



Dental Management of Patients With a History of Bisphosphonate Therapy: Clinical Dilemma

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ABSTRACT Bisphosphonate osteonecrosis, BON, was recently described in the literature. Lack of scientific evidence explaining the pathophysiologic mechanisms involved in the development of this oral complication has generated uncertainties about proper management of patients treated with a bisphosphonate. This manuscript discusses the dental management of two breast cancer patients treated with intravenous bisphosphonates as part of their cancer management and who developed oral disease. Clinical management decisions will be presented as well as the treatment outcomes.

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Bisphosphonate osteonecrosis, BON, was first reported in 2003.^{1,2} Since the first reports, it became evident that most of the cases develop in cancer patients receiving intravenous bisphosphonates.³⁻⁵ A number of publications including case series, white papers, and guidelines addressed management strategies with the objective of guiding the dental clinician on the proper management of patients with this oral complication.⁵⁻⁹ However, due to the lack of a universally accept treatment protocol, dentists are uncertain on how to best manage a patient with this oral complication.

BON is defined as the unexpected appearance of necrotic bone anywhere in the oral cavity of a patient taking a bisphosphonate who has no history of radiation therapy to the head and neck. The necrotic area persists for six to eight weeks despite the provision of standard care.⁶ Patients usually complain of pain and have active infection with pus at the area of necrosis. This definition is representative of cases where necrotic bone is found during the intraoral examination. However, there may be patients who fit the profile previously described but who do not have visible exposed bone in the mouth.¹⁰

Because of the awareness the reports of BON have generated in the dental and

medical communities, it is not uncommon that a patient on bisphosphonate therapy who has signs and symptoms of oral disease, even without the presence of visible intraoral necrotic bone, will be given a possible diagnosis of BON. Once BON is suspected, the dentist may be reluctant to provide routine dental care to the patient involved. The authors have recently received a number of referrals of patients in this situation who have been denied care by dental colleagues.

Following is the presentation of two of these cases and a discussion on the management decisions during the treatment of both patients.

Case No. 1

Antonia S., an 84-year-old woman, was referred to the oral medicine clinic at NSU College of Dental Medicine in Fort Lauderdale, Fla., for evaluation of an oral infection. The patient complained of severe pain and swelling of the upper anterior jaw that was present for several weeks. The patient was being treated by her dentist who was trying to control dental deterioration by grinding the patient's teeth down to the gingival level to avoid extraction and with the use of antibiotics.

In a recent dental consultation, the patient had tooth No. 5 extracted. The patient could not recall the exact date of the extraction but reported that the healing was delayed. She had to be treated with antibiotics and topical mouthrinses until healing, with closure of the alveolar socket eventually occurring. Prior to the referral, the dentist told the patient that her medical and dental problems were too complex and that he could not continue treating her. The patient was then referred to the NSU oral medicine clinic.

The patient's medical history was significant for breast cancer diagnosed 11 years ago. Antonia had been treated with



FIGURE 1A. Breast cancer patient complaining of pain on the anterior right maxilla. Clinical and radiographic findings. Note absence of clinically exposed necrotic bone.



FIGURE 1C. The periapical radiographs show with more detail the involved areas around tooth No. 6.

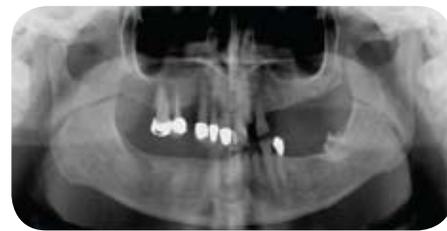


FIGURE 1B. Panoramic radiograph reveals radiolucency at the anterior right maxilla. Observe residual roots of teeth that had been ground down to the gingival level by the previous dentist to avoid extraction.



FIGURE 1D. Localization of the osseous defect with a gutta-percha point ending directly at the extraction site of tooth No. 5.

bilateral mastectomies, several cycles of chemotherapy, and radiation. She later developed several areas of skeletal metastasis and severe pain. Recently, she had her left leg irradiated due to intense pain and a fracture due to extensive metastasis. Two months prior to her visit to NSU, the patient experienced intense pain. At that time, she was submitted to surgery for a complete hip replacement. The patient was receiving only hormonal therapy and no other cancer treatment modality.

The medical history was also significant for well-controlled diabetes and hypertension. Because of the skeletal metastasis the patient had been treated with zoledronic acid 4 mg IV infusions every three to four weeks for the past three years. Due to the delayed healing episode after the extraction of tooth No. 5, her medical oncologist discontinued the use of zoledronic acid prior to the initial visit to NSU.

The clinical examination revealed minor swelling of the buccal plate of tooth No. 6 and the extraction area distal to No.

6. The anterior right maxilla was painful upon palpation and teeth Nos. 6 and 7 were sensitive to percussion and palpation. Purulence could be expressed from the sulcus around No. 6; however, no visible necrotic bone could be found during the clinical examination (**FIGURE 1A**). Panoramic and periapical radiographs revealed radiolucency and evidence of bone loss around the root of tooth No. 6 as well as a vertical defect with an irregular contour on the distal surface at the alveolar crest. A localization radiograph showed a gutta-percha point that was introduced through the sulcus, distal of No. 6 and localized at the extraction site of tooth No. 5 (**FIGURES 1B-C**). Vitality pulp testing confirmed a necrotic pulp for No. 6 and positive for No. 7 and the contralateral teeth.

Could a Diagnosis of BON Be Made at This Point?

The patient's clinical presentation did not fit in the classical definition of BON due to the absence of clinically visible necrotic bone. However, the history of long-



FIGURE 2. Final radiograph after endodontic therapy. Observe sclerosis at the lamina around tooth No. 6. This may be an early sign of BON.



FIGURE 3A. Clinical view of tooth No. 6 after crown preparation. Note absence of any necrotic bone exposure in the area.



FIGURE 3B. Buccal view of the temporary crown and the removable partial bridge. No evidence of exposed necrotic bone.

term IV bisphosphonate therapy (three years of zoledronic acid), the patient's advanced age, history of recent extraction, presence of active infection in the area, no response to antibiotic therapy, and delayed healing, allowed the authors to suspect BON without visible exposed necrotic bone. The presence of diabetes in her medical history could also be considered an additional predisposing factor. Radiographically, the authors found a track leading to the area of extraction, a radiolucency around the root of tooth No. 6, and evidence of sclerosis periradicular at the lamina dura area. This has been considered an early sign of BON (**FIGURE 1D**).

With the Working Diagnosis of BON, What Would be the Best Way to Manage the Patient?

The first concern in spite of the possible diagnosis of BON was to treat the acute symptoms to alleviate pain. After a brief discussion with the patient's medical oncologist for confirmation of current medical status, the patient was given a course of 500 mg amoxicillin q.i.d., and chlorhexidine mouthrinses b.i.d. In addition, the patient was given oral hygiene instructions and was told not to use the removable partial denture to minimize trauma to the area.

What was the Treatment Plan Proposed in This Case?

A consultation with the patient's medical oncologist confirmed an advanced stage of breast cancer (stage 4: Tumor had spread beyond the breast and internal

mammary lymphnodes, lymphnodes above the collar bone, lung, liver bones, and brain) when no curative therapy could be offered to the patient. At this point, maintaining the patient's quality of life was the most important objective. The oncologist also revealed no desire to start zoledronic acid infusions again.

A consultation with an oral and maxillofacial surgeon discarded the extraction of the involved tooth, especially considering the working diagnosis of BON. The patient was informed about the nature of her dental disease and the possibility of BON, related to the use of a bisphosphonate. She was told that the authors would not do any invasive therapy at that point. She had a consultation with an endodontist and a prosthodontist to evaluate continuation of dental care after the resolution of the acute phase. The patient was offered to have endodontic treatment and a temporary crown of No. 6, and adjustment of the existing maxillary partial bridge. She agreed with the proposed treatment plan and signed an informed consent. She received endodontic treatment of No. 6 while on amoxicillin (**FIGURE 2**).

The use of antibiotic therapy throughout the endodontic treatment was elected based on the recent hip replacement and the presence of active infection. The patient responded well to endodontic therapy and became pain-free. However, a persistent purulent secretion continued to drain from the periodontal sulcus. She was seen by the prosthodontist who constructed a temporary acrylic crown on No.

6 and adjusted it to fit the existing partial bridge (**FIGURES 3A-B**). The patient was placed on follow-up visits every month. She was instructed to continue taking amoxicillin 500 mg q.i.d. and to clean the area around tooth No. 6 with the help of a cotton swab and chlorhexidine. In subsequent follow-up visits, it was observed that the clinical lesions had improved considerably and that only minimal amounts of pus could be expressed after palpation of the area. The patient is now considering the possibility of having further routine dental care for restoration of the remaining teeth. She remains pain-free after several months of periodic follow-up.

The working diagnosis for this patient continues to be BON second to the use of zoledronic acid, without evidence of intraoral exposed necrotic bone.

Case No. 2

Annette S., a 70-year-old woman, came to the NSU oral medicine clinic in June 2007 complaining of severe pain and swelling of the anterior right maxilla. Pain was present for months. After being denied dental treatment by several colleagues, Annette was told that the only place she could find help was at the authors' clinic. The medical history review was significant for breast cancer (stage 4), for which she was currently under treatment. She had a history of thyroid cancer treated with radioactive iodine. Annette was a former smoker and now had chronic obstructive pulmonary disease. She was dependent on oxygen and used an oxygen dispenser most of the day. Annette had

active gout and rheumatoid arthritis that caused pain and discomfort while walking.

She was recently diagnosed with myasthenia gravis that affected mostly the eye muscles but was under control. Because of metastatic breast cancer to the skeleton, the patient was treated with pamidronate and zoledronic acid IV infusions daily for a total of six years. Following a discussion with the medical oncologist in August 2006, she had discontinued the use of bisphosphonates, due to the development of oral signs and symptoms. Because of active skeletal metastasis, the medical oncologist was waiting for the resolution of the oral problems to restart the use of IV bisphosphonates. The oral examination revealed deteriorating oral health. Annette had pain and swelling of the anterior right maxilla. No visible necrotic exposed bone could be seen (**FIGURE 4A**).

In the past week, the pain became almost unbearable to her. She presented with several areas of decay under the crowns of an existing maxillary bridge despite the fact that she was brushing and flossing twice daily, and rinsing with peroxide. Her desire was to have all maxillary teeth extracted and a new maxillary full denture. A panoramic radiograph confirmed the poor dental health revealing a failing fixed bridge (**FIGURE 4B**). There was radiolucency around the roots of teeth Nos. 6 and 7, as well as a failing implant in the left maxilla, confirming that the best treatment plan for the patient at this point would probably be the extraction of all maxillary teeth, the removal of the dental implant, and a full maxillary denture.

At this point, the patient revealed that she had no financial means to afford any dental therapy. Additionally, her husband was also under therapy for gastric cancer and that she was responsible for taking care of him. At this



FIGURE 4A. Breast cancer patient referred to the clinic for evaluation and treatment of infection in the anterior maxilla. Note swelling and redness at the apical area of teeth Nos. 6 and 7. Areas were painful upon palpation and percussion.

point, the first question that comes to mind is: Is this a case of BON?

Once again, despite the history of long-term use of IV bisphosphonates for six years, the clinical presentation in this case does not fit the classical definition of BON due to the absence of visible exposed necrotic bone. Therefore, the authors could not be certain of a definitive diagnosis for the oral disease. In the differential diagnosis, one should include the possibility of BON without exposed necrotic bone or just a routine dental infection.

How to Manage the Acute Oral Cavity Symptoms in View of This Patient's History of Long-term IV Bisphosphonate Therapy?

The authors chose to be conservative at first to see how the patient would respond to routine antibiotic therapy and no invasive procedures. Annette was prescribed penicillin V-K 500 mg to take q.i.d. and was given a chlorhexidine mouth rinse to use b.i.d. She received oral hygiene instructions, was asked to avoid the use of the removable partial to prevent further trauma, and was asked to return to the clinic in a week. In the meantime, the authors presented the case to an oral and maxillofacial surgeon for evaluation and management decision. In the discussion with the surgeon, the authors agreed that full maxillary extraction was the only viable treatment in view of the deterioration of oral health, the patient's medical history, and the financial constraints. Although the patient had



FIGURE 4B. Panoramic radiograph shows a suspicious area around the root of No. 6. Observe extensive decay, bone loss and a failing dental implant.

advanced cancer and many other medical complications, having all maxillary teeth extracted and a new full maxillary denture constructed would have an immediate impact on the patient's quality of life, nutrition, and would be financially feasible.

Other treatment alternatives like endodontic therapy, new implants and crown and bridge, would require many visits to the dental office, a very high cost that could not be afforded by the patient, and a questionable investment based on the short life expectancy for this patient. In addition, having all teeth extracted and a full maxillary denture was the initial desire of the patient.

Although the radical treatment could result in the exposure of necrotic bone and confirm the diagnosis of BON, the authors felt that the proposed treatment was the best option for the patient. The treatment plan was discussed with the medical oncologist, who informed the authors that the patient was in an advanced stage of breast cancer and that only palliative therapy and maintenance of quality of life were being considered. Additionally, the medical oncologist said her complex medical history was under control and should not prevent the authors from providing her with radical treatment.

On the following visit the patient felt much better and the swelling had improved. She claimed the pain was gone and that she had been able to eat. At this time, the authors had the oral surgeon explain to the patient the need for full maxillary extraction. The authors discussed



FIGURE 5A. Note the outcome of the various steps of therapy. Patient at the day of surgery. Observe the great improvement of the infection at the area of teeth Nos. 6 and 7.



FIGURE 5B. View immediately after extraction of all remaining maxillary teeth and the dental implant. Note normal bleeding.



FIGURE 5C. Final healing several weeks post-extraction. Note that the tissues are normal and there is no evidence of osteonecrosis.

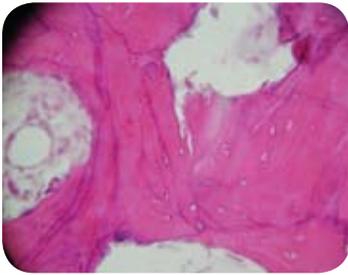


FIGURE 6. H and E section demonstrating the presence of vital bone. This was observed in all bone samples collected at the time of surgery. (Courtesy Dr. Ines Velez)



FIGURE 7A. Final view of the patient wearing a full maxillary denture.



FIGURE 7B. No complications have been observed several months after the delivery of the denture.

with her the risks involved with surgery and that it was believed this was the best treatment for her. After she signed an informed consent, she was instructed about the need for continuing on antibiotic therapy and maintaining good oral hygiene. The authors continued to follow the patient for a few more weeks to observe the progress of the clinical infection.

At the time of the August 2007 surgery, the patient was completely asymptomatic and the clinical findings presented considerable improvement (**FIGURE 5A**). At this time, the patient was informed that the dental treatment was going to be made almost completely free of charge, as a didactic case, and that she had to pay only for the prosthodontic laboratory fees. The surgical procedure went well and no major complications or bleeding developed (**FIGURE 5B**).

During surgery, bone samples for histopathology were obtained. At the time of surgery, the authors requested a consultation with a prosthodontist who agreed to build a maxillary full denture

and to adjust to fit the existing mandibular removable bridge. The postoperative visit was done a week later. The patient did not have any complaints and was still taking penicillin. Healing was progressing well and no evident dehiscence or exposed bone could be seen (**FIGURE 5C**). The pathology report confirmed vital bone and inflammation (**FIGURE 6**). One month later the oral tissues had healed and the prosthodontic work was initiated. The dentures were delivered September 2007 (**FIGURES 7A-B**) and no signs of osteonecrosis could be found.

The patient continues periodic follow-up and is maintaining good oral health. Occasional denture adjustments have been made to avoid trauma to the soft tissues. The final diagnosis was that of periapical abscess of tooth No. 6.

Discussion

The authors presented two patients with stage 4 breast cancer who had been treated with IV bisphosphonate for prolonged periods and who developed

oral disease during their therapy. Because of the medical history and the use of IV bisphosphonates, both had been denied dental care, despite the presence of severe pain and infection. Neither patients presented the classical intraoral findings of BON, exposed necrotic bone, associated with the oral disease. Therefore, even assuming there was a potential for BON in both cases, despite years of experience managing these individuals, the authors could not make a definitive diagnosis at the time the patients came to the clinic for consultation.

The authors understand that dental colleagues may not feel equipped or comfortable to provide dental care to patients with such history. The goal of this case presentation is to inform the dental practitioner how the authors treated the patients. In both cases the initial management procedure was to address the acute oral disease. If there is pain and evidence of infection, conservative therapy with systemic antibiotics and topical measures are usually enough to control symptoms.

A review of the medical history of these individuals is important. The use of IV bisphosphonates has been associated with about 10 percent incidence of BON. Therefore, there are about 90 percent of patients who use the same medication and who do not develop BON. The longer the time on bisphosphonate therapy, the higher the risk for BON.^{5,9}

In the presented cases, the patient with three years' history of therapy developed BON. The other patient had six years' history of IV bisphosphonate use and was treated surgically. She healed well without complications and did not develop BON. The reader should keep in mind that neither of the cases presented here represented classical cases of BON where exposed necrotic bone that does not heal and is progressive. Therefore, the authors did not have a final diagnosis for the dental disease when first seeing the patients. It is possible the patient in case No. 1 was an example of the type of clinical situation faced by dental colleagues prior to the discovery of BON. During the diagnostic phase and management of this patient, the authors became certain that there was necrotic bone in the area of tooth No. 5. The lack of good response to the endodontic therapy of tooth No. 6 and the persistence of infection and purulent secretion confirmed the impression that we were dealing with a BON case. A less-experienced clinician would probably have performed an apical surgery or extracted No. 6, exposing the necrotic bone to the oral cavity.

It is also important to notice that in both cases, there was not a definitive diagnosis. Nevertheless, the patients were treated based on what was felt to be the best treatment for each of the cases. In presenting the treatment plan to the patients, it was discussed the risk

for BON based on the medical history and a signed informed consent was obtained. The management decision for each patient involved the participation of a multiprofessional team of dental experts and the medical oncologists. It is believed this is fundamental in the management of patients who have been medicated with a bisphosphonate drug.

As risk factors for BON become more evident from prospective controlled studies, and as more is learned about the pathophysiology of this complication, new guidelines based on science will become available. This should make dental professionals more secure to provide care to these patients. In the meantime, using good clinical judgment and keeping in mind that all patients deserve to be cared for, should guide the clinician in the management of patients on bisphosphonate therapy. ■■■■

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