Quality Resource Guide

Bisphosphonate and Other Medication-Related Jaw Necrosis

Part Two - Clinical Management

Author Acknowledgement

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Educational Objectives

Following this unit of instruction, the practitioner should be able to:

1. Describe the typical early characteristics of early or developing bisphosphonate and other medication-related jaw necrosis (MRONJ).
2. Interpret the radiographic alterations associated with MRONJ.
3. Understand the three components of an established case of MRONJ.
4. Discuss the criteria-based MRONJ clinical staging system.
5. Understand the chief initiators of MRONJ and the role of prevention strategies concerning this problem.
6. Appreciate the newer advances in the management of all stages of MRONJ.

This article describes the clinical management of Bisphosphonate-Related Osteonecrosis. Readers should review Part One: Bisphosphonate and Other Medication-Related Osteonecrosis: Background, Incidence and Risk Factors prior to starting this paper.

MetLife designates this activity for **1.5 continuing education credits** for the review of this Quality Resource Guide and successful completion of the post test.

The following commentary highlights fundamental and commonly accepted practices on the subject matter. The information is intended as a general overview and is for educational purposes only. This information does not constitute legal advice, which can only be provided by an attorney.

Originally published November 2007. Updated and revised September 2010, June 2014, March 2017, April 2020 and August 2023. Expiration date: August 2026.

The content of this Guide is subject to change as new scientific information becomes available.

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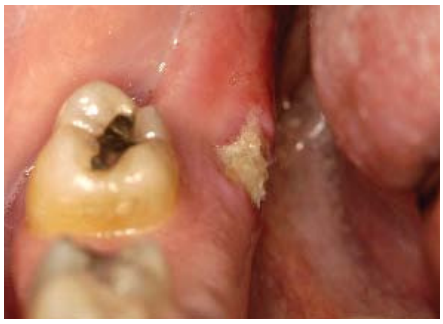
Clinical Presentation

The original working definition of Bisphosphonate-Related Osteonecrosis, now with the preferred term "medication-related osteonecrosis of the jaws" (MRONJ) relies upon three clinical factors (**Table 1**). MRONJ signs and symptoms include the presence or absence of exposed or necrotic bone, infection, pain, pathologic fracture, extraoral fistula formation and osteolysis.[1] MRONJ is typically and most commonly characterized by the discovery of a painless ulceration and area of underlying, usually insensate, exposed bone on routine examination, most commonly, but not always, following dentoalveolar surgery. Occasionally, the exposure may be spontaneous without a recent history of a dental extraction, dental implant placement or jaw surgery (**Figure 1**). Early stage disease often presents without pain, while in some cases pain alone may be the presenting symptom without bone exposure or obvious radiographic alterations. The pain , when present, is often described as "diffuse" or difficult to localize, or with a deep or penetrating quality. Accompanying gingival erythema and swelling along with purulent drainage from a dental extraction socket may be noted, but usually as a later finding or higher stage disease (**Figure 2**). A mandibular location is noted in approximately two thirds of cases. This contrasts with radiation-induced bone necrosis (osteoradionecrosis) where a mandibular location is noted in the vast majority of cases. Areas overlying mandibular and palatal tori are also sites of MRONJ involvement in many patients, likely related to the density of this type of predominantly cortical bone, and a relatively minimal level of vascularity of these areas, as well as their frequent association with function-related trauma. These statements are currently within a broader context than just the use of bisphosphonates. Medications associated with development of osteonecrosis now extend to other classes of agents including: a specific monoclonal antibody used in bone stabilization (denosumab); tyrosine kinase inhibitors used as antineoplastic agents (sunitinib; sorafenib, others) and inhibitors of vascular growth signaling cascade (bevacizumab).[2]

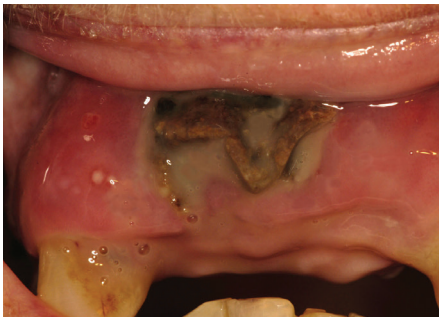
Appropriate radiographic imaging for suspicion of MRONJ includes routine intraoral dental and panoramic films as well as CT images. Radiological images will show an initially subtle and later more obvious level of osseous sclerosis similar to that seen in benign fibro-osseous lesions of the jaws (**Figure 3**). The alveolar process is most commonly involved with variable degrees of lamina dura thickening or obfuscation as well as full thickness poorly marginated sclerosis of the alveolus. Recent studies have emphasized subtle intramedullary sclerosis or ground glass alterations as a possible harbinger of necrosis, or so-called "Stage 0" disease, where there is no sign of exposed bone with or without associated symptoms.[3] Less common alterations include poorly healing extraction sockets without evidence of remodeling or bony fill-in (**Figure 4**), periapical radiolucencies, periodontal membrane space

Figure 1



Exposed, asymptomatic lingual cortical bone along the mylohyoid ridge with a rough surface but without drainage or signs of infection.

Figure 2

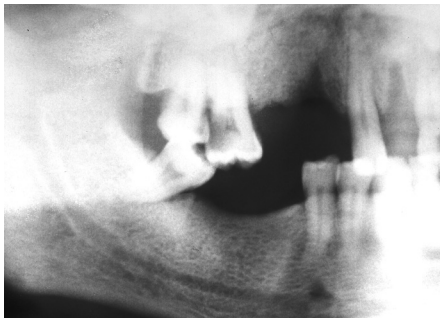


An asymptomatic, draining anterior maxillary defect with sharp edges and no signs of remodeling that developed several weeks following routine and uncomplicated dental extractions.

Table 1 - MRONJ case definition[1]

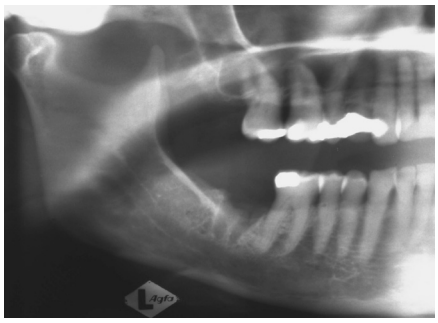
1. Current or previous treatment with a bisphosphonate or other medication affecting vascular growth.
2. Exposed bone in the maxillofacial region persisting for more than eight weeks.
3. No history of prior radiation therapy to the jaws.

Figure 3



Posterior maxillary MRONJ showing a ground glass-like pattern of alveolar trabecular bone sclerosis. A previous sequestrum was shed spontaneously, while the maxillary canine and molar teeth are invested in the affected alveolar bone.

Figure 4



A non-healing extraction socket with concomitant asymptomatic exposed alveolar bone with a ground glass sclerotic quality is present in an elderly woman who used alendronate for several years to manage osteoporosis.

widening, osteolysis and sequestrum formation.[4] The usefulness of more sophisticated imaging techniques including volumetric cone-beam tomography has been described,[5] though routinely available imaging is generally adequate to support the diagnosis. The use of bone scintigraphy has also been advocated. Almost two-thirds of patients having these scans before clinical evidence of MRONJ ultimately developing the condition at a subclinical level.[6] Others have stressed the role of magnetic resonance imaging (MRI) in defining the preclinical definition of MRONJ, citing alterations in the resonance signal of the fatty marrow compartment evident in areas of future of developing MRONJ lesions. In established or more advanced cases, MRI evaluation will show soft tissue edema, thickening of the inferior nerve and pterygoid musculature enhancement.[7]

The onset of MRONJ of the jaws may be silent or subtle in terms of symptoms. Symptom free periods may extend over many months with the recognition of clinical damage being heralded by localized or diffuse jaw pain or incidental discovery of asymptomatic exposed alveolar bone or tori. Symptoms usually occur later as pain due to incidental adjacent soft tissue trauma produced by sharp exposed bone, or as suppuration from an active secondary odontogenic infection. Diagnosis may be made by: 1) a history of bisphosphonate use, denosumab administration or use of a wide number of other drugs including antiangiogenic agents; 2) the presence of exposed maxillary or mandibular bone for eight weeks or longer; and 3) absence of prior radiation treatment to the jaws. The clinician should rule out other conditions such as odontalgia of pulpal origin, chronic periodontitis, myofascial/ temporomandibular dysfunction associated pain, sinusitis, atypical facial pain, florid cemento-osseous dysplasia and idiopathic lingual mandibular sequestration prior to making a final diagnosis.

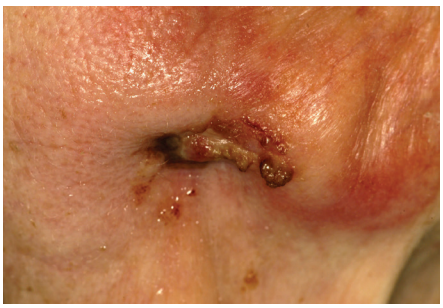
Most cases of MRONJ are noted in the mandible (65%) while 26% localize in the maxilla alone and 9% may affect both sites. Performance of a dental surgical procedure prior to the onset of symptoms has been noted in 60% of cases, with the remainder of cases resulting from trauma and/or infection.[8] The progression rate is highly variable as is the extent of clinical involvement. Some patients present with minor or small areas of exposed alveolar bone, without drainage or pain. Others may demonstrate extraoral fistula formation and drainage (**Figure 5**). Progression rate is in part due to the overall duration or exposure to bisphosphonates or medication(s) in question, particularly with use or administration of the more potent intravenous bisphosphonates and other drugs affecting vascular growth by way of inhibition of vascular endothelial growth factors. The evolution of this disease from initial discovery to sequestrum formation can be rapid, though a several months span is more characteristic. [See accompanying case report]

A useful criteria-based staging system has been developed to allow patient stratification (**Table 2**).[9] Criteria relate to the presence or absence of pain, exposure of insensate bone, inflammatory swelling, secondary infection, and extraoral or cutaneous fistula formation. Based on this stratification, rational treatment plans can evolve which have been developed since the initial description of jawbone osteonecrosis. Aiding in further clinical decision making is use of panoramic and tomographic imaging, though symptoms may precede demonstrable radiographic changes by several weeks to a few months. Dental providers must therefore maintain an index of suspicion, with medical and medication histories carefully evaluated on a routine basis.

Management

Prevention of MRONJ is often the major clinical goal, as only a small number of patients receiving nitrogen-containing bisphosphonates develop MRONJ and less commonly in relation to non-resorptive agents in the absence of proximate dental treatment, trauma or infection. Routine dentoalveolar surgery, including simple dental extractions, apical surgery and dental implant placement is the chief initiator of MRONJ. Prevention strategies must be established to maintain optimal dental and oral health in anticipation of resorptive and non-resorptive drug treatment or during actual exposure to these bone-stabilizing agents and those drugs known to interfere with vascular/blood vessel growth. Key to the prevention strategy are measures that reduce microbial loads that can lead to oral infection, construction of well-fitting prostheses and avoidance of dentoalveolar surgery, the prime and most consistent risk factor. If possible, treatment with the types of drugs mentioned should be delayed until appropriate dental evaluation, management and optimal dental status are achieved.

Figure 5



Stage 3 - An extraoral fistula that was draining foul smelling purulent material that required multiple antibiotics in this patient on a long course of intravenous bisphosphonate treatment.

Table 2 - Staging of MRONJ[8]

Stage 0 - Absence of necrotic bone, but with non-specific clinical findings and symptoms.

Stage 1 - Presence of asymptomatic exposed/necrotic bone with no evidence of infection.

Stage 2 - Presence of pain, infection and exposed/necrotic bone.

Stage 3 - Presence of pain, infection and exposed/necrotic bone in association with at least one of the following: pathologic fracture, full thickness osteolysis of the mandible or extra-oral fistula formation.

As with the patient beginning or in the process of undergoing radiation therapy in the region of the jaws, emphasis must be placed on prevention. At-risk dental and periodontal conditions that could compromise the status of the jaws and dentition should be eliminated prior to initiating drug therapy. An active and aggressive prevention program to obtain optimal oral health should be established prior to and maintained during bisphosphonate or denosumab treatment. Invasive procedures including dental extractions and periodontal therapy ideally should also be completed prior to starting bisphosphonate therapy. Following the performance of necessary extractions or other dentoalveolar surgery an ideal time to allow for healing is 4 to 8 weeks.[10,11] Assessing bone turnover rates to determine potential risk for MRONJ, or for patients diagnosed with MRONJ, may be helpful when clinicians are contemplating dentoalveolar or oral surgical procedures for a patient previously managed with bisphosphonates or non-resorptive vascular-targeted agents. However, this concept has not been fully endorsed and remains controversial. The early rationale for this testing is that increased osteoclastic activity will create a corresponding increase in the levels of collagen telopeptide fragments, as well as other markers, in urine and serum. Bone turnover tests assess type I collagen C-telopeptide (CTX) fragment assay, N-telopeptide fragment assay, and urine pyridinoline assay.[11] The general utility and validity of bone turnover testing has been challenged regarding its benefit in a prospective clinical study.[13,14] with recent evidence not supporting the use of serum markers of bone matrix fragments.[15]

To assist patients accessing their dental providers, the dental and medical (oncology) communities must establish rapid assessment, open communication, and timely referral patterns. Oral benefits may be gained by termination of bisphosphonate drugs for three months prior to, and three months following, invasive dental surgery if other health conditions allow. However, in cases of metastatic cancer and multiple myeloma where more intense treatment with intravenous bisphosphonates is being utilized, this may not be feasible or effective.

A collective decision by the dentist and the treating medical oncologist is required regarding the possible discontinuance of intravenous bisphosphonates and non-resorptive agent use in proximity to invasive dental treatment (**Table 3**). The discussion should include consideration of elimination or reduction of bisphosphonate administration (drug holidays) during cancer management. However, the wisdom of this strategy can be questioned given the persistence and half-life of these agents once incorporated into bone. When considering long-term discontinuation of intravenous bisphosphonate treatment for stabilization of established asymptomatic MRONJ, a risk-benefit assessment is in order, assuming systemic conditions permit. This assessment is multipartite in nature with dental and oral factors considered in tandem with the reason for bisphosphonate administration. For cancer patients, the clinicians must decide whether the patient's risk of developing MRONJ outweighs the possibility of advancement of their malignancy and associated morbidity of known, but managed, metastatic disease. When osteopenia or osteoporosis is being managed with orally administered bisphosphonates, it is uncertain whether bisphosphonate therapy should continue or be stopped until after healing following a dental /oral surgical procedure.[16] A recent study failed to demonstrate significant differences in outcomes of MRONJ management in patients who had continued treatment versus those who were withdrawn from treatment with bisphosphonates following the diagnosis of MRONJ.[17] Management of all stages of MRONJ remains problematic at times, with no agreed-upon and routinely effective strategy currently available. Recently, one clinical trial described the results of employing an adjunctive program of hyperbaric oxygen treatment in cases of BRON. Results were minimally encouraging with only 2 of 16 patients achieving stabilization. General outcome improvement was noted only in association with cessation of bisphosphonate therapy.[18]

Chlorhexidine rinses (2-3 times daily) are suggested in all stages of MRONJ management. Orally administered antibiotics in the form of penicillin VK or penicillin family agents, and alternatives such as doxycycline, or other suitable agents, including metronidazole, clindamycin, quinolones and erythromycin in the face of penicillin allergy, are advised during periods of active infection and associated pain and drainage. As with chronic administration of many antibiotics, consideration must be given to development of side effects including candidiasis, pseudomembranous colitis, hypersensitivity and outgrowth of resistant strains of bacteria, among others.

Table 3 - Drug classes associated with MRONJ development

Anti-resorptive agents
- Bisphosphonates
- Denosumab

Tyrosine kinases inhibiting vascular growth and vascular/endothelial renewal
- Bevacizumab
- Everolimus
- Sorafenib
- Sunitinib

Corticosteroids
- Prednisone / prednisolone
- Dexamethasone

A more complete listing of drugs associated with jawbone necrosis may be accessed in the work of Ahdi H, et al.[25]

In cases of advanced stage MRONJ where control of bone destruction or infection is not possible, or in cases of pathologic fracture, an alveolectomy, sequestrectomy or resection of affected bone and reconstruction may be necessary. Placement of a titanium reconstruction plate following resolution of the infection will permit re-establishment of normal contour and acceptable levels of function.

Generally, conservative management strategies are advocated with minimal surgical entry into small areas of necrotic bone associated with the use of oral bisphosphonates, with the exception of reducing any minor areas of uneven or sharp bone edges impinging on oral soft tissues. Approximately 60% of patients with oral bisphosphonate-associated MRONJ will heal after 6 to 12 months following discontinuation of the bisphosphonate without significant surgical intervention. The remaining patients may require surgical debridement.[5] [See **Table 4** for stage-specific management strategies]

Recent studies concerning the use of alternatives to bisphosphonate agents, monoclonal antibodies (denosumab) that bind to mediators of osteoclast differentiation, activation and survival or calcium analogues (strontium ranelate) have shown efficacy, however, MRONJ has also been noted following the use of denosumab, which blocks the RANKL pathway and interferes with osteoclast activation and function.[19,20,21,22] An additional management strategy has been described that places platelet-derived growth factors into defects created following marginal resection of necrotic alveolar bone. Results of this technique, though only used in a small number of patients, demonstrated complete healing, with mucosal coverage at previous defect sites.[23] Other therapies include utilization of vitamin D in conjunction with pentoxifylline, teriparatide, a parathormone analog and hyperbaric oxygen. oxygen.[24] Clear is the fact that treatment remains controversial with absence of a so-called "gold standard" protocol, which is uniformly effective. That said, approaches range from non-invasive ones where medical intervention of laser surface application may be attempted as an initial approach, clinical factors permitting. Invasive/ surgical procedures range from conservative to aggressive withn the former involving debridement and sequestrectomy with the latter involving resection of the affected area and reconstruction. Finally, combined surgical and less aggressive / less invasive procedures may be considered as dictated by clinical circumstances.

Treatment goals should be directed toward management of pain, control and elimination of infection and reducing the progression of necrosis. Achieving these goals will eliminate the negative impact on quality of life in these patients.[25]

Table 4 - Stage-specific management of established osteonecrosis of the jaws[1]

Stage 0

- No treatment - observe

Stage 1

- Chlorhexidine 0.125% rinses twice daily
- Patient education; quarterly follow-up
- Evaluate and adjust any ill-fitting prostheses
- Re-evaluate indications for continued bisphosphonate treatment

Stage 2

- Chlorhexidine rinses 0.12% twice daily
- Oral antibiotics, *e.g.,* penicillin VK, cephalexin, 1st generation fluoroquinolone*
- Pain management
- Superficial debridement if soft tissue irritation is present

Stage 3

- Chlorhexidine rinses 0.12% twice daily
- Antibiotic treatment *
- Pain management*
- Surgical debridement; Resection of infected bone for longer term palliation and pain control*

* The specific duration of antibiotic and analgesic administration should be guided by the clinical response obtained. The American Dental Association recommends a 14-day time span of antibiotic administration for the dental patient being treated with oral bisphosphonates, having unexpected pain, purulence or active sequestration after a dental procedure.[21] Far more problematic is determination of antibiotic use following surgical debridement of established stage 3 MRONJ cases. Clinical judgment with regard to severity on the part of the treating clinician would seem to be most appropriate. Marx advocates the rare use of continuous long-term intravenous antibiotics with or without concomitant use of prednisone in MRONJ cases with refractory infection.[23]

Caveats: When symptomatic teeth are present within segments of exposed and necrotic bone, their extraction may be a valid consideration, given that such treatment will not likely accelerate or exacerbate necrosis. Atraumatic removal of a mobile sequestrum without exposure of uninvolved bone should be considered.

In cases of oral bisphosphonate-related osteonecrosis, consideration should be given to discontinuation of the drug, if clinical circumstances permit, in concert with the patient's treating physician. In cases of MRONJ-related use of intravenous bisphosphonates, there is no evidence of short-term benefit following discontinuation of the drug; however, there may be stabilization of existing MRONJ sites and a reduction of local symptoms over time when the drug is discontinued. A discussion with the patient and their oncologist should precede this decision.

Case Report

To illustrate the clinical presentation, progression and overall behavior of a typical advanced case of bisphosphonate related osteonecrosis of the jaws (MRONJ), the following is described:

Mrs. M is a 61-year-old woman who presented with two painless ovoid areas of exposed bone over an edentulous segment of the left mandibular body. They had been present for several months. She had the teeth in the area extracted many years prior and a removable partial denture placed. The denture was ill fitting and had been recently adjusted. The area of exposed bone did not heal following the adjustment.

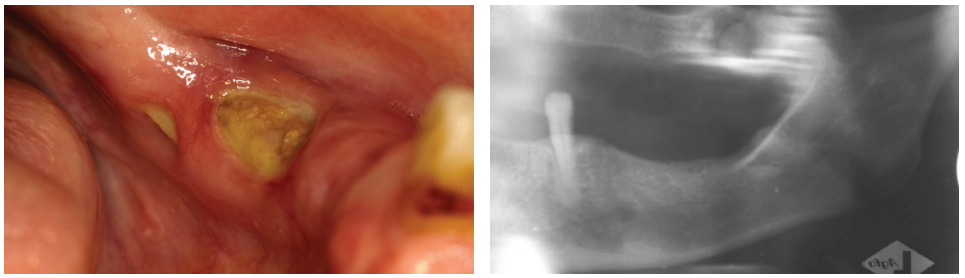
Her medical history indicated that she was treated for breast cancer over 19 years ago. Four years ago, she was diagnosed with metastatic lesions to multiple bony sites. Bisphosphonate therapy was initiated with intravenous pamidronate (Aredia®) for one year and switched to intravenous zoledronic acid (Zometa®) three years ago (4 mg once a month), along with docetaxel. Her metastatic disease has been stable during the treatment interval.

At the initial examination an ovoid area of insensate exposed bone measuring 2.0 x 1.8 cm was present over the alveolar crest of the left mandible with a well-defined but undermined mucosal margin surrounding the exposed bone. A smaller area of exposed bone was noted along the ipsilateral mylohyoid region (**Figure 6a**). No signs of drainage or suppuration were present, nor was there a history of such. A routine panoramic radiograph demonstrated a suggestion of increased bone density in the corresponding area of exposed bone with no evidence of osteolysis (**Figure 6b**). A working diagnosis of Stage 1 BRON was made.

She was placed on twice daily chlorhexidine rinses with recall visits scheduled every three months. In the meantime, discussions were held with the patient's oncologist and the patient. It was decided to empirically reduce the frequency of her zoledronic acid to quarterly infusions at the typical dose, while the chemotherapy regimen continued as usual. Over the next several months, the area of exposed bone slowly increased, as did the degree of bony sclerosis in the left mandible. There was early indication of separation between the emerging sequestrum and the lower portion of the mandible (**Figure 7a and b**). During this time, she experienced modest pain and developed a suppurating infection. Pain was managed with ibuprofen (400 mg three times daily) and oral penicillin VK (500 mg four times daily) was administered for 21 days to treat the infection.

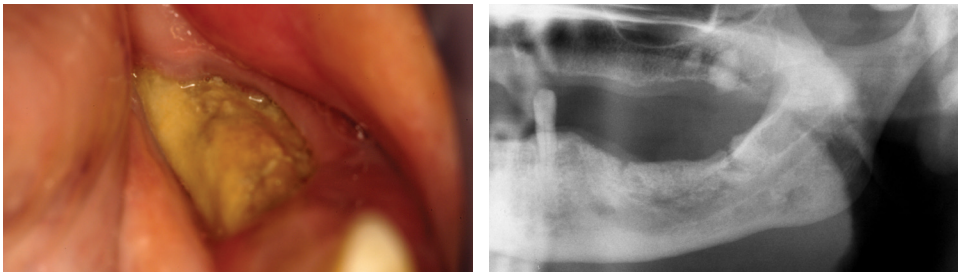
Continued sequestrum development and a greater level of exposed bone were noted (**Figure 8a and b**), until there was loosening allowing simple removal and leaving a thin strut of mandible (**Figure 9**). Bony destruction continued until there was a spontaneous pathologic fracture at 26 months following her initial presentation (**Figure 10**). Following this latter complication, a conservative resection was performed with placement of a titanium fixation plate over the defect (**Figure 11**). Four months after the reconstruction plate was placed, she remains comfortable and is free of infection, though areas of intraoral bone remain exposed bone.

Figure 6 (a and b)



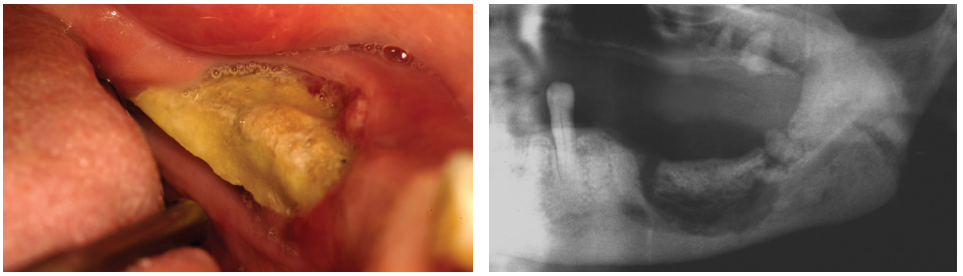
Manifestation of stage 1 BRONJ with asymptomatic exposed alveolar bone and subtle radiographic features of an emerging ground glass or sclerotic alteration of alveolar bone.

Figure 7 (a and b)



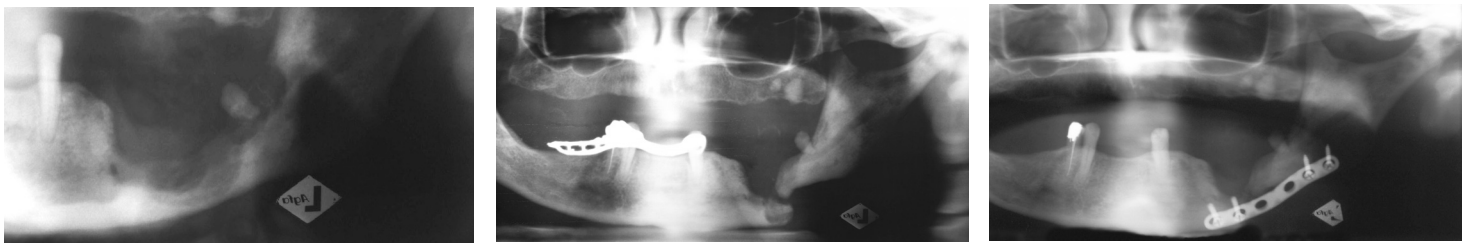
Four months later the area of exposed alveolar bone had increased in size with a clear radiographic delineation between the forming sequestrum and deeper mandibular bone.

Figure 8 (a and b)



An undermined minimally mobile, resorbing sequestrum was present 14 months following the presentation. Radiographic evidence shows separation of the sequestrum..

Figures 9-11



Progression of BRONJ from removal of the mobile sequestrum - to sustaining a pathologic fracture - to the repair or stabilization of the jaw with a reconstruction plate.

The following publications are suggested reading for individuals interested in more in-depth exploration of this topic:

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POST-TEST

Internet Users: This page is intended to assist you in fast and accurate testing when completing the "Online Exam." We suggest reviewing the questions and then circling your answers on this page prior to completing the online exam.

(1.5 CE Credit Contact Hour) Please circle the correct answer. 70% equals passing grade.

1. **The diagnosis of MRONJ relies on satisfaction of several clinical criteria including a history of bisphosphonate intake, absence of prior radiation therapy to the jaws, or:**
   a. use of certain tyrosine kinase inhibitors.
   b. throbbing jaw pain radiating to the ear or lateral temporal area.
   c. paresthesia along the course of trigeminal nerve distribution.
   d. presence of metastatic cancer or myeloma.

2. **In addition to antiresorptive agents which drug or drug class has been associated with MRONJ development?**
   a. Bevacizumab (Avastin®)
   b. Cis-platinum
   c. Pembrolizumab (Keytruda®)
   d. Nivolumab (Opdivo®)

3. **Typical early cases of medication-related osteonecrosis are most often characterized by the presence of:**
   a. Draining dental abscess with extraoral fistula formation.
   b. Loosening of a single tooth or multiple teeth.
   c. Sclerotic alveolar bone on routine dental imaging.
   d. Paresthesia in the involved quadrant.

4. **Early panoramic and intraoral radiographic images of MRONJ may demonstrate osseous alterations that are similar to which process or condition?**
   a. Periapical granuloma formation
   b. Fibro-osseous disease of bone
   c. An odontogenic keratocyst
   d. Osteoporosis

5. **Management goals for MRONJ include all of the following except:**
   a. Elimination of pain
   b. Clearance of infection
   c. Restoration of bone integrity
   d. Reducing progress of bone necrosis

6. **Which factor most influences the philosophy of whether to have so-called "drug holidays" or discontinuation of intravenous bisphosphonate use during cancer management when oral surgical procedures are planned?**
   a. Age of the patient
   b. Extent of MRONJ involvement
   c. Half-life of the bisphosphonate used
   d. The type of cancer being treated

7. **Which imaging technique may afford an early indication of developing MRONJ prior to traditional radiographic or clinical manifestation?**
   a. PET scan
   b. Technetium bone scanning
   c. Ultrasonography
   d. Scintigraphy

8. **What does a patient beginning radiation therapy encompassing the jaws share with one about to begin intravenous bisphosphonate therapy as a component of myeloma management?**
   a. Immediate removal of teeth containing metallic restorations
   b. Overall evaluation by the medical oncologist
   c. Pre-treatment nutritional counseling
   d. A dental evaluation and prevention strategy formulation

9. **Stage 2 MRONJ may include all the following except:**
   a. Pain
   b. Infection
   c. Exposed bone
   d. Extraoral drainage

10. **Alternatives to bisphosphonate management of osteoporosis might include use of:**
    a. Calmodulin antagonists
    b. Dietary calcium supplementation
    c. A specific monoclonal antibody
    d. Osteoblast growth factors

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Evaluation - Bisphosphonate and Other Medication-Related Jaw Necrosis Part Two: Clinical Management (6th Edition)

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