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Case Challenge
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Pain in the Right Posterior Mandible

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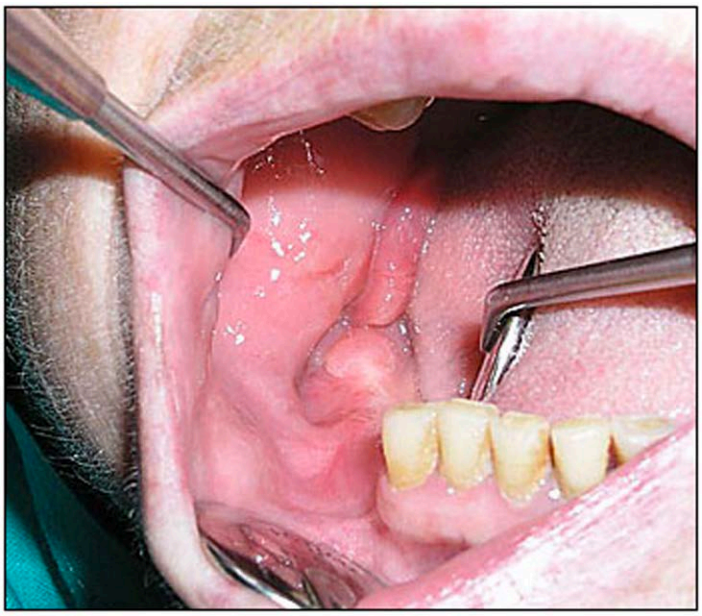


The following Case Challenge is provided in conjunction with the American Academy of Oral and Maxillofacial Pathology.

Case Summary

An 82-year-old Caucasian female presented to the Department of Oral Medicine at Valencia University in Valencia, Spain with a complaint of pain in the right posterior mandible. The pain was controlled with several over-the-counter analgesics but exudate drained intermittently from an opening in the skin in this area.

After you have finished reviewing the available diagnostic information, make the diagnosis.

Diagnostic Information

Medical History

A review of the patient's past medical history was significant for osteoporosis and arthritis. She had been treated for osteoporosis with alendronate (Fosamax) at a dosage of 70 mg per week for three years.

Oral Findings

Upon examination, the right posterior mandibular alveolar ridge appeared to be covered by intact mucosa (Figure 1). On closer inspection, however, a small ulcer with an adjacent small fistula was discovered hidden beneath the mucosal fold covering the superficial part of the right posterior alveolar ridge close to the retromolar pad area (not apparent in this photograph).

The skin overlying the jaw, however, showed a large cutaneous fistula (Figure 2) which intermittently drained exudate for a period of six months.

Radiographic Findings

Panoramic and CT-scan radiographs were performed. The panoramic radiograph revealed large pieces of bony sequestra in the right posterior mandible surrounded by an irregular radiolucency and what appeared to be a pathologic fracture (Figure 3).

The latter was confirmed with a CT-scan sagittal image (Figure 4). The CT scan also clearly demonstrated a large bony sequestrum undergoing resorption surrounded by the irregular radiolucency. Both radiographs showed evidence of sclerotic bone surrounding the lesion.

Incisional Biopsy Findings

Under local anesthesia the biopsy specimens were obtained using simple local curettage of the area (Figures 5 and 6). Histologic examination of the curetted material revealed multiple pieces of decalcified hard and soft tissue. The latter was made up of granulation tissue covered by stratified squamous epithelium (Figure 5) and infiltrated by many neutrophils, lymphocytes, and plasma cells. The bony fragments comprised a significant portion of the specimen (Figure 6) and were mostly lamellar in type with Haversian systems devoid of viable osteocytes. The bony fragments showed evidence of external resorption covered by bacterial colonies of mixed oral flora.

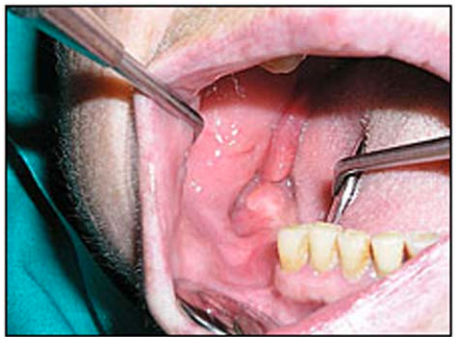


Figure 1. Irregular swelling on the right mandibular alveolar ridge. The alveolar mucosa appears intact but a small sinus is present below the fold in the posterior mandible. (Not visible in the photograph.)

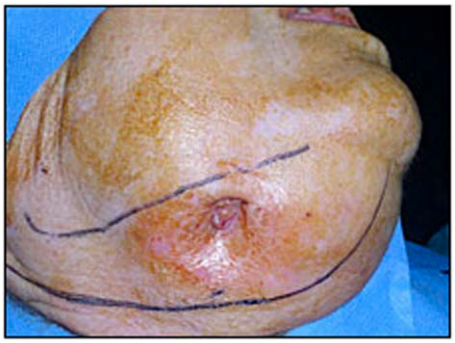


Figure 2. The skin overlying the jaw with a large cutaneous fistula, which was reported to intermittently drain exudate.

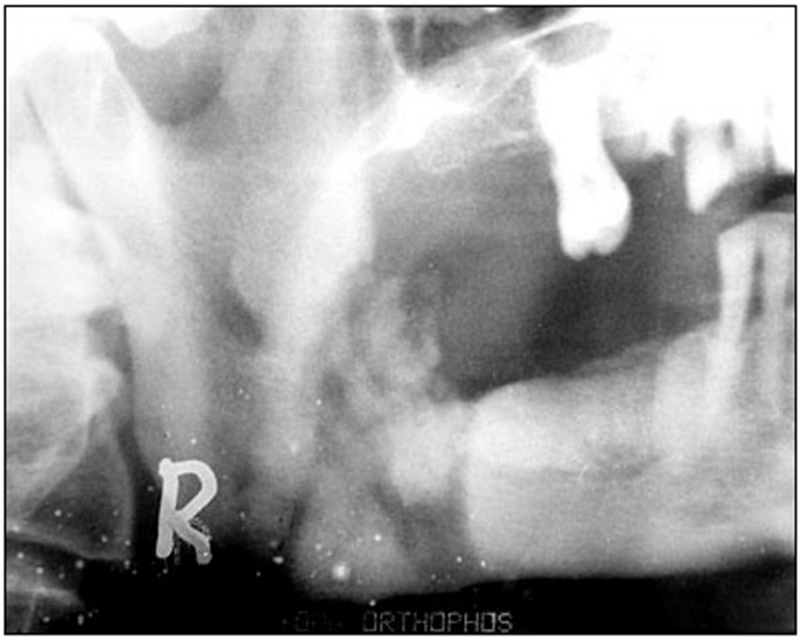


Figure 3. A portion of a panoramic radiograph demonstrating a large and ill-defined mixed radiolucent and radiopaque lesion in the right posterior mandible with a pathologic fracture and large bony sequestration.

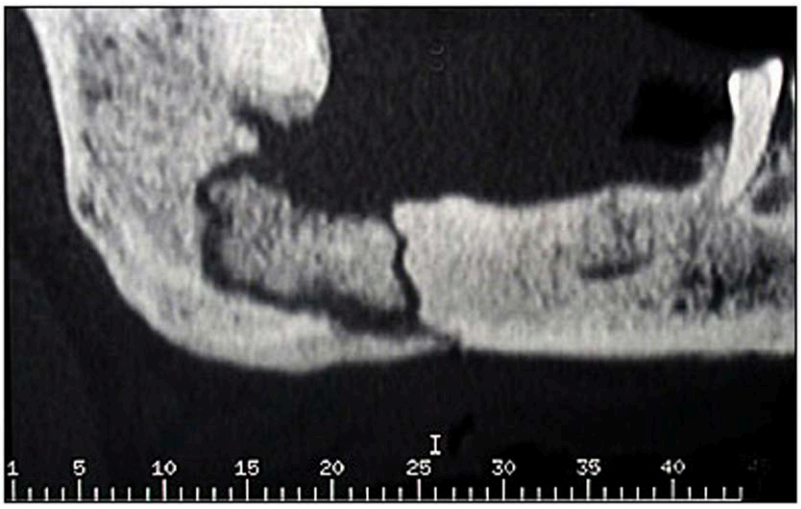


Figure 4. A CT-scan (sagittal view) of the right posterior mandible demonstrating a large and irregular bony sequestrum, pathologic fracture, and sclerosis of the bone surrounding the lesion.

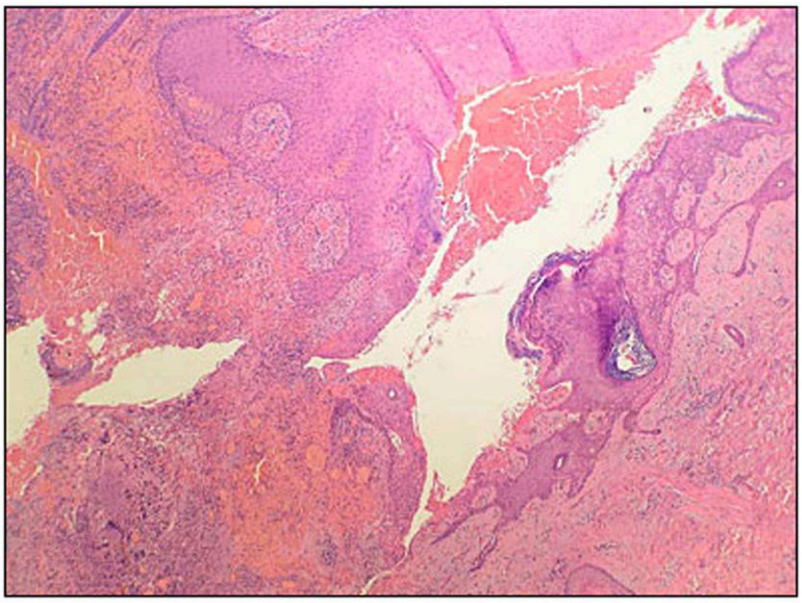


Figure 5. Low power (x100) histology illustrating the soft tissue component made up of heavily inflamed granulation tissue covered by epithelium.

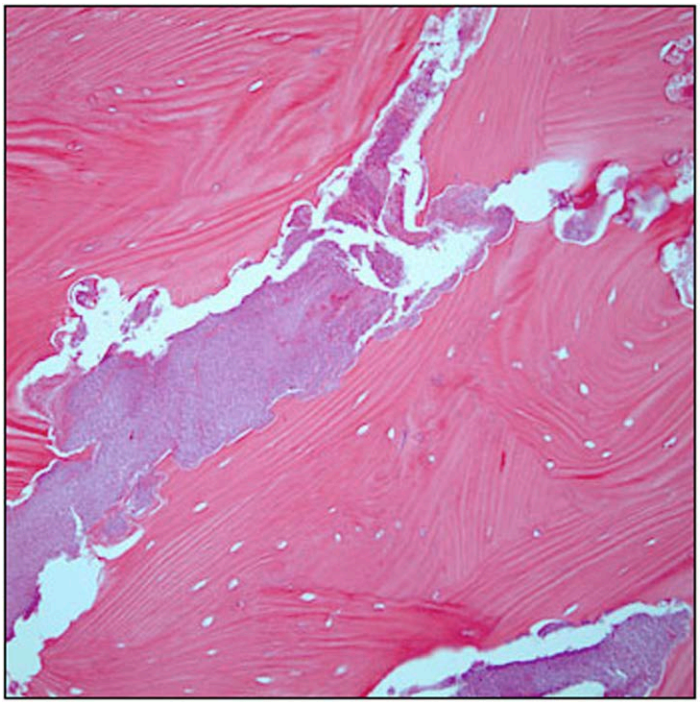
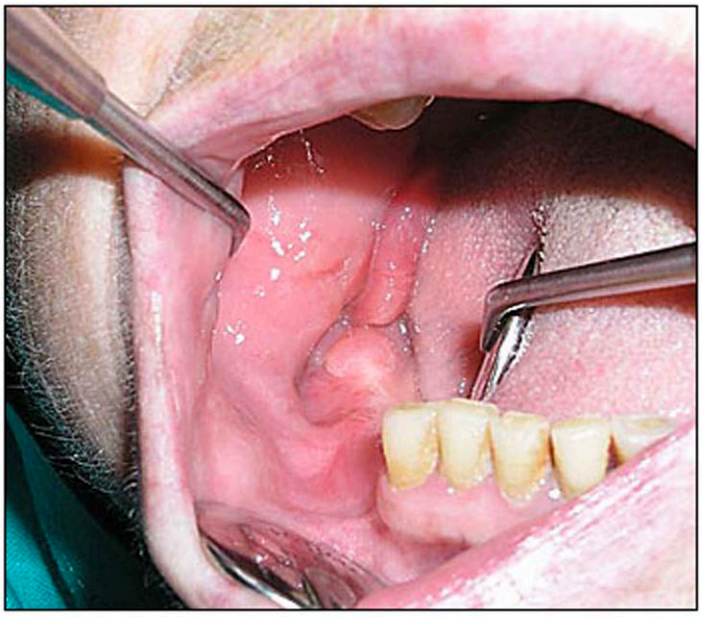


Figure 6. Higher power (x200) histology illustrating bony trabeculae devoid of viable osteocytes. The bone shows evidence of resorption surrounded by bacterial colonies.

Can you make the diagnosis?

An 82-year-old Caucasian female presented with a complaint of pain in the right posterior mandible. The pain was controlled with several over-the-counter analgesics but exudate drained intermittently from an opening in the skin in this area.



Select the Correct Diagnosis

A. Osteoradionecrosis (ORN)
B. Chondrosarcoma
C. Osteosarcoma
D. Metastatic Malignancy
E. Bisphosphonate-associated Osteonecrosis (BON) of the Jaws

Osteoradionecrosis (ORN)

Choice A. Sorry, this is not the correct diagnosis.

Osteoradionecrosis (ORN) is a serious post-radiation therapy complication of bone. Only bone directly in the path of the radiation is at risk.[1,2] Reuthner et al.[1] reported an incidence of 8.2% based on a retrospective study of 830 head and neck cancer patients treated with radiation. Factors influencing death of the irradiated bone center on the principle of "3 Hs" (hypovascularity, hypocellularity, and hypoxia) along with bone marrow fibrosis.[1-4] Radiation exposure permanently damages the blood vessels and osteocytes, causing reduced vascularity and bone marrow fibrosis, which render the bone vulnerable to infection. Radiation dose correlates with the development and the extent of ORN. Patients receiving doses of 60Gy and higher are more likely to develop ORN and to have more extensive involvement.[1] ORN is more common in males (3:1, M to F ratio) and more common in the body/posterior mandible. The clinical presentation ranges from small and asymptomatic bone exposure to serious infection with bony sequestration, cutaneous fistulas, soft tissue dehiscence, and pathologic fractures.[1-3] All of these features were present in this patient. However, the patient had no history of radiation therapy.

The most frequently implicated risk factor in the development of ORN is trauma (such as post-radiation tooth extraction), which accounted for 50% of cases in one study.[1] Other factors include pre-surgery radiation, smoking, drinking, and ill-fitting dentures.[1,2] Prevention is the key to avoiding ORN and includes full-mouth dental evaluation and comprehensive treatment of the patient about to receive significant radiation to the head and neck area. Based on the grade of the disease, treatment ranges from curettage, antibiotics, and chlorhexidine rinses to surgical resection, with and without hyperbaric oxygen.[1-4] The literature is not in uniform agreement regarding the usefulness of hyperbaric oxygen therapy in ORN.[1-4] Tooth extraction should be avoided in irradiated areas, if possible.

Please re-evaluate the information about this case.

Chondrosarcoma

Choice B. Sorry, this is not the correct diagnosis.

Chondrosarcoma of the jaws is rare, accounting for about 1-12% of chondrosarcomas of all sites.[5] It is a malignant neoplasm of cartilage where the tumor cells produce cartilage and not osteoid.[5] It is generally more common in the pelvic bone, long bones, and ribs. The head and neck chondrosarcoma presents more commonly in the maxilla (the incisor teeth area) and in the nasal and paranasal region followed by the mandible, base of the skull, and larynx.[5-7] It is described in a wide age range, 19-83 or older, with an average of 41 years of age.[6] While some reports suggest equal gender distribution, others suggest a slight male predominance.[6,7] Unlike osteosarcoma, chondrosarcoma has a low tendency for metastasis. It commonly presents as an asymptomatic swelling with buccal and lingual expansion. Patients may experience unexplained paresthesia, headache, and loosening or loss of teeth.[5,6] Radiographically, it presents as an ill-defined, mottled radiolucency with snowflake or punctate calcifications.[5-7] Widened periodontal ligament has been reported, especially in the early stages of this disease.[5-7] Histologically, it is characterized by immature and pleomorphic cartilage, but at times the cartilage is benign-looking and can be mistaken for chondroma. However, the latter tumor is rare in the jaws.

Bony sequestration and suppuration with cutaneous fistula formation would be most unusual for chondrosarcoma. In addition, the histology in this case was not supportive of this diagnosis.

Please re-evaluate the information about this case.

Osteosarcoma

Choice C. Sorry, this is not the correct diagnosis.

Osteosarcomas of the head and neck area are rare compared to the long bones. Approximately 10% of all osteosarcomas occur in the head and neck area, mostly located in the mandible or maxilla.9 Other bones of the facial skeleton are affected far less often. Long bone osteosarcomas, on the other hand, are the third most common malignancy in adolescents[9] with a peak incidence between the ages of 10 and 14 years, coinciding with a major growth spurt. Osteosarcomas of the jaws typically occur in the third or fourth decade, being 10-15 years older than the mean age of the long bone osteosarcomas.[8-10] There is a slight male predominance in the long bone osteosarcomas and equal gender to slight male predominance in the jaws. The risk for developing osteosarcoma increases in patients with Paget's disease, irradiated fibrous dysplasia, and generally in areas of prior radiation therapy.[8-10] An equal frequency of occurrence of osteosarcoma in the maxilla and mandible has been reported, while other studies suggest a slight predominance in the mandible.[9] Clinically, the tumor presents with pain, swelling, paresthesia, and/or loosening of teeth.[8-10] Radiographically, they range from a completely ill-defined radiolucency to a predominantly sclerotic area. The majority present as ill-defined mixed radiolucent and radiopaque lesions.[8-10] Other radiographic findings include: symmetric widening of the periodontal ligament space (PDL), diffuse borders of the lesion, periosteal reaction, "spiked" roots, or the classic "sunburst" or "sun ray" appearance caused by osteophytic bone deposition at the periphery.[8-10] Osteosarcoma often exhibits aggressive local growth and the propensity to spread systemically via hematogenous routes, especially to the lungs.

Suppuration with cutaneous fistula has been reported in advanced osteosarcomas but is rare. Histologically, osteosarcomas display considerable variability and are characterized by the formation of osteoid by malignant mesenchymal cells, although some tumors also produce significant amounts of cartilage (chondroblastic) or fibrous tissue (fibroblastic).[9] The histology in this case, however, is not supportive of this diagnosis.

Please re-evaluate the information about this case.

Metastatic Malignancy

Choice D. Sorry, this is not the correct diagnosis.

Cancer metastasis to the oral cavity is rare, constituting less than 1% of all oral malignant neoplasms. Theoretically, any malignant neoplasm can metastasize to the oral cavity but in actuality few do. The most common malignant neoplasms that metastasize to the mouth are carcinomas of the breast, lung, kidney, and prostate.[11,12] Breast cancer is the most common neoplasm to metastasize to the oral cavity regardless of gender.[11] Lung and prostate cancers are the most common neoplasms to metastasize to the oral cavity in men. Rare neoplasms such as cervical cancer have also been reported to metastasize to the mandible.[13] In most cases the oral presentation is a late occurrence, constituting a secondary diagnosis because the primary malignancy in the distant organ has been diagnosed previously and the patient has had or is undergoing treatment for it. On rare occasions, the oral lesion is the first manifestation of the disease. By far the most common location for metastatic disease is the posterior mandible, where 80% of cases occur, with the gingiva accounting for the second greatest number of cases.[11,12] It is mostly described in adults over the age of 30 and rarely in children. While pain and swelling are the most common clinical symptoms, tooth loosening, displacement, and root resorption producing a sharply pointed root architecture have also been described.[11] The radiographic appearance of irregular bone destruction, pathologic fracture, and a combined radiopaque and radiolucent lesion is a common presentation for metastatic neoplasms to the mandible.[11-13] Therefore, suppuration with fistula formation in an area of a malignant neoplasm (primary or metastatic) is not necessarily unusual. The majority of neoplasms cause bony destruction with ill-defined borders and a moth-eaten appearance indicating aggressive behavior. However, the histopathology in this case was not supportive of a metastatic malignant neoplasm.

Please re-evaluate the information about this case.

Bisphosphonate-associated Osteonecrosis (BON) of the Jaws

Choice E. Congratulations! You are correct.

Bisphosphonates (BPS) are synthetic analogs of inorganic pyrophosphate with a high affinity for calcium.[14,15] They were first developed in 1865 for industrial use as anticorrosive and water softening agents.[16] In the 1960s their use in medicine was investigated, especially for the treatment of Paget's disease. One of the first generation BPS is etidronate which was first prescribed for Paget's disease patients to treat hypercalcemia.[17] The more recent and the more potent generations of BPS have been associated with bone osteonecrosis.[14,15] BPS can be simply classified into those containing nitrogen (more potent) and those without. To date, all of the BPS reported to cause osteonecrosis have nitrogen attached to the side chain and are known as aminobisphosphonates. The five most prescribed nitrogen-containing BPS are: pamidronate (Aredia®, Novartis®), zoledronate (Zometa®, Novartis®), alendronate (Fosamax®, Merck), ibandronate (Boniva®, Roche laboratories), and risedronate (Actonel®, Procter & Gamble). Pamidronate and zoledronate are primarily used to treat primary bone cancer, such as multiple myeloma or metastatic bone cancer, such as breast carcinoma. They are administered intravenously either once a week or once a month. Alendronate, ibandronate (also approved for IV intake), and risedronate are taken orally in daily, weekly, or monthly doses for the prevention/ treatment of osteoporosis, mostly in post-menopausal women.[17-27]

The mechanism of action of BPS includes inhibition of osteoclast development from precursor cells, an increase in osteoclast apoptosis, and stimulation of osteoclast inhibitory factor.17-22 It is also important to note while the BPS are actively inhibiting bone resorption, they are also depositing inorganic material along the bone which becomes denser, stronger, and better able to withstand stress. While excessive accumulation of the inorganic substances has its own set of adverse effects leading to osteonecrosis as suggested by Ott,26 it needs to be emphasized the anti-osteoclastic effect of BPS has been of benefit to multiple myeloma and metastatic bone cancer patients in controlling hypercalcemia.

Once deposited, BPS are known to stay in bone for long periods of time (the half life of alendronate is 12 years and zoledronate is 20 years) because the P-C-P bond is indigestible. When the chemical is ingested, it stays in the bone for many years, if not for the life of the patient.[16] It is released by the bone during resorption only to be recycled back into the bone at a lower concentration. For example, if a patient was on alendronate for ten years, he/she would recycle the drug at 25% of the original dose for many years without a single new pill being taken by the patient.

BPS osteonecrosis (BON) was first reported in September 2003[21] and to date hundreds of cases have been reported worldwide. However, it is important to emphasize the IV BPS, especially zoledronate and pamidronate, are by far most responsible for the jaw osteonecrosis.[21,23,28] The incidence of BON is much lower with oral BPS.[24,26] The incidence of jaw osteonecrosis cases has increased with increased active clinical use of BPS, especially in multiple myeloma where up to 10% of the patients using zoledronate develop BON after 36 months of use.[28] The risk was found to be time-dependent and became significant after 12 months of use, with a further increase after 36 months. One report shows BON developing as early as four months after initiation of zoledronate therapy.[29] In a study of 250 patients who had received pamidronate and zoledronate for seven years, 6.7% developed BON representing 9.9% of multiple myeloma patients, 2.9% of breast cancer patients, 6.5% of prostate cancer patients, and 4% of those with other neoplasms. Occurrence was 1.5% in patients treated for four-12 months and 7.7% for 37-48 months.[30] All but two had dental procedures within the last year.[30] Alendronate, on the other hand, is not as potent in terms of inducing jaw osteonecrosis.[26] According to the manufacturer, less than 1 in 100,000 patients develop BON. One study reports 10% of their BON patients were on oral BPS (predominantly alendronate).[23] It is obvious the number of patients with osteonecrosis who are taking alendronate is much less than the IV BPS; but the true incidence of BON associated with alendronate is neither as low as the company

claims nor as high as 10%. Alendronate use and the development of BON is also dose- and time-dependent. The higher the doses and the longer the time of use, the higher the incidence. BON has been described as early as two years after alendronate use[21,22] but is usually more common in individuals who have been taking it for five or more years. This patient developed a serious case of BON (Figure 2) after three years of use. She had no history of extraction in the area and, thus, her BON would be classified as spontaneous.

The most significant risk factors found in patients with BON include extraction, periodontal surgery, or any other surgical manipulation of the jaw bones.[21,27] Other risk factors include ulceration of bone-bound mucosa (exposing the bone to the bacteria-laden oral cavity), the age of the patient (which may be significant in our patient since she was 82-years of age), steroid use, ill-fitting dentures, periapical lesions, badly carious teeth, partially erupted teeth, large tori and exostoses, and implants.[20-30]

BON is rarely described in bones other than the jaws. The reason the jaw bones appear to be specifically targeted is theorized to be poor local vascularity and impaired wound healing,[20] especially in the posterior lingual mandible.[21] Olson et al.[25] suggest blood flow in the end arteries of the posterior mandible is weak and the bone is thick, rendering the area more susceptible to necrosis, especially in case of trauma. In addition, the mandible and maxilla are the only bones connected to an exterior cavity housing bacteria-laden teeth and periodontium.

Treatment of BON has proven to be difficult, especially when it occurs while the patients are on BPS. This is especially true with the IV BPS. The treatment of choice is non-aggressive removal of the sequestered bone, infection control with antibiotics, twice-a-day chlorhexidine rinses, and pain control medications. This patient was treated with local curettage, chlorhexidine rinses, and several courses of antibiotics (amoxicillin-clavulanic acid 875 mg, three times per day).

The area did not respond to the treatment, and the sequestration recurred with pain and a small oral fistula. The condition slowly progressed to increased pain and additional difficulty with normal feeding. Resection is rarely used as a mode of treatment but was thought necessary in this instance (Figure 7). In this case, the resected jaw defect was replaced with a titanium plate. One year follow-up revealed adequate healing with no symptoms or recurrence. The patient was able to eat without difficulty.

Conclusion

The overall philosophy of treating BON follows the criteria used for treating radiation therapy patients. It is recommended patients have all necessary dental treatment completed prior to placing them on BPS.[19,22,27] Once BPS therapy has been initiated, surgery involving the jaw bone should be avoided; extraction should be replaced with endodontic treatment whenever possible; and mild to moderately mobile teeth splinted rather than extracted.[19,22,27] If extraction is inevitable, the area should be handled gently with minimum damage to the soft and hard tissue; the area should be sutured; and the patient should be placed on antibiotics (for two weeks to start and more if necessary) and twice a day chlorhexidine rinses (for at least two months).[19,22,27] A panel of experts representing the American Dental Association produced an excellent protocol for the prevention and treatment of BON, and those recommendations should be consulted if treating patients on BPS.[31]

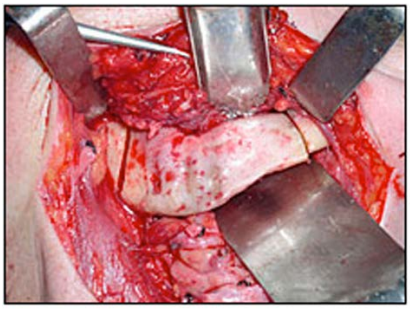


Figure 7. This clinical photograph was taken during the partial jaw resection surgery. Resection is an unusual mode of treatment for this condition.

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Note: Bio information was provided at the time the case challenge was developed.

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