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CASE REPORT

Osteonecrosis of Maxilla Secondary to Bisphosphonate Therapy: A Case Report

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Abstract Bisphosphonate chemotherapy is commonly used in the treatment of bone diseases such as osteoporosis, Paget disease, and multiple myeloma and to limit bone pain and hypercalcemia associated with malignant metastatic bone lesions. The introduction of bisphosphonate therapy has improved the quality of life in a vast majority of patients. However, since 2003 a growing number of reports have described necrotic bone lesions (bisphosphonate—associated Osteonecrosis of the jaw [BR-ONJ]) a bone lesion affecting maxillofacial bones in patients who have received high dosage chemotherapy with intravenous bisphosphonate therapy especially when the patient undergoes subsequent dental procedures.

Sequential removal of sequestra as required seems to be the current conservative approach, but if large-volume debridement becomes necessary, removal of the bone sequestrum with minimal epithelial manipulation associated with topical and systemic antibiotics seem to be the treatment modality of choice. In our case, surgical salvage was performed successfully for BR-ONJ. Our experience indicates that with appropriate technique, primary surgical treatment may offer benefit to selected patients with BR-ONJ.

Keywords Osteonecrosis · Maxilla · Bisphosphonate

Introduction

Bisphosphonates have been developed over the past three decades and have been used in the treatment of many skeletal disorders, such as bone metastases, osteoporosis, Pagets disease, hypercalcemia of malignancy, and bone pain. The main pharmacological effect of bisphosphonates is the inhibition of bone resorption caused by osteoclasts decreased function, whereas other effects, like inhibition of calcification in the treatment of hypercalcemia of malignancy and reduction of joint inflammatory reaction in the treatment of arthritis, are of secondary magnitude.

In the last 2 years, there has been an increased referral of patients with exposed necrotic jawbone, diagnosed elsewhere as chronic refractory osteomyelitis of jaws mostly after teeth extractions. Most of these patients had a past history of malignancy, and the only thing in common was the long-term intravenous administration of bisphosphonates.

Reports of bisphosphonate-associated osteonecrosis of the jaw (BRONJ) associated with the use of Zometa (zolendronic acid) and Aredia (pamidronate) began to surface in 2003. The majority of reported cases have been associated with dental procedures such as tooth extraction; however, less commonly BR-ONJ appears to occur spontaneously in patients taking these drugs [1, 2]. Zolendronic acid and pamidronate are intravenous (i.v.) bisphosphonates used to reduce bone pain, hypercalcemia and skeletal complications in patients with multiple myeloma, breast cancer, lung cancer and other cancers including Paget's disease of bone. The typical clinical presentation of BR-ONJ includes pain, soft-tissue swelling and infection, loosening of teeth, purulent discharge, and exposed bone. These symptoms may occur spontaneously, or more commonly, at the site of previous tooth extraction. Patients may also present with feelings of numbness, heaviness and dysesthesias of the jaw. However, BR-ONJ may remain asymptomatic for weeks or months, and may only become evident after finding exposed bone in the jaw.

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Case Report

A 62-year-old man was referred to our unit with chief complaint of pain and pus discharge from extraction socket in left maxilla. His medical history revealed prostate cancer for which he had undergone bilateral Orchidectomy in 2006. He was diagnosed of diabetes since 6 months and known hypertensive since last 2 years. The patient was undergoing bisphosphonate therapy every 2 months with one dose of intravenous zoledronate 4 mg infusions. In addition to the bisphosphonate therapy, his medication included tablet Nebicard 5 mg once a day for hypertension, tablet Glycomet 1 gm twice a day for Diabetes mellitus.

Patient complained of discomfort and discharge in the left upper molar area one and half years after initiating bisphosphonate therapy. Patient underwent extraction of upper left second and third molar, following which the extraction socket never healed and pain and pus discharge had increased. Extraoral examination revealed no significant changes in facial contour. On intraoral examination, left edentulous posterior maxilla (Fig. 1) presented with a sinus on buccal vestibule near upper left canine. Purulent discharge was present from the sinus opening (Fig. 2).

CT scan revealed sequestrum and osteolysis in upper left maxillary area (Figs. 3, 4) multiple diffuse nodular sclerotic densities in vertebra (Fig. 5). Considering the medical history, clinical and CT scan examination, patient was diagnosed and treated for chronic maxillary sinusitis and Osteonecrosis of the maxilla secondary to bisphosphonate therapy.

Conservative treatment included simultaneous antibiotic therapy with hyperbaric oxygen therapy (Four dives for 90 min). Pain and pus discharge decreased but persisted over a period of 3 weeks following conservative treatment. After optimization, patient was considered for surgery. Partial maxillectomy of necrotic maxilla and primary closure with intranasal antrostomy was preformed. Postoperatively healing was uneventful except for development of

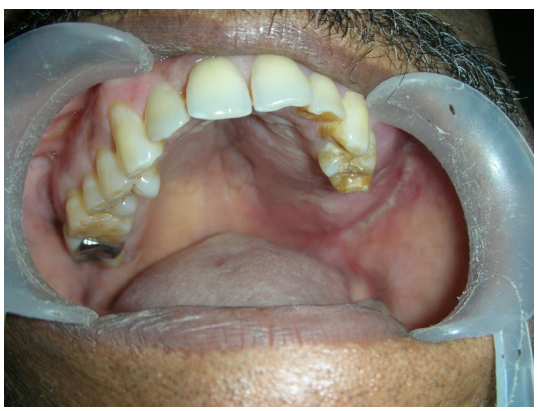

Fig. 1 Shows swelling in Lt edentulous upper maxillary area

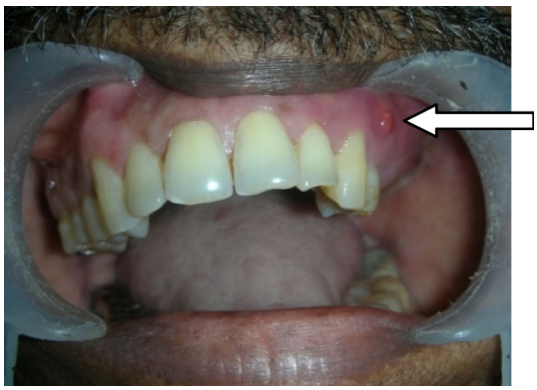

Fig. 2 *Arrow* shows sinus opening in buccal vestibule at upper left canine region

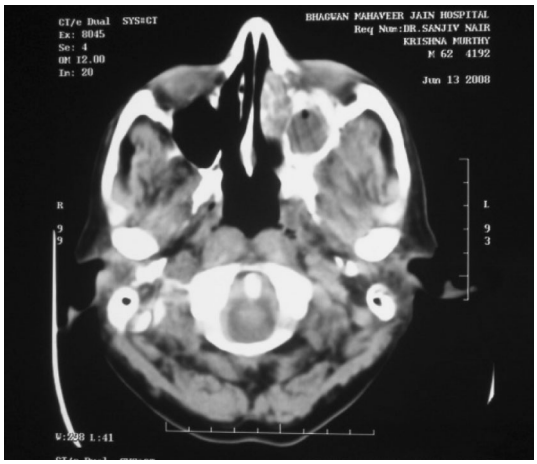

Fig. 3 Sequestrum in Lt maxilla

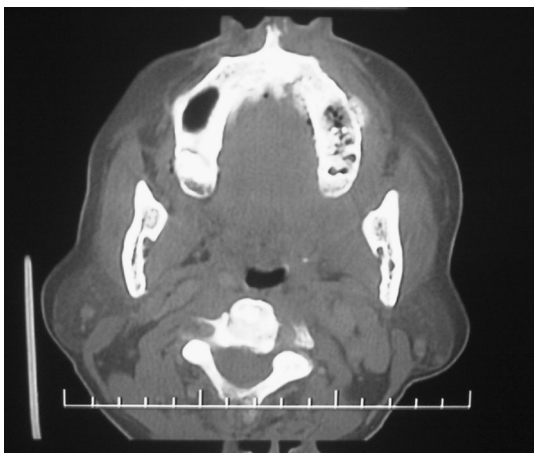

Fig. 4 Osteolysis of Lt maxilla

an oroantral communication on sixth day after surgery (Fig. 6). Histopathology examination revealed tissue lined by ciliated columnar epithelium and subepithlial connective tissue infiltrated by neutrophils, lymphocytes, and plasma cells. Acellular tissue with fungal filaments, fungal

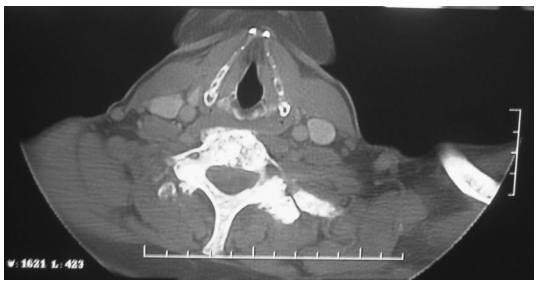

Fig. 5 Multiple diffuse nodular sclerotic densities in vertebra

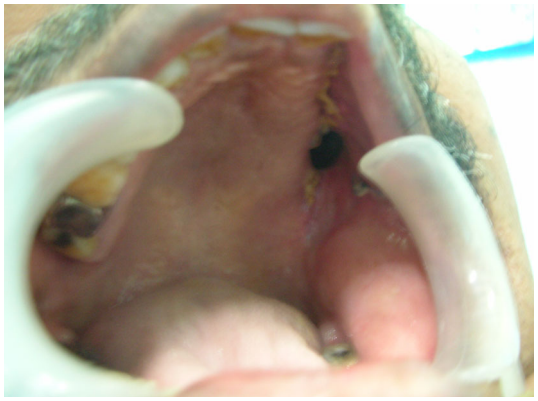

Fig. 6 Healed Lt maxillary area

elements were seen within bony trabaculae thereby giving impression of chronic rhinosinusitis and chronic Osteomyelitis secondary to Fungal infection. The patient was followed up with antibiotic and antifungal therapy. After tenth day of surgery, the pain had completely subsided. The patient was advised for hyperbaric oxygen therapy (ten dives for 90 min) 3 weeks post surgery. The patient was rehabilitated with a denture in the edentulous area. Later oroantral communication healed satisfactory.

Discussion

The high incidence of osteonecrosis—especially maxillary—in patients who are receiving bisphosphonates and have not previously received radiation therapy in the head and neck region is in contrast with the current knowledge. Marx et al. [3] first reported osteonecrotic lesions of the jaws similar to those of osteoradionecrosis, which they called drug-induced avascular osteonecrosis, implying that the destruction of the vascular complexity of the jaws mediated by the use of bisphosphonates is responsible for necrosis and secondary infection of the bone matrix.

Bone remodeling is a physiologically coordinated process that involves bone formation by osteoblasts and bone resorption by osteoclasts. Imbalances between osteoclast and osteoblast activities result in skeletal abnormalities characterized by decreased or increased bone density [4, 5]. Increased osteoclast activities are seen in osteopenic disorders such as postmenopausal osteoporosis, Paget's disease, lytic bone metastases, and rheumatoid arthritis. Nitrogen-containing bisphosphonates, such as zolendronate, are potent inhibitors of osteoclastic bone resorption. In the present report, the patient developed bisphosphonate-associated osteonecrosis. The patient had been treated with zolendronate for a period of 2 years owing to prostate cancer.

An increasing number of cases of bisphosphonate-associated osteonecrosis have been reported recently, and the majority of patients had metastatic bone disease [6, 7, 8, 9, 10]. The biologic potency of individual bisphosphonates is related to bone uptake and retention. Studies have shown that zolendronate has the highest skeletal retention [4]. The fact that zolendronate has been proven in vitro to be the most potent bisphosphonate may explain the increasing numbers of recently reported cases of osteonecrosis. It is likely that the skeleton acts as a reservoir of bisphosphonate that produces concentrations located in the vicinity of bone cells that are related to the adsorption and desorption properties of bisphosphonates on and off bone surfaces. The effects of bisphosphonates seem to persist for extended periods, and this could explain why osteonecrosis appears after long-term treatment, and even in cases in which bisphosphonate treatment was discontinued [11, 12].

Bisphosphonate-associated osteonecrosis have been described for jaws, and in a high percentage of the cases osteomyelitis also was present. The bisphosphonates have been shown to have potent antiangiogenic properties. A marked reduction in the number of blood vessels was reported in the bone marrow of patients after bisphosphonate treatment. Santani [13] showed that there is a significant decrease in the circulating levels of vascular endothelial growth factor (a strong angiogenic factor) in breast cancer patients taking bisphosphonates. These antiangiogenic properties have been the basis for the use of bisphosphonates as antitumor agents. This antiangiogenic property may be an important factor in the development of Osteonecrosis in patients because of reduced oxidative blood to the area of insult. The jaws are unique because they are the only bones in the body that are exposed directly to the external environment through the teeth. The mandible is also an end-artery system. Periodontal and pulpal infections demand an increase in bone turnover. In a normal, healthy environment, restoration processes quickly ensue. However, in an environment of bone microdamage, no bone turnover, hypermineralization, decreased angiogenesis, and small insults such as dental extractions can proceed into a nonhealing wound, with continued infection from oral contamination, leading to bone necrosis, as seen

in osteoradionecrosis. These patients also tend to be on other chemotherapeutic agents and steroids, which can potentiates the disease process. Some authors have suggested that the predilection for this location may be attributed to the fact that the jaws are the only bone structures submitted to continuous trauma with exposure to the environment and to oral microorganisms. Although, dental extractions have been identified as a predisposing factor for osteonecrosis in many of the reported cases, there are reports of "spontaneous" exposures and necrosis of the alveolar bone. Osteonecrosis of the jaw probably results from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling owing to physiologic stress (mastication), iatrogenic trauma (tooth extraction or denture injury), or tooth infection in an environment that is trauma intense and bacteria laden.

Hellstein et al. [9, 10] also believe that bisphosphonates are agents that inhibit the recruitment and function of osteoclasts. When administered over an extended period, increased medullary bone density may be induced, similar to the sclerosis found in osteopetrosis. The adaptability of dense medullary bone is different from normal medullary bone. In the present report, CT displayed sclerotic areas in vertebrae. Thus, although the sclerotic areas may represent an effect of the bisphosphonate therapy, we cannot reject the possibility that they may also indicate metastatic lesions.

The management of bisphosphonate-associated osteonecrosis of the jaws represents an additional challenge to professionals. At present, there is no effective treatment for the condition [14]. Sequential removal of sequestra as required seems to be the current conservative approach, but if large-volume debridement becomes necessary the goal should be to remove as little bone as possible. Removal of the bone sequestrum with minimal epithelial manipulation associated with topical and systemic antibiotics seem to be the treatment modality of choice [10]. Benefits from HBO_2 therapy have been reported in patients treated at other institutions [15, 16, 17]. In a small group of patients with BP-ONJ, adjunctive HBO_2 with a goal of 40 sessions led to remission or improvement in 62.5% of patients [18].

In the present case, after HBO_2 therapy we decided for a removal of necrotic bone (conservative sequestrectomy) associated with chlorhexidine mouthwash and antibiotic therapy. Post surgery, the pain completely subsided. We are maintaining a regular follow-up of the patient. Owing to the difficulty in treating this disease, the focus should be on prevention. When intravenous or high-dose oral bisphosphonates are considered appropriate, referral for full dental assessment and treatment before the start of therapy should be considered. If the patient requires tooth extractions, this should be done before starting bisphosphonate therapy. Once bisphosphonate therapy has begun, there should be regular clinical monitoring of oral health, and invasive dental procedures should be avoided if possible. Edentulous patients must have maximum prosthetic adjustment. Dental caries and periodontal disease should be controlled [9]. Computerized tomography played an important role in the characterization of the bisphosphonate-associated osteonecrosis of the maxilla. With CT, it was possible, in our report, to observe sinusitis secondary to osteonecrosis, and the sclerotic areas in the c-spine.

In conclusion, many issues regarding the pathogenesis of the bisphosphonate-associated osteonecrosis still remain unclear. Further research with animal model and prospective clinical trials may elucidate doubts. The cases reported serve to alert us of the risks of the therapy. Special attention should be given to all patients submitted to long-term protocols with bisphosphonates. These patients should receive prophylactic attention in order to maintain their oral health. Preventive measures must be taken before, during, and after the treatment with bisphosphonates.

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