CASE REPORT

Bisphosphonate-induced osteoradionecrosis

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ABSTRACT

Bisphosphonates (BPs) are a class of agents used to treat osteoporosis and malignant bone metastasis. Despite these benefits, osteonecrosis of the jaws has recently emerged as a significant complication in a subset of patients receiving these drugs.

This case presentation focuses on a 62-year-old man with a 3-year history of monthly use of Zometa (zolendronic acid) for treatment of multiple myeloma, resulting in BP-related osteoradionecrosis of the jaws (BRONJ). This new entity remains a challenge with diagnosis as well as treatment. The goal of this paper is to improve clinicians understanding and provide a guideline for establishing a stage-specific diagnosis and prevention of BRONJ.

Key words: BRONJ, multiple myeloma, zolendronic acid

INTRODUCTION

With the introduction of newer drugs to treat various skeletal disorders, the adverse effects of these drugs are also challenging to deal with. One such drug is bisphosphonate (BP). They are synthetic analogous of pyrophosphate, a natural regulator of bone metabolism found in bone matrix. They inhibit the differentiation of osteoclastic precursors, induce apoptosis of osteoclasts and stimulate release of osteoclastic inhibitory factors to osteoblasts. Besides they interfere with cellular metabolism through adenosine triphosphate (ATP) analogous.[1-5]

Despite the various benefits, BP-related osteoradionecrosis of the jaws (BRONJ) is significant complications in group of patients receiving these drugs. BRONJ was first recognized and reported in 2003 by Marx.[6,7]

These days, oral BPs like alendronate are usually prescribed to treat osteoporosis and intravenous BPs are extensively used to treat osteolytic bone lesions related to multiple myeloma and bone metastasis of solid cancer, breast cancer or prostate cancer.

The initial appearance of the disease is variable and thus, it often comes to the attention of the clinician late, when it has become symptomatic. Thus, it remains a challenge with respect to diagnosis and management.

The goal of this paper is to improve the clinicians understanding of BRONJ by presentation of a classic case and highlighting current concepts and preventive strategies.

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CASE REPORT

A 62-year-old, average built, male with average nutrition status of middle income group reported to Oral and Maxillofacial Surgery Clinic with complaint of swelling over left lower jaw since 4 months [Figure 1]. He suffered from orofacial pain and reduced oral opening. The symptoms were acute which subsequently became chronic with foul smelling discharge with a cutaneous fistula and numbness over left lower lip for last 3 months.

His past medical history was significant for multiple myeloma diagnosed 3 years back for which he underwent chemotherapy (26 cycles) and was on monthly doses of Zometa. He also underwent radiotherapy of knee and spine a year back. He was being treated for hypertension and diabetes which was being efficiently treated.

Past dental history revealed that he underwent sequestrectomy on the left alveolus 1 year back.

The local examination revealed he was partially edentulous with dehiscence in the alveolar mucosa in left body of mandible and exposure of bone looking yellowish-white in the posterior mandibular region [Figure 2]. Sensory testing of the left lower lip revealed parasthesia of V_3. There was mild purulent discharge from the intraoral wound and cutaneous

fistula, which was sent for culture sensitivity test. The cultures revealed presence of *Staphylococcus aureus*, moderate growth of *Streptococcus viridans*, gram-negative rods and gram-positive cocci.

Orthopantogram showed diffuse osteolytic lesions and erosion of left side body of mandible involving both buccal and lingual cortical plates [Figure 3]. The routine hemogram was not very significant except raised erythrocyte sedimentation rate (ESR) which was- 86 mm first hour. The scintigraphy which is a definite diagnostic tool for osteomyelitis could not be done because of nonavailability.

Fine needle aspiration (FNA) was performed and pieces of bone were sent for histopathology to rule out multiple myeloma lesions. The FNA revealed inflammatory cells–predominantly atypical lymphocytes and neutrophils–and also was positive for actinomyces. Histopathologically there was anastomizing lamellar bony trabeculae and inflammatory cell infiltration comprising of lymphocytes, plasma cells and histiocytes with congested blood vessels suggestive of chronic osteomyelitis [Figure 4].

Correlating history, clinical evaluation and investigations, diagnosis of BRONJ was derived and sequestrectomy with aggressive debridement under antibiotic coverage was done. Six months follow-up showed no recurrence. Patient is currently under regular follow-up.

DISCUSSION

As BRONJ is fairly a new entity in the dental and medical literature, definition by the American Association of Oral and Maxillofacial Surgeons (AAOMS) is used to make the diagnosis.[8]

Patient may be considered to have BRONJ if all the following three characteristics are present:

- Current or previous treatment with BPs
- Exposed bone in the maxillofacial region that has persisted for more than 8 weeks and
- No history of radiation therapy to jaw.

In general, intravenous BPs shows higher incidence of BRONJ (0.8-12%) as compared to oral forms (0.01-0.04%).[8,9] Intravenous preparation used in treatment of metastatic disease

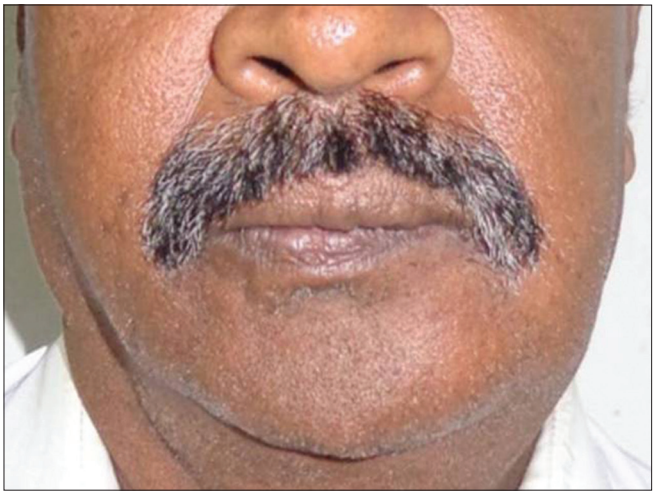

Figure 1: Extraoral initial examination showed moderate edema of the left face

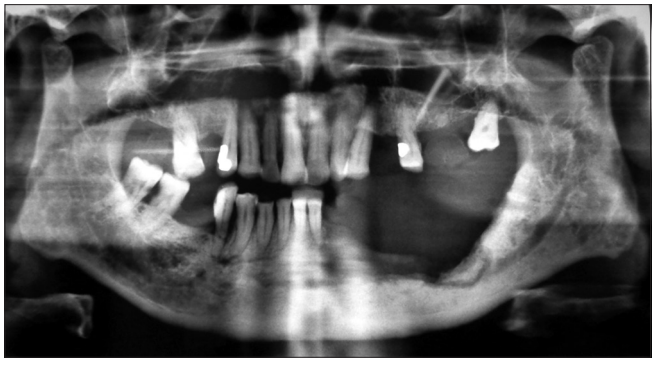

Figure 3: Panoramic radiograph showing the diffuse osteolytic lesions and erosions on left posterior body of mandible

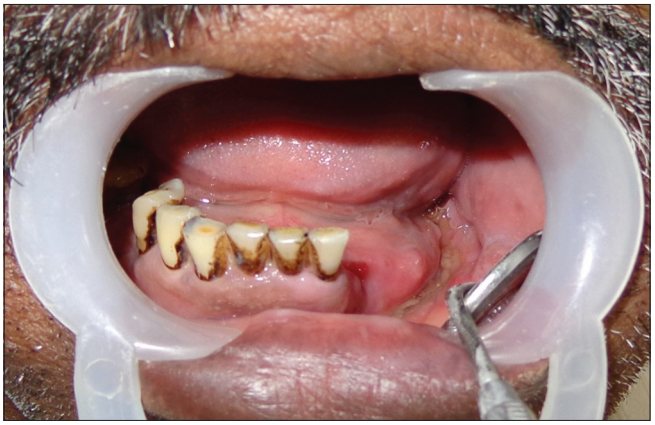

Figure 2: Exposed necrotic bone on left posterior body of mandible

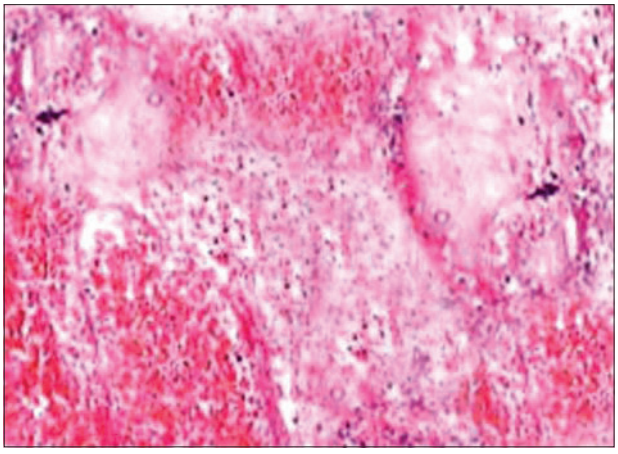

Figure 4: Photomicrograph showing inflammatory cell infiltration comprising of lymphocytes, plasma cells and histiocytes. (H&E stain, ×100)

irreversibly inhibit osteoclasts via interrupting the mevalonate pathway and the resulting toxicity causes osteoclast apoptosis. BPs are thought to concentrate in jaws owing to greater degree of vascularization and daily remodeling that occurs around periodontal ligament of the teeth.[2]

In the present case, patient had history of intravenous nitrogen BPs (zoledronic acid) for 3 years after being diagnosed of multiple myeloma and presented with swelling and exposed non vital bone in left alveolus region with purulent discharge for past 4 months.

In order to direct rational treatment guidelines, the AAOMS proposes use of the staging categories and their respective treatments as outlined in Table 1.[4]

The patient described was classified to be in Stage II and histology revealed chronic osteomyelitis. Therefore, sequestrectomy with aggressive debridement under antibiotic coverage was done.

Given the many unknowns associated with BRONJ, it would seem prudent to develop a coordinated pretreatment and intratreatment protocol aimed at prevention and patient education. Preventative strategies such as establishment of meticulous oral hygiene regimes in conjunction with timely surgical procedures should be undertaken prior to commencing therapy. During therapy, strict review and maintenance of oral hygiene programs are essential in order to prevent the development of pathology.[10-12]

It is critical that the dentist and oncologist should be aware of this significant complication which can occur spontaneously or after any dentoalveolar procedure in the population receiving BPs and further investigation is needed to completely elucidate this phenomenon.

Table 1: Staging of osteoradionecrosis

Stage 0	Dull aching bone pain in the body of the mandible, odontalgia with no odontogenic cause, sinus pain, periodontally involved teeth not explained by dental origin	Symptomatic treatment, conservative management of local factors, including chronic pain management and possible antibiotic therapy
Stage 1	Exposed/necrotic bone, asymptomatic, no evidence of infection	Antimicrobial rinses and no surgical intervention
Stage II	Exposed/necrotic bone, pain, erythema, ±purulent drainage	Antimicrobial rinses, systemic antibiotics or antifungals, analgesics
Stage III	Exposed/necrotic bone, pain/infection, pathologic fracture, extraoral fistula, osteolysis to inferior border	Antimicrobial rinses, systemic antibiotics or antifungals, analgesics, surgical debridement or resection

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