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Total mandibulectomy defect in the setting of chronic bisphosphonate use☆

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ABSTRACT

Bisphosphonates are among several drugs known in modern medicine to have a potentially deleterious effect on the mandible with chronic use. While purportedly causing a necrotic reaction in the bone, the complete mechanism is not fully elucidated yet as cases are quite rare in the general public. Despite the esoteric nature of this entity, patients suffering from bisphosphonate induced necrosis have a complicated and prolonged course often involving varying degrees of mandibular debridement with severe cases requiring reconstruction. In this report, we present the unique case of a patient with a progressive mandibular osteonecrosis requiring complete mandibulectomy and fibula flap reconstruction.

1. Introduction

Bisphosphonates (BPs) are pharmacologic inhibitors of bone turnover, which suppress osteoclast activity. They have become a mainstay of treatment for osteoporosis. BPs also slow angiogenesis and promote tumor suppression activities, making them useful in the management of boney metastases [1]. However the use of BPs has not been without adverse events. One of the most feared complications is bisphosphonate related osteonecrosis of the jaw (BRONJ).

Medication induced osteonecrosis of the jaw (MRONJ) was first reported in the early 2000s [2–5]. Healthy bone requires both osteoclastic and osteoblastic cell activity. Bisphosphonates inhibit osteoclastic activity. While the exact mechanism of BRONJ is not fully understood it is thought that suppressed osteoclastic activity results in progression of devitalization of bone. It is thought that osteoclastic bone resorption may result in the release of cytokines that promote bone growth and turnover. With this suppressed bone can become progressively devitalized, ultimately resulting in osteonecrosis [2]. The mandible is particularly active in terms of bony turnover and thus is thought to be particularly at risk of BP related osteonecrosis. Similar to osteoradionecrosis (ORN) BP use is associated with infection, trauma, and eventual decreased bone vascularity – leading to bne breakdown [5]. Ultimately MRONJ is defined as (1) treatment with BPs (2) exposed necrotic bone for at least 8 weeks with no history of prior radiotherapy.

Management of MRONJ has continued to be challenging. Attempts at applying conservative measures, used for ORN in the past, have proved mediocre at best. The American Association of Oral and Maxillofacial Surgeons (AAOMS) has published a staging system and treatment algorithms associated with each stage. Treatments range from local antibacterial rinses, systemic antibiotics, hyperbaric oxygen, to local surgical debridement [5,6]. Prior to recent studies the management strategy of MRONJ was palliation and salvage of existing bone, while recent studies have shown high rates of success of clinical control after surgical resection [7]. Vascularized bone grafting with free tissue reconstruction has also been shown to be effective in the treatment of advanced osteonecrosis [8].

Here we discuss an aggressive case of MRONJ causing total mandibular necrosis. Additionally we discuss the complex nature of the reconstruction of a total mandibulectomy defect with a fibula free flap and custom total mandibular titanium plate anchored by bilateral condylar head prostheses.

2. Case presentation

Here we present the case of a 62-year-old male with a past medical history of rheumatoid arthritis. He had been treated with chronic steroids and long-term bisphosphonates each for greater than 10 years. He developed ORN of the mandible that was initially treated with

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Fig. 1. Image of the hemimandibulectomy specimen. Grayish discoloration of the necrotic bone can be seen.

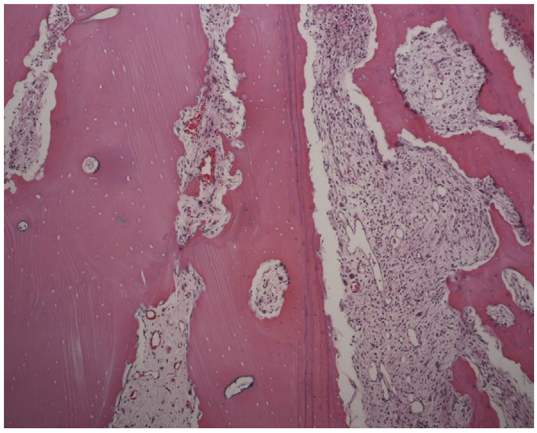

Fig. 2. 10× magnification. Necrotic bone can be seen at the left of the figure with some new periosteum formation at the right. Empty lacunae can be seen in the necrotic bone. The marrow on the right is marked by chronic inflammation as evidenced by the lymphocytes.

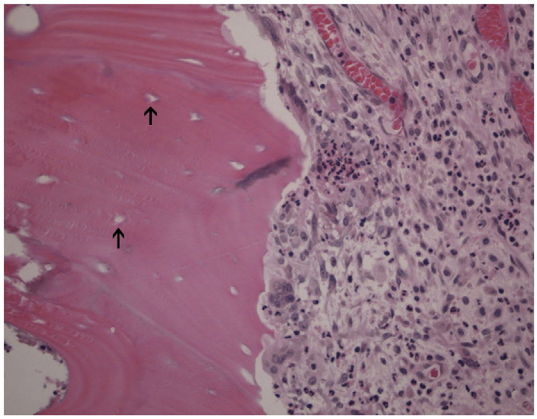

Fig. 3. 200× magnification. Higher magnification demonstrating necrotic bone with empty lacunae (arrows) and some osteoclasts resorbing dead bone in the center of the image resulting in a scalloped contour. Proliferating fibroblasts, lymphocytes, and neutrophils can be seen on the right.

debridements; however, the ORN continued to progress. Throughout this he also had multiple bouts of osteomyelitis necessitating several extended courses of intravenous antibiotics. Ultimately as the ORN progressed he had several segmental mandibulectomies with external fixator and plate placement. Given the poor appearance of the bone,

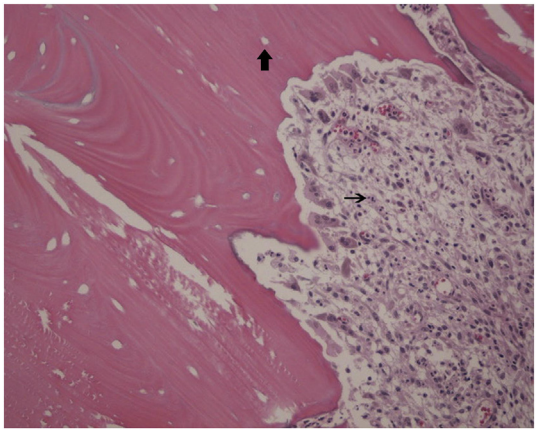

Fig. 4. 200× magnification. Another section of bone at higher magnification demonstrating necrotic bone with empty lacunae (thick arrow) on the left and inflammation with lymphocytes (thin arrow) on the right.

reconstruction was deferred several times given the risk of complications and flap necrosis. Hyperbaric oxygen was also utilized; however, its use was limited by patient discomfort. Ultimately he underwent a total mandibulectomy (from condyle to condyle). The specimen (Fig. 1) was noted to be clearly diseased in appearance with a grayish hue on gross examination. Figs. 1–4 demonstrate the characteristic appearance of the necrotic bone on pathologic examination. The total mandibular defect was reconstructed with a fibula free flap, titanium plate, and condylar head prostheses. Postoperatively, the flap did well; however, the post-operative course was marked by poor wound healing necessitating multiple return trips to the operating room for oral dehiscence closure and washout.

3. Discussion

Bisphosphonates are structural analogs of pyrophosphates that have a high affinity for calcium and thus accumulate in bone. There are two classes of BPs, non-nitrogen containing, and nitrogen containing BPs (N-BPs). All BPs are taken up by osteoclasts. Non-nitrogen containing bisphosphonates compete with pyrophosphate in Adenosine Triphosphate (ATP) synthesis. Ultimately toxic bisphosphonate containing metabolites accumulate in osteoclasts in lieu of functional ATP resulting in osteoclast apoptosis and thus reduced bone resorption. N-BPs differ in that they interfere with farnesyl diphosphate synthase (an enzyme in the HMG CoA-Reductase pathway) and cause osteocyte death [1]. These N-BPs are hundreds to thousands of times more potent than non-nitrogen containing BPs. BPs are used for a variety of indications ranging from hypercalcemia to the management of metastatic disease. N-BPs specifically have been shown to reduce skeletal tumor burden and reduce the morbidity associated with several cancers. N-BPs have also been shown to have some modest benefit on the overall survival of patients with advanced cancers [9].

While bisphosphonates have been in use now for several decades, only recently has BRONJ been identified and described. The vast majority of BRONJ is limited and only stage 1 and 2. However stage 3 disease that has failed conservative treatment measures does necessitate larger resection. There has been some debate in the literature regarding bony reconstruction for BRONJ related mandibular defects. There has been some concern that vascularized bone transfer may transplant malignant cells from a donor site. While the American Association of Oral and Maxillofacial Surgeons has published some guidance on the management of BRONJ, there is a paucity of literature to guide the management of advanced and extensive BRONJ [5]. There is a particular lack of guidance regarding the role of free tissue reconstruction for advanced BRONJ. There has been concern that there can be recurrent BRONJ at the margins or non-union after

reconstruction with vascularized bone. However recent literature has shown that reconstruction of BRONJ related defects with vascularized bone can be successful. Here we present a unique case of BRONJ that involved the entire mandible that was reconstructed in a delayed fashion with a fibula free flap with a custom total mandibular titanium plate anchored by bilateral condylar head prostheses.

The extent of osteonecrosis in our case was unique in that the entirety of the mandible was devitalized and resected. In this case we did multiple debridements and segmental mandibulectomies with rigid fixation. Ultimately the entire mandible was necrotic and resected including both condyles. After a lengthy course of IV antibiotics our patient then underwent reconstruction with a fibula free flap with a custom total mandibular titanium plate anchored by bilateral condylar head prostheses. By delaying reconstruction we were able to ensure clear margins with complete resection of necrotic bone and clearance of infection, thus reducing the risk of postoperative infection or nonunion. Our reconstruction was also unique in that we performed a single midline osteotomy, thereby minimizing the needed osteotomies and thus reducing the risk of bone necrosis. Ultimately here the flap did well however the post operative course was complicated by poor wound healing necessitating multiple trips to the operating room and cultures grew multi-drug resistant pseudomonas.

BRONJ is rare but devastating complication of BP use. The management of BRONJ is guided by the degree of necrosis. Conservative treatments include antibiotics and antiseptic mouthwashes. Advanced BRONJ with exposed bone necessitates operative treatment with debridements. However the treatment of very advanced BRONJ remains somewhat controversial. Fixation plates and obturators may be used. However large, segmental mandible defects may require reconstruction with vascularized bone. Nevertheless it is important to note that this patient population is particularly challenging and often suffers from poor wound healing and chronic infection. It is important for both the surgeon and the patient to be understand this, especially in the context of otherwise limited treatment options. Here we demonstrate a case of extensive BRONJ that required total mandibulectomy including resection of both condylar heads that was successfully reconstructed with a fibula free flap with a custom total mandibular plate with bilateral condylar head prosthesis.

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