CASE REPORT

Nonresolving Osteomyelitis of the Maxilla and Maxillary Sinus after Long-term Use of Oral Bisphosphonates

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Abstract

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a complication of Bisphosphonate (BP), medications used for treatment of osteoporosis, multiple myeloma and cancer bone metastasis. Manifestations of BRONJ include bone necrosis, exposure to the oral cavity, inflammation suppuration and pain with nonspecific radiographic changes.

Case history: A 64-year-old woman had been treated with oral BP since 1991 for arthritic pain and osteoporosis. There were no other medical problems, no other medications used, she did not smoke nor drink alcohol.

In 2005, the left maxillary molars had been extracted. The extraction site failed to heal, but she continued to use BP. Eighteen months later she presented with swelling and pain, suppuration and an area of 2 x 1 cm of exposed necrotic bone in the left posterior maxilla and oroantral fistula (OAF).

Panoramic radiograph showed partial opacification of the maxillary sinus, unhealed extraction site, and sclerosis of adjacent maxillary alveolus. Histopathological analysis diagnosed osteomyelitis associated with actinomycosis, consistent with BRONJ.

Treatment: BP was discontinued, followed by 7 months of PO antibiotics and iodoform gauze packs. The wound seemed to be completely closed but within 2 months signs and symptoms and OAF recurred. Treatment continued with antibiotics daily rinses and weekly irrigation with Chlorhexidine 2%, and several repeated sequesterctomies, however, the patient still had pain. A course of 30 hyperbaric oxygen treatment was administered. Three years from onset symptoms improved, and sequstered bone is no longer visible. However, the OAF is still present, requiring irrigations, and the radiographs still present bony abnormality.

An unusually severe BRONJ of 3 years duration associated with 15 years oral BP use is presented.

Keywords: Bisphosphonates, osteonecrosis of jaw, osteomyelitis.

INTRODUCTION

Bisphosphonates (BP) are a group of medications affecting bone metabolism. Oral BP have been successfully used to prevent and treat osteoporosis, whereas intravenous (IV) BP have an important role in treatment of multiple myeloma and bone metastasis from different cancer types. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a complication of BP reported only in the jaws, in which necrosis of bone is followed by exposure to the oral cavity. Inflammation suppuration and pain are typical, with a chronic course. It is a debilitating condition, which is often resistant to treatment.[1] The majority of BRONJ cases are associated with IV BP treatment, whereas, it is considered rare in oral BP users.

A case of unresolving BRONJ of 3 years duration, following dental extractions in a patient treated by oral BP for 15 years.

CASE PRESENTATION

Case History

The patient was a skinny 64 years old woman, with a history of arthritic pain and osteoporosis since age 47. For these problems she had been treated with oral Bisphosphonates (BP) since 1991, (most of this period Alendronate). She also used NSID's occasionally. There were no other medical problems, no other medications used, she did not smoke nor drink alcohol.

In 2005, the left maxillary molars had been extracted by the local dentist.

The extraction site failed to heal; in January 2007, she presented with swelling and pain in the left posterior maxillary region.

Examination revealed swelling, erythema and suppuration with an area of 2 × 1 cm of exposed necrotic

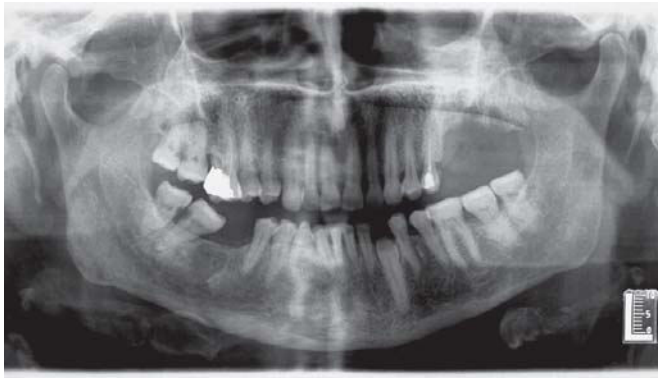


Fig. 1: Sclerosis of maxillary alveolus

bone, an oroantral fistula (OAF) and abundant granulation tissue protruding through the OAF.

Panoramic radiograph showed the extraction site had not filled up with bone as would be expected. The maxillary alveolus presented sclerosis and partial opacification of the maxillary sinus was obserevd (Fig. 1).

The necrotic bone and soft tissues were debrided and submitted for histopathology.

Diagnosis

Osteomyelitis associated with actinomycosis, consistent with BRONJ (Figs 2A and B).

Treatment

BP was discontinued, and for the following 7 months continuous PO antibiotics were prescribed, (Penicillin, Flagyl, continued with Dalacin). In addition to iodoform gauze packs in the sinus space. The wound seemed to be completely closed in August 2008 and treatment discontinued.

Disease Evolution

Within 2 months the patient returned with pain, swelling and suppuration, and a recurrent OAF (Fig. 3). Cultures were positive for *Staph. aureus*.

A repeated panoramic X-ray and CT scans (Figs 4A and B) demonstrated erosion of the maxillary sinus walls, intense sclerosis of surrounding bone and complete opacification of the sinus.

Treatment

Repeated antibiotic treatment (Amoxillin, Augmentin) and oral rinses with Chlorhexidine 2% for another 4 months

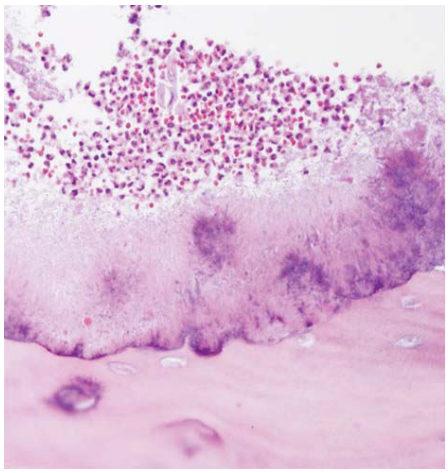


Fig. 2A: Histopathologic section showing the keratinizing squamous epithelial cyst lining, with both aggregates of sebaceous cells within the lining, and well-formed sebaceous glands in the underlying cyst wall. Inflammation is absent. The lumen is filled with "onion skin" keratin (H&E, original magnification X 100, inset X 200)

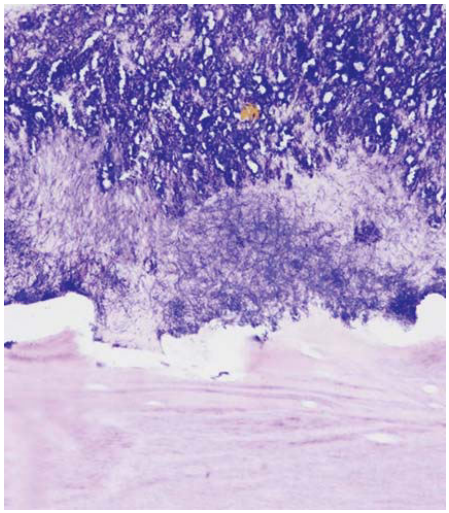


Fig. 2B: In a different area of the lining well- formed sebaceous glands are abundant. The underlying connective tissue is cellular, collagenized and free of inflammation (H&E, original magnification X 100)

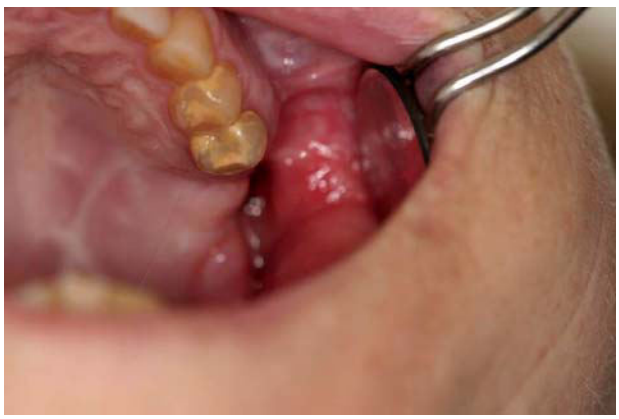
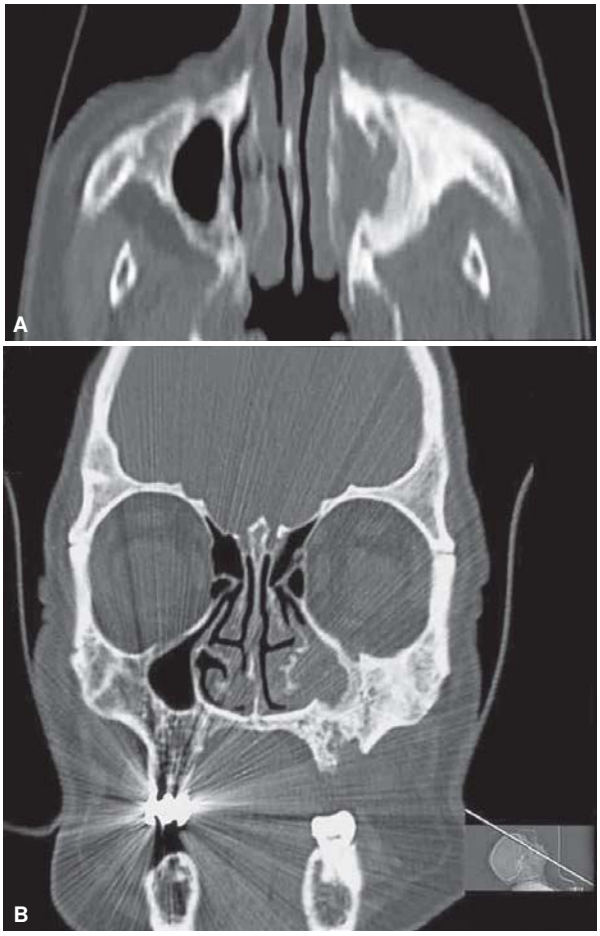


Fig. 3: Osteomyelitis associated with actinomycosis



Figs 4A and B: CT scan, axial view at the level of the angle of the mandible. Expansion is evident, with thinning of the cortical plate on the buccal aspect and cortical perforation on the lingual aspect. Within the lesion the crown of an impacted tooth is protruding

improved symptoms and suppuration was no longer observed. Treatment continued by weekly irrigation of the sinus with chlorhexidine 2% performed at the clinic, and repeated sequesterctomies as loose bone fragments became apparent.

As the patient reported constant pain and discomfort for another 18 months, hyperbaric oxygen treatment was initiated, 30 dives. Symptoms improved, and sequstered bone is no longer visible. However, the OAF is still open, requiring irrigations, and the radiographs still present bony abnormality.

Surgery to close the OAF is planned for the future.

DISCUSSION

BRONJ was first reported in 2003, and has since been reported intensively in the literature. Approximately 90% of patients reported with BRONJ were treated by IV BP, and the remaining 10% oral BP.[1]

A prevalence of 0.10% has been recently reported among oral BP users, more frequently in patients using the medications for over 4 years.[2]

Some conditions have been identified to increase the risk of BRONJ, such as high potency BP (Zomera, Aredia), corticosteroid therapy, therapy duration, dentoalveolar surgery, certain local anatomy (tori), and several concomitant diseases such as diabetes, renal dialysis, anemia and obesity.

The AAOMS position paper from 2006 and its modification from 2009 suggested a set of criteria for diagnosis and treatment of BRONJ. The requirements for diagnosis of BRONJ include current or previous treatment with BP, exposed bone in the maxillofacial region for more than 8 weeks, and no history of radiation therapy to the jaws.

In the 2009 modification, patients with no clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms have been added as Stage 0 BRONJ: unexplained odontalgia, dull, aching bone or sinus pain, loosening of teeth or periapical/periodontal fistula not associated with pulpal or periodontal disease, bone loss/resorption not attributable to periodontal disease, dense woven bone and persistence of unremodeled bone in extraction sockets, thickening/obscuring of periodontal ligament or inferior alveolar canal narrowing.[3]

BRONJ associated with Oral BP is generally considered less severe, and is thought to benefit from discontinuation of BP.

Treatment modalities suggested differ according to the clinical stage, and include prolonged antibiotic treatment, sequestrectomy, surgical debridement, and even resection in certain cases. Hyperbaric oxygen treatment may also be indicated, however, there is not enough information in the literature nor are there well-established protocols regarding management of BRONJ.[4-6]

The case reported here, with its prolonged course, had the clinical and radiographic characteristics of stage 3 BRONJ- although she only used oral BP.

The patient was initially treated conservatively, but when the response was unsatisfactory, treatment protocols suggested for stage 3 disease were employed, including hyperbaric oxygen. After almost 3 years since the drug was discontinued, with the patient in constant pain, presenting several times each month to the OMS clinic for treatment, resolution has not been achieved. The disruption of the

patient's routine life, as well as the economic cost were considerable.

The patient had been using oral BP for 15 years prior to the extractions which triggered BRONJ, and continued to use the medication for another 18 months after extractions, before her condition was correctly diagnosed. As there was no other recognized confounding condition or medication, these factors may possibly explain the severe clinical and radiographic presentation, and the limited success of treatment.

The correlation between risk for BRONJ and duration of BP treatment has been recognized, with an empiric threshold of 3 to 4 years suggested for oral BP. The case presented here may indicate that this risk continues to increase with duration of BP treatment, so patients using oral BP for long periods may have a grater risk for this complication.

There may also be a correlation between the initial duration of BP use and the time required for healing after the drug is discontinued- whereas the literature proposes 6 to 12 months as a period sufficient for resolution of BRONJ associated with oral BP, in the present case 3 years after BP discontinuation resolution is still not complete.

Another aspect to consider is whether it is justified at all to treat with oral BP for such long periods, given the long half-life of even the first generation BP's and the lack of evidence of any additional benefit on bone metabolism after 5 to 7 years BP.

In conclusion, the case presented here developed post-extraction nonresolving BRONJ following an unusually long time of oral BP treatment, with a course similar to advanced BRONJ in IV BP.

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