

## OSTEONECROSIS RELATED TO ORAL BISPHOSPHONATE USAGE: CASE REPORT AND REVIEW OF TREATMENT STRATEGIES

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### Abstract

Bisphosphonates are a class of agents used to treat osteoclast-mediated bone diseases and many neoplasm types. Osteonecrosis of the jaw is a common side effect of bisphosphonate therapy, presenting as exposed and necrotic maxillary and/or mandibular bone.

In this report, we present a case of bisphosphonate-related osteonecrosis of the jaw in a patient who received oral alendronate therapy due to osteoporosis.

According to the literature, oral bisphosphonate therapy typically causes less severe manifestations than observed in the case presented here. We discuss treatment modalities and the benefits of piezosurgical treatment.

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### Introduction

Osteonecrosis of the jaw is a well-known side effect of bisphosphonate intake.<sup>1</sup>

A growing number of cancer patients receiving intravenous bisphosphonate therapy have developed exposed and necrotic bone of the jaw. This condition may remain asymptomatic, or may result in pain or exposed maxillary or mandibular bone. This complication may occur spontaneously or after simple dentoalveolar surgery.<sup>1,2</sup> Similar clinical findings have been noted in some patients taking lower-dosage oral bisphosphonates for the treatment or prevention of osteoporosis.<sup>2,3</sup>

The active ingredients in these oral tablets may be alendronate, risedronate, or ibandronate sodium. Although a few cases of bisphosphonate-related osteonecrosis have been reported in patients receiving alendronate,<sup>2-4</sup> the evidence

indicates that such therapy for osteoporosis poses little or no risk of osteonecrosis of the jaw because the dosage is lower than that used for cancer patients.<sup>5</sup>

We present here a case of osteonecrosis following dental extraction in a patient taking oral bisphosphonate-alendronate therapy for osteoporosis. We also discuss treatment modalities and the option of piezosurgery to manage this condition.

### Case Report

A 78-year-old man was referred to our oral and maxillofacial surgery clinic with exposed bone and pain on the left side of the mandible. His mandibular left second premolar had been extracted 4 months previously, and he had experienced persistent discomfort due to the unhealed extraction socket. According to the patient's history, the extracted tooth was luxated and the extraction was simple.

Intra-oral examination revealed inflammation signs in the area of the left mandibular molars, erythema, mucosal swelling, and exposed necrotic alveolar bone (Fig.1). Evaluation of panoramic radiographs revealed a comparative radiolucent change in the bone architecture (Fig. 2).

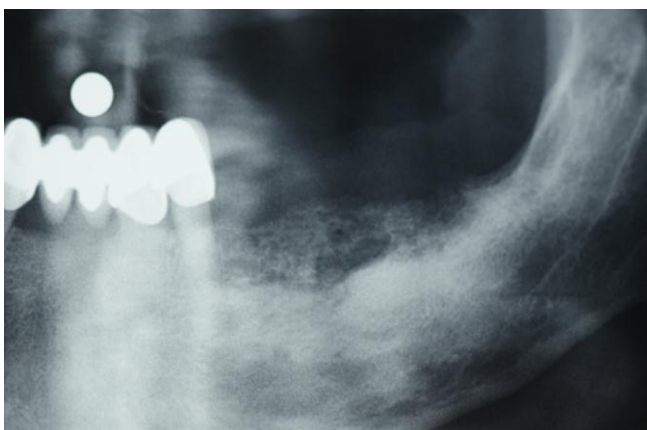
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**Figure 1.** Clinical view of erythema, mucosal swelling, pu formation and exposed bone necrosis.

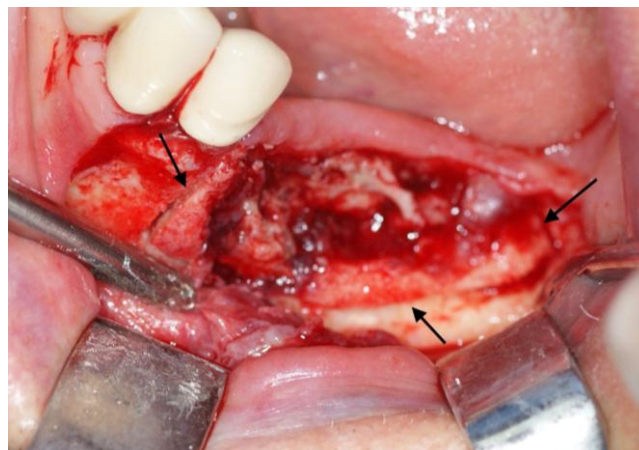


**Figure 2.** Panoramic radiograph shows affected bony area.

The patient had a history of osteoporosis that had been treated with oral bisphosphonates. He had taken 70 mg of alendronate (Fosamax®, Merck & Co., Inc., Whitehouse Station, NJ, USA) once weekly for 4 years. Based on clinical and radiographic evaluation, we diagnosed this case as bisphosphonate-related osteonecrosis of the jaw.

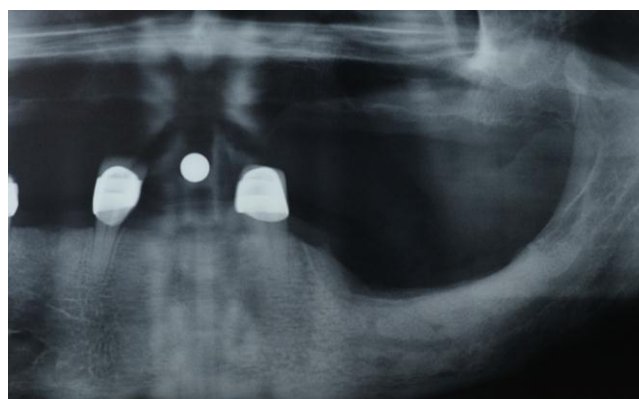
Initial treatment consisted of the combined administration of oral antibiotherapy, clindamycin, and metronidazole for approximately 20 days. This treatment was supported with 0.12% chlorhexidine oral rinses twice daily. Because the continuation of bisphosphonate therapy could affect the progression of osteonecrosis, a physician was consulted to re-evaluate the potential risks and benefits of the patient's osteoporosis therapy. The alendronate regime was consequently stopped. Although the patient's pain and discomfort subsided after antibiotherapy, we decided to perform a marginal mandibular

resection due to the large area of affected bone, which extended from the left mandibular first premolar to the retromolar area. Piezosurgery (Mectron S.P.A., Carasco, Italy) was performed under local anaesthesia to remove the necrotic bone. The surgery included one vertical osteotomy from the distal left canine and one horizontal osteotomy extending to the retromolar area (Fig. 3).



**Figure 3.** Black arrows show osteotomy borders.

Areas of bone that are a constant source of soft-tissue irritation were removed and trimmed. After removing the necrotic bone, the bleeding bone was used to define a margin. The mucosal closure was primary. The surgery was performed approximately 1 month after the cessation of bisphosphonate therapy. Postoperative clindamycin and 0.12% chlorhexidine oral rinses were prescribed for 15 days.



**Figure 4.** 1 year follow up panoramic radiograph.

The patient had no complaints at a 1-month clinical follow-up examination (Fig. 4). The mandibular left canine was extracted during prosthetic treatment and the patient began to

wear removable dentures. After 1 year of follow-up, he remained complaint-free and the mucosa and bone appeared normal.

## Discussion

Bisphosphonate-related osteonecrosis of the jaw is a major complication of bisphosphonate therapy. The pathogenesis of this process occurs when impaired osteoclast function interferes with normal bone turnover and resorption. In a histomorphometric study in rats, Aguirre et al.<sup>6</sup> showed that alendronate transiently decreased bone formation and vascularity.

Allen and Burr<sup>7</sup> found that 3 years of alendronate administration in beagle dogs reduced alveolar bone turnover and increased the incidence of matrix necrosis in the mandible. Bisphosphonates also exhibit anti-angiogenic properties due to their ability to significantly decrease the circulating levels of the potent angiogenic factor VEGF, as Santini et al.<sup>8</sup> demonstrated in cancer patients with bone metastases. These properties may be the reason for the necrotic changes observed in our patient after a tooth extraction.

Durie et al.<sup>9</sup> showed that intravenously administered bisphosphonates were more potent and problematic than oral bisphosphonate medications, and that the duration of bisphosphonate therapy also appeared to be related to the development of necrosis. Some studies have estimated that bisphosphonate-related osteonecrosis occurs in about 0.8–12% of cancer patients receiving bisphosphonates intravenously and in 0–0.04% of patients taking these drugs orally.<sup>10</sup>

Our patient had been prescribed Fosamax<sup>®</sup>, an oral alendronate that is the most commonly prescribed oral bisphosphonate. The manufacturer (Merck & Co., Inc.) has reported an estimated incidence of osteonecrosis of the jaw of 0.7 cases per 100,000 person-years exposure.<sup>11</sup> Necrosis appears to manifest less severely and respond more readily to sequestrectomy or marginal resection in patients who receive oral bisphosphonate therapy.

The cessation of bisphosphonate treatment presents a challenge. According to Ruggiero et al.,<sup>12</sup> the cessation of such treatment has not had a major impact on the progression or treatment of osteonecrosis. The amount of bisphosphonate that binds to circulating calcium

may affect new bone formation after sequestrectomy, and cessation may thus facilitate healthy new bone formation. In our case, bisphosphonate therapy was stopped after consulting a physician.

The American Association of Oral and Maxillofacial Surgeons (AAOMS) categorised the clinical manifestations (pain, infection, fistula, radiological evidence) and treatment strategies for bisphosphonate-related osteonecrosis into 4 stages (stages 0–3).<sup>10</sup> Our case was severe (stage 2), characterised by exposed, necrotic bone, associated with pain, erythema, and inflammation. The recommended treatment strategy for stage-2 bisphosphonate-related osteonecrosis is symptomatic treatment with broad-spectrum oral antibiotics, oral antibacterial mouth rinse, pain control, and superficial debridement to relieve soft-tissue irritation.<sup>10</sup> However, Chiu et al.<sup>13</sup> presented modified therapeutic strategies, and suggested primary closure of the exposed wound with mucosal flaps and superficial debridement of symptomatic bony lesions. Ruggiero et al.<sup>3</sup> found that 61 of 63 patients had undergone surgical treatment, such as sequestrectomy, partial maxillectomy, or marginal mandibulectomy.

The authors recommended that necrotic bone areas be removed because they were a source of infection and were unresponsive to irrigation and antibiotic therapy. They also suggested long-term antibiotic maintenance or a course of intravenous antibiotherapy in some stage-2 refractory cases.<sup>12</sup>

Carlson and Basile<sup>14</sup> have reported that radical surgical techniques, such as marginal or segmental resections of the mandible and partial or total maxillectomies with good margins of healthy bone, have resulted in cure rates reaching 91.6%. Filleul et al.<sup>15</sup> hypothesised that radical surgery may be beneficial for the treatment of osteonecrosis related to osteoporosis therapy. Although the AAOMS treatment guidelines report that surgery is only indicated in stage-3 cases, Hong et al.<sup>16</sup> performed surgical treatment in stage-2 cases. Disagreement regarding the treatment of stage-2 patients is apparent in the literature. Although our case fit the AAOMS guidelines for stage-2 osteonecrosis, we modified the patient's treatment from the AAOMS recommendations. The patient's symptoms were relieved with antibiotherapy, and marginal mandibular



resection was performed to allow the patient to wear dentures and improve his quality of life.

Osseous surgery has been performed by piezosurgery. The overheating of adjacent tissue may alter or delay the healing response. Piezosurgery allows an effective osteotomy through micro-vibration, producing less vibration and noise. Performed under local anaesthesia, this technique minimised surgical trauma and initiated a good healing response in our case. In our experience, it is important to obtain a surgical margin with viable and undamaged bleeding bone.

Romeo et al.<sup>17</sup> found no thermal damage in their piezosurgery samples. The specialised properties of piezosurgery make this technique particularly beneficial for bisphosphonate-related osteonecrosis patients.

### Conclusions

Optimum dental health should be the main goal of bisphosphonate therapy. The literature presents some controversy about treatment strategies for bisphosphonate-related osteonecrosis patients. In this case report, we discussed management approaches to these patients and presented a stage-2 bisphosphonate-related osteonecrosis case that was treated with a surgical approach.

The patient achieved good health within a short time after treatment, and began to use a removable prosthesis. The patient's quality of life during follow-up period was not affected by this treatment approach and he has used the prosthesis for 1 year without problem.

### Declaration of Interest

The authors report no conflict of interest and the article is not funded or supported by any research grant.

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