescribing oral antibiotics (spiramycin + metronidazole), recommending daily chlorhexidine 0.12% rinses, and regular monitoring every three months—helped temporarily stabilize the condition. However, over time, the disease progressed to stage 3, marked by complete exposure of the maxillary alveolar bone, development of a cutaneous fistula with purulent drainage in the chin region, and lesion extension to the mandibular basal border. Surgical intervention was then indicated and performed, including extraction of affected mandibular teeth, removal of necrotic bone, and debridement of the fistulous tract. Postoperative recovery was favorable, with fistula closure observed within four days and significant pain reduction. Follow-up at two years showed stable healing and no recurrence; however, at the four-year mark, slight serous discharge was noted at the fistula site. The patient continued to be monitored and managed conservatively with oral hygiene guidance and antibiotics when indicated. This case underscores the importance of early detection, close interdisciplinary coordination, and individualized treatment strategies in managing BRONJ, especially in elderly patients receiving long-term bisphosphonate therapy.

6. CONCLUSION

Although BRONJ is a relatively rare complication, it can result in severe and long-lasting consequences. A commonly observed feature among BRONJ patients is poor oral hygiene, which highlights the critical role of bacterial infection in its pathogenesis. Therefore, prevention remains the cornerstone of BRONJ management. Prior to initiating bisphosphonate therapy, patients should undergo a comprehensive dental evaluation to identify and eliminate potential risk factors. During treatment, patients should be informed about the risk of BRONJ, and any decision regarding the continuation or discontinuation of bisphosphonates should be made by the treating physician in consultation with the dental team. Ultimately, a close collaboration between internal medicine specialists and dental professionals is essential to minimize complications such as BRONJ and to achieve the best possible treatment outcomes for patients.

7. RECOMMENDATIONS

Given the severe symptoms and long-term consequences that patients may experience from BRONJ), we propose the following recommendations to improve prevention, diagnosis, and management of this condition [9]:

7.1. For Internal Medicine Physicians Managing Patients on Bisphosphonates:

- Educate patients about the potential adverse effects of bisphosphonates, especially the risk of jaw osteonecrosis, particularly with long-term intravenous administration.
- In patients exhibiting early oral or dental symptoms, carefully evaluate the need to discontinue bisphosphonate therapy in consultation with a dental specialist.

7.2. For Dental and Oral-Maxillofacial Practitioners Managing Patients on Bisphosphonates:

- Always inquire about the history of bisphosphonate use, especially intravenous forms, before any dental procedure.

Patients not yet on bisphosphonate therapy	Patients already receiving bisphos-phonates

- Perform a comprehensive dental examination and treatment plan - Extract teeth with clear indications - Manage periodontal disease surgically if necessary - Replace or adjust existing prosthetics	- Emphasize oral hygiene, scaling, and plaque removal - Avoid invasive procedures such as tooth extractions or periodontal surgery - Prefer root canal treatment over tooth extraction

Table 3. Dental management in patients with or without bisphosphonate therapy

For patients who require tooth extraction despite bisphosphonate therapy:

- Consult with the prescribing physician regarding temporary discontinuation of bisphosphonates if possible.
- Choose atraumatic extraction techniques; avoid flap elevation when feasible.
- Ensure strict aseptic technique during the procedure.
- Maintain chlorhexidine 0.12% mouth rinses twice daily for at least two months post-procedure.
- If feasible, consider crown amputation and retaining the root following endodontic therapy.

For patients with confirmed or suspected BRONJ:

In cases of suspected BRONJ, obtain panoramic X-ray or Cone Beam CT to assess lesion extent and location.

Perform microbial cultures from swollen or draining soft tissue sites to identify superinfections and guide appropriate antibiotic therapy.

- Avoid any further dental or surgical trauma.
- Accurate staging and recognition of clinical signs are essential for appropriate management and treatment planning.

7.3. For Patients Receiving Bisphosphonate Therapy:

- Be informed about the early signs and symptoms of BRONJ and report any concerns promptly to healthcare providers.
- Understand the importance of maintaining excellent oral hygiene and adhere strictly to oral care instructions.
- Attend regular dental check-ups every three months to ensure early detection and prevention of complications.

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