

# Bisphosphonate-Associated Osteonecrosis of the Jaws and Endodontic Treatment: Two Case Reports

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## Abstract

Bisphosphonates are commonly used in the management of bone diseases, such as osteoporosis and Paget's disease, and to prevent bone complications and to treat malignant hypercalcemia in certain types of cancer. Although this class of drugs has clear evidence of medical efficacy, there are an increasing number of reports of bisphosphonate-associated osteonecrosis of the jaws that have substantial implications for the patient and for the treating dentist. This case report reviews proposed possible mechanisms of bisphosphonate-associated osteonecrosis of the jaws and describes two case reports where nonsurgical and surgical root canal treatments were precipitating factors. Recommendations for prevention and treatment of the disease follow. Thorough history taking and timely consultation with the patient's oral surgeon and oncologist are emphasized.

## Key Words

Bisphosphonates, osteonecrosis, jaws, endodontics, pamidronate, zoledronate, alendronate

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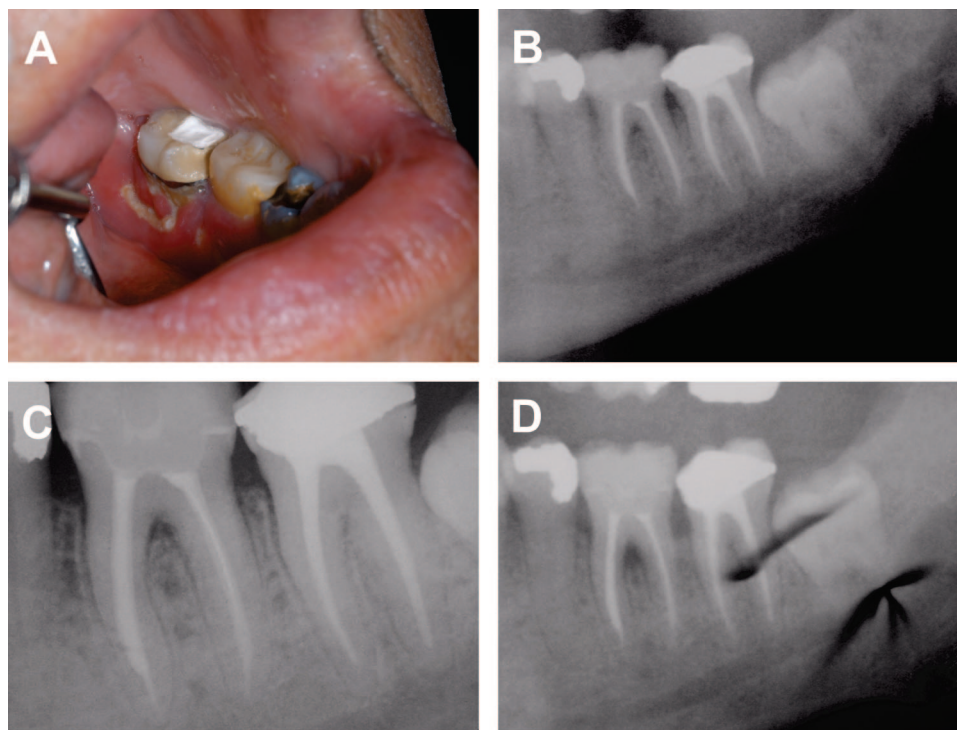
Bisphosphonates are commonly used in the management of bone diseases, such as osteoporosis and Paget's disease, and for the prevention of bone complications and the treatment of malignant hypercalcemia in patients with multiple myeloma or bone metastases from breast and prostate cancers (1–3). Bisphosphonates are carbon-substituted analogs of pyrophosphate that are potent inhibitors of osteoclast-mediated bone resorption. These compounds have specificity for bone because of their high binding affinity for calcium phosphates. These drugs are not metabolized well and are slowly released over extended periods of time. The latest generations of these drugs include alendronate (Fosamax, Merck, Whitehouse Station, NJ), risedronate (Actonel, Aventis, Bridgewater, NJ), pamidronate (Aredia, Novartis, East Hanover, NJ), and zoledronate (Zometa, Novartis, East Hanover, NJ). All four of these represent a third-generation of bisphosphonates that contain a nitrogen group and have greater potency and better selectivity at lower concentrations. Their mode of action is still unclear, but they are known to inhibit osteoclastic function, induce apoptosis of osteoclasts, and inhibit osteoclast differentiation from precursors (4). Their mechanism of action for altering angiogenesis is also unclear and may be variable. However, a study by Wood and co-workers found that zoledronate was a potent inhibitor of angiogenesis by reducing vessel sprouting (5). Pamidronate therapy was found to cause a significant and lasting decrease in vascular endothelial growth factor (VEGF) levels in patients, and thus may negatively affect angiogenesis (6). This may lead to prolonged interference with the normal homeostatic mechanisms of bone (1).

Recently, several clinicians have reported the potentially serious side effect of osteonecrosis of the jaws (ONJ) after chronic administration of these drugs. Most reports have been with patients taking zoledronate and pamidronate, with fewer published reports on alendronate or risedronate. Patients usually present with a complaint of pain accompanied by soft tissue ulceration and/or more commonly exposed bone of the mandible or maxilla. The exposed bone may proceed to frank sequestration. This osteonecrosis has generally followed a dental extraction or other dental event; however, there are a significant number of cases that appeared to occur spontaneously. Importantly, the successful treatment of these lesions has thus far been elusive (3, 7, 8).

To date there have been no reports in the literature of bisphosphonate-associated ONJ precipitated by endodontic procedures. The purpose of this paper is to present two case reports in which endodontic treatment was a precipitating factor and to discuss prevention and treatment of ONJ in the dental practice.

## Case Report 1

A 72 yr-old male presented to the Oral and Maxillofacial Surgery Department at the National Naval Medical Center for evaluation of "ulcerated areas" on the lingual mucosa of teeth #18 and 19. The lesions had been present for approximately 10 months. The patient complained of general discomfort in the area and intermittent tingling and burning sensations in the distribution of the left inferior alveolar nerve, which got worse after discontinuance of antibiotics. The patient's past medical history included prostate cancer, diabetes mellitus (DM), and gastroesophageal reflux disease (GERD). The patient underwent a radical prostatectomy to treat his prostate cancer. The patient was also treated with intravenous zoledronate once per month for 15 months to reduce skeletal complications associated with prostate cancer, receiving his last dose 5 months before presenting to the dental clinic. The patient's current medications included omeprazole, dutasteride, celecoxib, glimepiride, aspirin, lycopene, silibin, calcitriol, coenzyme Q-10, and melatonin. The patient had a distant history of nonsurgical endodon-



**Figure 1.** (A) Lingual area of tooth #18 showing bone exposure. (B) Close-up of panoramic film demonstrating left mandibular quadrant. (C) Periapical radiograph showing bone loss and furcation involvement tooth #19. (D) A 9-month postoperative close-up of panoramic film demonstrating increased bone loss and furcation involvement around tooth #19.

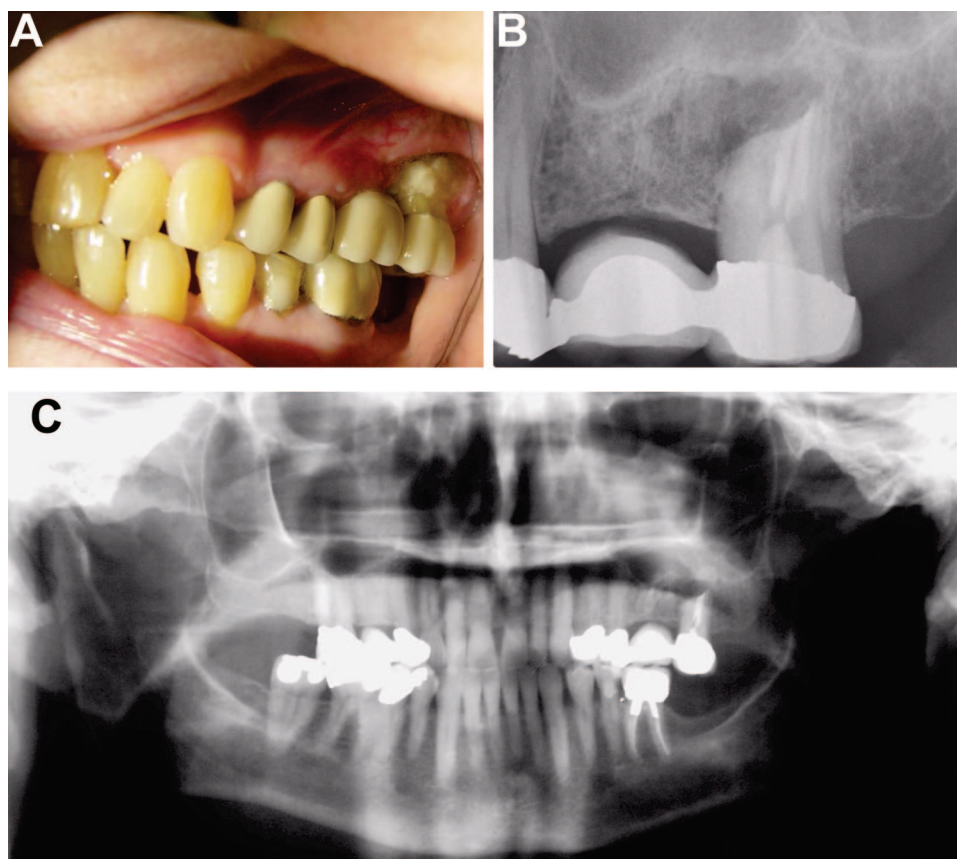
tic therapy on tooth #19. Ten months after starting the zoledronate infusions, an area of ulceration with exposed bone and some gingival recession appeared in the lingual area of tooth #18. This caused the patient intermittent burning and tingling in the area. Conservative treatment with antibiotics and local palliative measures failed to resolve the patient's discomfort and his general dentist referred him to an endodontist for evaluation. The endodontist determined that radiographs showed a possible widening of the PDL on tooth #18 and nonsurgical endodontic treatment was performed in hopes of removing any odontogenic etiology. No pulpal or periradicular test results or diagnoses are available. After a routine postoperative course of antibiotics, a biopsy was performed with no pathology identified. The patient was then treated with alternating courses of penicillin VK and amoxicillin with temporary relief of his symptoms, which would return after discontinuance of the antibiotics. Two additional local debridements were performed; however, the osteonecrosis continued to expand slightly towards the mesial and now included some small exposed areas lingual to tooth #19.

Clinical examination showed a 1 cm × 0.3 cm dehiscence of mucosa lingual to tooth #18. There were two smaller areas of bone exposure lingual to tooth #19. Tooth #18 also had a porcelain fused to metal crown with a temporary restoration in the occlusal surface (Fig. 1A). Neither tooth #18 or #19 had any evidence of mobility. Probing depths in the area were less than 3 mm with an area of 3 mm of gingival recession in the area lingual to tooth #18. Cranial nerve examination revealed no detectable sensory changes in either the left inferior alveolar or the left infraorbital nerve distribution. Radiographic examination showed the patient had a full bony impacted tooth #17, nonsurgical endodontic treatment on teeth #18 and 19 and furcation involvement on tooth #19 (Fig. 1B, C). The patient was placed on a 1-month course of penicillin VK 500 mg 1 tablet po q6h and metronidazole 500 mg 1 tablet po q6h. On follow-up, the patient reported subjective improvement in

symptoms, although clinically there was only minimal improvement in the areas of bone exposure. A conservative debridement was performed at this time and the patient was continued on penicillin VK and metronidazole for an additional month. Radiographic examination 9 months later showed progression of the furcation involvement and periodontal bone loss around tooth #19 (Fig. 1D). Although the progression of the lingual osteonecrosis had stopped at this point and his symptoms were decreased, the antibiotics had only slowed the progression of furcal bone loss on tooth #19. The patient ultimately declined continued therapy on the prescribed antibiotic regimen secondary to interference with his quality of life.

## Case Report 2

A 74 yr-old male presented to the Oral and Maxillofacial Surgery Department at the National Naval Medical Center for evaluation of a "painful area" in the left maxilla. The patient was initially evaluated 3-months ago by his general dentist, who referred him to an endodontist for evaluation of tooth #15, which had pre-existing nonsurgical root canal treatment. The patient's chief complaint was spontaneous and masticatory pain in the area of tooth #15, as well as tenderness to palpation on the buccal mucosa of tooth #15. The determination was made that radiographs showed a possible widening of the PDL on tooth #15. No pulpal or periradicular test results or diagnoses are available. The patient was referred to his local oral surgeon for evaluation. By this time, a small area of bony exposure had developed on the buccal mucosal surface of #15. The patient subsequently underwent periradicular surgery 6-weeks before his appointment with the dental clinic without resolution of his chief complaint. The patient's past medical history was significant for hormone refractory prostate cancer diagnosed 15 yr ago, DM, and GERD. His prostate cancer was initially treated with radiation therapy. The patient had initially taken oral alendronate for 52 months.



**Figure 2.** (A) Clinical presentation of posterior left quadrant and exposed bone #15. (B) Periapical radiograph of tooth #15 at presentation. (C) Panoramic radiograph at presentation.

During this period he was also treated with a 14-month course of intravenous pamidronate followed by a 27-month course of intravenous zoledronate ending 1 month before his examination at the dental clinic. His treatment with bisphosphonates was to reduce skeletal complications associated with prostate cancer. Additionally his medications included sargramostim, transdermal estradiol, rosiglitazone maleate, celecoxib, isotretinoin, dutasteride, leuprolide acetate, doxycycline hyclate, atorvastatin, erythropoietin, esomeprazole magnesium, Peg-Interferon Alfa 2B, aspirin, calcium, co-enzyme Q-10, folic acid, green tea extract, vitamin E, lycopene, magnesium, Maitake mushroom extract, and Mega Soy extract. The patient reported no history of sinus problems.

Clinical examination showed a fixed partial denture (FPD) spanning teeth #13 to 15 with complete exposure of the facial and lingual bone adjacent to tooth #15, which showed class 2 mobility and was only marginally erythematous (Fig. 2A). Radiographic exam showed the FPD in place and evidence of nonsurgical and surgical endodontic treatment on tooth #15. There was no radiographic evidence of sinus disease (Fig. 2B, C). The patient was placed on routine follow-up. One month later the patient returned to the clinic with increasing mobility and pain in the area of tooth #15. The FPD was now mobile secondary to a loss of cementation of the abutment retainer on tooth #15. The pontic was removed in hopes that conservative treatment would render the patient asymptomatic. The patient returned 2 weeks later for follow-up with continued complaints of pain and foul odor. The soft tissue margins were severely erythematous, but without swelling (Fig. 3A, B).

A plan was formulated to take the patient to the main operating room for a partial maxillectomy. The patient underwent debridement of

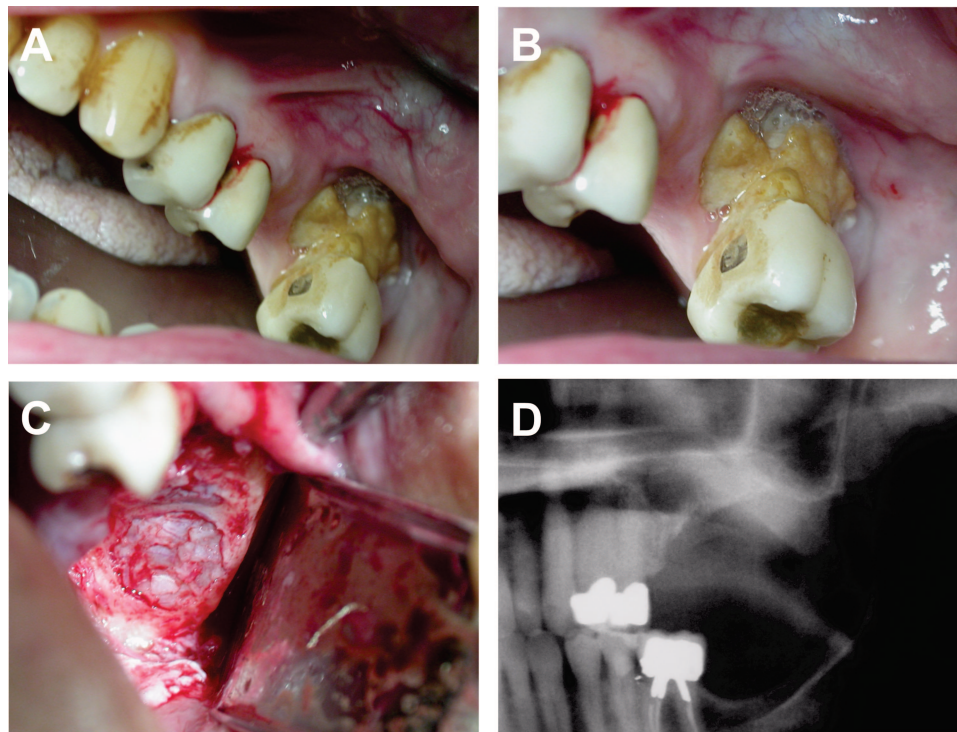
the left maxilla with extraction of tooth #15. The debridement was undertaken in such a manner as to leave the sinus mucosa intact (Fig. 3C, D). Primary closure of the wound was achieved. The patient was placed on a long-term course of penicillin VK 500 mg 1 tablet po q6h and metronidazole 500 mg 1 tablet po q6h. The patient showed excellent immediate postoperative results without exposure of bone. Biopsy results from the specimen showed osteonecrosis and osteomyelitis. Culture results from the specimen noted only "normal oral flora." At 6-month follow-up, the patient continued without exposure of bone and reported subjective improvement in symptoms (Fig. 4A, B).

## Discussion

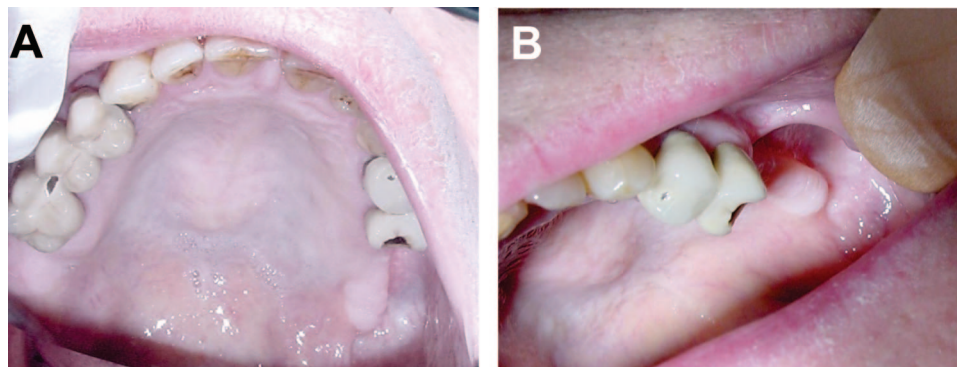
In 2003, Marx first described a series of 36 cases of exposed necrotic bone detected in patients who were receiving intravenous pamidronate or zoledronate bisphosphonate therapy as part of their treatment. Seventy-eight percent of the painful exposures occurred after dental extractions and 22% were spontaneous (9).

In a 2004 retrospective review of patients with refractory osteomyelitis and a history of chronic bisphosphonate therapy, Ruggiero et al. reported 63 cases over 4 months meeting the criteria. Fifty-six patients had received the intravenous bisphosphonates pamidronate or zoledronate for at least 1 yr and seven patients were on chronic oral bisphosphonate therapy for osteoporosis, including alendronate and risendronate. The typical presenting lesion was a nonhealing socket after extraction, but nine of the cases involved spontaneous exposure of the jawbone with no history of a recent dentoalveolar procedure. Both types





**Figure 3.** (A) View of upper left quadrant after sectioning of pontic. (B) Close-up view of tooth #15 and bone exposure. (C) Intraoperative view demonstrating intact sinus membrane. (D) Immediate postoperative close-up of panoramic film of operative site showing intact sinus wall.



**Figure 4.** (A) A 6-month postoperative occlusal view of surgical site. (B) A 6-month postoperative facial view of surgical site.

were refractory to conservative debridement and antibiotic therapy. Biopsies showed no metastatic disease (8).

In 2005, Migliorati et al. reported bisphosphonate-associated osteonecrosis in 17 cancer patients taking intravenous pamidronate or zoledronate. Two of the cases developed ONJ spontaneously. There was one case of an osteoporosis patient taking oral alendronate for 3 yr, then developing osteonecrosis after extractions, but before implant placement. Most lesions did not respond well to therapy (7).

Many more case series and letters to the editor have been published relating development of bisphosphonate-associated osteonecrosis in the jaws, mainly associated with long-term intravenous administration of pamidronate or zoledronate (10–13). In a letter to the editor, Durie, Katz and Crowley reported the findings of a Web-based study by the International Myeloma Foundation in 2004 that found that after 36 months of administration, the estimated incidence of osteonecrosis in patients taking zoledronate was 10% and 4% for those taking pamidronate (14).

Interestingly, although most of the attention lies on zoledronate and pamidronate, Migliorati writes that it should be kept in mind that in the case series of both Marx and Ruggiero et al., there were a total of eight cases of noncancer patients taking a less potent type of bisphosphonate for the treatment of osteoporosis that developed osteonecrosis of the jaws. Similar cases may soon be reported. Considering the large number of patients around the world using bisphosphonates for prevention or treatment of osteoporosis, dentists may be dealing with a significant potential complication (15).

It is interesting to speculate why the mandible and maxilla are the only bones affected by this condition. As the housing for the teeth, these are the only bones connected to the exterior, potentially exposing them to periodontal disease or microtrauma. It seems reasonable that the antiangiogenic effect attributed to bisphosphonates might play a role, together with microtrauma and inflammation, in causing ischemic changes in this area (16).

In the present case reports, both individuals were men over the age of 70 with well-controlled diabetes mellitus. It is possible that their advanced age and diabetes might have affected the initiation, progression and/or ultimate healing of their osteonecrosis. It should also be pointed out that many of the drugs they were taking have significant effects on calcium metabolism and/or antiangiogenesis, most notably estradiol, omeprazole, rosiglitazone, dutasteride, atorvastatin, isotretinoin, esomeprazole, and even celecoxib. With so many variables, it would be difficult to conclude a cause and effect relationship; though it seems reasonable that other associations might exist between these drugs and the disease. Nonetheless, the common thread that runs through all the cases reported in this paper is the development of osteonecrosis after long-term treatment with bisphosphonates.

The Federal Drug and Food Administration issued Patient Safety News Bulletin #4 in December of 2004, stating that Novartis has notified healthcare professionals, including a change in labeling, about the risks of developing osteonecrosis from the company's two bisphosphonate drugs, zoledronate, and pamidronate (17).

Novartis has issued a drug precaution for dental health professionals with patients being treated for cancer. They state that preventive dentistry should be considered before treatment with bisphosphonates with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene). They also warn while in treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (18).

Oncologists and dentists should be widely alerted about this possible complication so patients taking bisphosphonates and considering elective dental procedures can be properly counseled (19). A thorough dental examination and necessary tooth extractions with time for healing is recommended before commencing bisphosphonate therapy (1). For patients already receiving bisphosphonate therapy, close collaboration with the oral surgeon and oncologist are essential. It would seem prudent to take measures to prevent osteonecrosis in those at risk. This might include appropriate preventive dentistry with caries control, avoiding invasive periodontal procedures or dental implant placement and using soft liners on dentures (1, 9). Because it appears extractions precipitate the majority of this condition, it would seem prudent to recommend alternatives to tooth extraction or other dental surgical procedures including surgical endodontic procedures in patients with a history of receiving bisphosphonates (1). Suitable alternatives might include nonsurgical root canal treatment if pulpal disease is identified. Both these cases illustrate that accurate pulpal and periradicular tests resulting in clear diagnoses are paramount before proceeding with endodontic treatment. Care should be taken in the placement of rubber dam clamps to avoid mucosal injury that may precipitate inflammation and the disease. Surgical endodontic treatment is not recommended and should be considered contraindicated in patients taking pamidronate or zoledronate.

Patients may present with ongoing dental problems during or after the course of treatment with bisphosphonates. They frequently present with complaints of burning, tingling and possibly pain localized to a fairly defined location. Once manifested, bisphosphonate-associated osteonecrosis is difficult to treat, and referral to an oral and maxillofacial surgeon is recommended. However, there is no known definitive

treatment for this phenomenon. A number of treatment options have been utilized, including long-term or intermittent antibiotic therapy (usually of the penicillin family), irrigation with antimicrobial rinses such as 0.12% chlorhexidine, limited debridement of sequestering bone, up to full resection to vital bone. Hyperbaric oxygen treatment has generally not shown any benefit (2). Radical resection appears to be of limited use and may be contraindicated; the disease may progress despite surgery and cessation of bisphosphonate therapy (7, 12). Despite the best treatment, few of the cases go onto complete resolution.

Until further is known about the disease, prevention will be the key in limiting its development. Careful and thoughtful history taking, thorough examinations, and timely consultation with the patient's oral surgeon and oncologist will go a long way in preventing this complication.

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