Denosumab Related Osteonecrosis of the Jaw in a Breast Cancer Patient: A Case Report.

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Abstract:
Background*: Medication Related Osteonecrosis of the Jaws (MRONJ) is a well-known complication associated with treatment of metastatic bone disease. Recently, denosumab was introduced as an alternative to bisphosphonates which are known to cause MRONJ, as it has a different mechanism of action. This report highlights the radiographic features of MRONJin a patient undergoingdenosumab therapy. Findings: A 75-year-old female with history of breast carcinoma, chemotherapy, and IV denosumab therapy is presented with history of ulceration progressing to bone exposure/necrosis of the hard palate. The lesion appeared five months post first use of denosumab in the patient with no prior evidence of MRONJ. Cone Beam Computed Tomography(CBCT) study revealed a mixed-density lesion in the left maxilla with osteolysis, disruption of facial and palatal cortices, and an oro-antral defect. Interpretation: All typical clinical and radiographic manifestations consistent with MRONJ were noted; however, superimposed chronic diffuse sclerosing osteomyelitis was noted as well. Discussion: Caution needs to be exercised when prescribing denosumab in patients with no prior evidence of MRONJ despite previous oral bisphosphonate therapy. It is most likely that MRONJwas denosumab-related, although bisphosphonatewas used in the past but via the oral route which is not the most common cause of bisphosphonate-relatedMRONJ. Further investigation is needed to assess any unique risks and effects associated with denosumab usage, which will aid in yielding future recommendations for its use.*
Keywords: *Bisphosphonate, denosumab, osteonecrosis, MRONJ, breast cancer.*

I. Introduction

A common sequel of breast cancer is skeletal metastasis, with up to 65-80% of breast cancer patients affected [1]. Because of the adverse effects, morbidities, and contribution to mortality associated with skeletal metastatic disease [2], newer bone-targeted therapies have been and continue to be developed in order to offset these complications [3]. These bone-targeted therapies usually target the osteoclasts to prevent further resorptive activity that would otherwise worsen the systemic bone loss requiring treatment[4]. Bisphosphonates bind to the mineral component of bone and interfere with osteoclastic activity. This is in contrast to denosumab, which binds to receptor activator of nuclear factor kappa-B ligand (RANKL), a molecule that is essential for proper osteoclast viability and function, to decrease the amount of osteoclasts present at the bone surface[5]. In other words, bisphosphonates tend to disable osteoclasts, while denosumab tends to eliminate them. The bisphosphonates that bind to the bone tend to be buried within it after *de novo* bone forms around it[6]. However, their continued presence within the bone does not appear to reduce the rate of bone resorption with time (i.e. it is not biologically available to exert its effects locally) [7], and the patient continues to take the drug for as long as the anti-resorptive effects are desired to maintain a steady, lower rate of bone turnover (which typically manifests and stabilizes within 1-6 months of starting treatment[8]). Urinalysis has shown that the bisphosphonates released from the skeleton can be measured in small levels for weeks, months, or even years after discontinuing the treatment[9], which implies that it is present in circulation and available for reuptake in other parts of the skeleton throughout this time. This suggests that the effects of bisphosphonates are not so rapidly reversible[5]. On the other hand, denosumab, being a circulating monoclonal antibody, has been shown to be detectable in the circulation for up to several weeks with an overall half-life of about 26 days[10]. It has also been shown histomorphometrically that denosumab does not undergo sustained binding to bone surfaces [5]. A clinical trial showed that bone mineral density decreased to a greater extent in postmenopausal women who discontinued denosumab versus those who discontinued alendorate (a bisphosphonate)[11]. These collectively suggest that denosumab is relatively more reversible than bisphosphonates. Other comparisons between denosumab and bisphosphonates include faster onset of action, greater extent of reduction of bone resorption, and greater gains in bone mineral density at multiple skeletal sites with denosumab[5]. A meta-analysis regarding the safety and efficacy of denosumab versus bisphosphonates concluded that denosumab was more effective in preventing skeletal-related adverse events and pain in patients with breast cancer and bone metastases[4].The association between long-term bisphosphonate usage and osteonecrosis of the jaw osteonecrosis has been well documented[12]. Factors hypothesized to contribute to osteochemonecrosis of the jaw pathophysiology include 1)

inhibition of osteoclastic bone resorption and remodeling, 2) inflammation/infection, 3) inhibition of angiogenesis, and 4) soft-tissue toxicity. Even though, denosumab has not yet been linked to anti-angiogenic activity or soft-tissue toxicity [13],it has been shown in a number of recent clinical trials to be associated with osteochemonecrosis of the jaw[12]. The small size of most of these studies and the limited literature on the subject render it unclear exactly how much denosumab contributes to osteochemonecrosis of the jaw in these patients. This case report shows the radiographic features of osteochemonecrosis of the jaw with a history of treatment using denosumab with onset of osteochemonecrosis of the jaw clinical signs only five months after initial drug administration. Their findings will be described and discussed.

II. Clinical And Radiologic Findings

A 75-year-old female presented with an ulcerated lesion that progressed to bone exposure in the posterior left hard palate (Fig.1). Medical history indicateddiagnosis of breast cancer in March 2012 followed by chemotherapy and a monthly denosumab (Xgeva; Amgen Inc.Thousand Oaks, CA) IV injection for osteoporosis treatment. Denosumab intake was discontinued after five months. Medical records also reportthe use of bisphosphonate (Fosamax 10mg/d) for 10 years, which was discontinued in 2008(4-5 years prior to denosumab intake). The lesion was reported within five months following first use of denosumab. The biopsy reportindicated pyogenic granuloma with hyperkeratosis.A maxillofacial non-contrasted, thin-slice cone beam computed tomography (CBCT) of the maxilla was performed using the i-CAT (Imaging Sciences International, Hatsfield, PA, USA) using the following protocol: 120 kVp, 18 mA, 20 sec, at 0.4 voxel size. A mixed-density appearance was noted in the left maxillary alveolar ridge, extending from the region of the canine to that of the maxillary tuberosity (Fig.2). There was evidence of disruption of the facial and palatal cortical plates at several places including the maxillary tuberosity where a large area of osteolysis was noted (Fig.3). Disruption of the floor, lateral and medial walls of the left maxillary sinus was noted along the inferior aspect suggestive of oro-antral communication (Fig.4 and 5). The interior of the sinus shows a near-complete opacification with frothy mucous collection suggestive of chronic sinusitis. The findings were consistent with clinically known osteochemonecrosis of the jaw.
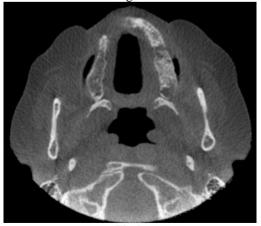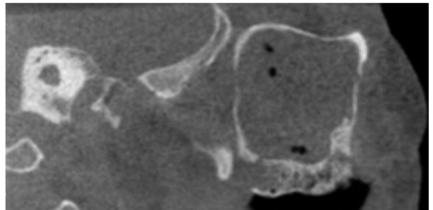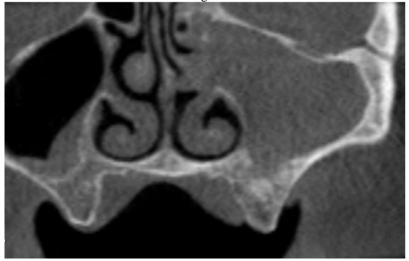
Figures

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III. Discussion

The radiographic features discussed in the report represent the classic appearance of medically related osteonecrosis of the jaws (MRONJ). Similarities were noted with outcomes seen in clinically confirmed bisphosphonate cases reported in the literature with no stark differences noted in the radiographic presentation. The main limitation of this case report is that the patient history indicates oral bisphosphonate usage in the past. However, the absence of osteonecrosis following 4-5 years of bisphosphonate use raises suspicion of the osteonecrosis being denosumab-related. It is possible that previous administration of bisphosphonates effectively potentiated or conditioned the osseous jaw structures to be more susceptible to necrosis, thus setting a lower threshold for denosumab to induce bone necrosis. It is still unclear whether this is a possible explanation

given the relative dearth of information available on the specific etiologies of denosumab-related osteonecrosis of the jaw in the literature. Also, larger sample size would be needed to effectively compare any potential differences in radiographic features of bisphosphonate-related versus denosumab-related osteonecrosis of the jaw, as presentation of any form of osteochemonecrosis is variable and often comorbid with other conditions such as periapical and periodontal disease [14]. Further research is also needed to determine whether denosumab indeed increased potency in increasing bone mineral density and decreasing bone resorption contributes to development of osteochemonecrosis, and whether there are any differences in the timing, severity, and prevalence, as compared to bisphosphonate-related osteonecrosis of the jaws (BRONJ). Drug administration variables such as dosage, route, and duration of use may also be studied as they relate to osteochemonecrosis. But the common denominator between denosumab and bisphosphonates, i.e. the inhibition of osteolytic activity, seems to otherwise increase susceptibility to infection and impair mucosal healing that may collectively contribute to osteochemonecrosis [13]. Further investigation will help establish standards and guidelines for safe and effective use of denosumab as it relates to treating metastatic disease while mitigating the potential for the undesirable sequela associated with osteochemonecrosis. This report assumes significance in light of the observed changes in bone in a previously asymptomatic patient who was treated with bisphosphonates but developed osteonecrosis only on initiation of treatment with denosumab, in the absence of any other triggering factors. Clinicians need to be aware of the possibility of developing MRONJ following administration of denosumab.

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