Management of bisphosphonate related osteonecrosis of jaw (BRONJ) with topical drug delivary using custom made tray: A case report

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Abstract
Bisphosphonates (BPs) are effective inhibitors of osteoclast mediated bone resorption and thus frequently used in patients with multiple myeloma, osteoporosis, metabolic bone diseases and metastatic bone cancer. Inspite of its benefits, patients are at increased risk of developingBRONJ which adversely affects their quality of life. BPs induced inhibition of osteoclast function may cause defect in jaw bone physiologic remodeling which along with its antiangiogenic properties may predispose the patient to osteonecrosis of jaw.
Here, we present a case in which patient with BRONJ who is terminally ill and only conservative management can be given responded favourably to topical medication using custom trays.

Keywords: Bronj, Bisphosphonates, Zolendronate, Osteonecrosis, Custom made tray.

Introduction
Bisphosphonates are effective inhibitors of osteoclast mediated bone resorption and thus frequently used in patients with multiple myeloma, osteoporosis, metabolic bone diseases like paget's disease and metastatic bone cancer.[1] Bisphosphonate Related Osteonecrosis Of Jaw (BRONJ) is a complication of this therapy affecting quality of life.
According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), three characteristics of BRONJ are:[2]

1. Current or previous treatment with bisphosphonates;
2. Exposed bone in the maxillofacial region that has persisted for more than eight weeks;
3. No history of radiation therapy to the jaw.

Later, as osteonecrosis secondary to other medications like anti resorptive and anti angiogenic agents was found, the AAOMSrecommended change in nomenclature to Medication Related Osteonecrosis of Jaw (MRONJ).[2]

Case Report
A 56 year old male patient reported to our department with chief complaint of pain on lower right back jaw region for past 2 months. Dull aching intermittent pain which was insidious in onset, aggravated on chewing and relieved temporarily over analgesics. Bleeding while brushing was noticed and patient refused using tooth brush. History revealed that he was under medication for hypertension for past 8 years and under insulin therapy since 2 years. History of fracture of left femur 3 years before for which steel plate insertion was done and further investigations revealed renal cell carcinoma with bone and lung metastasis in 2015. Underwent surgical removal of left kidney followed by chemotherapy with IV 4mg zolendronate weekly since 2015. In 2016, he underwentextraction of lower right back carious tooth which was followed by recurrent pain and bleeding in lower right back jaw region.

Clinical examination revealed a well defined yellowish white sloughing of alveolar mucosa with bone exposure in the lingual alveolar ridge in relation to edentulous 45 46 region. [Fig. 1] It was roughly ovoid measuring 6mm x 4mm in dimension approximately. On palpation, it was tender with bleeding on provocation.

Detailed history along with clinical findings lead us to a diagnosis of BRONJ. To stage BRONJ and to differentiate from metastasis, IOPAR and OPG were made, which revealed little ossification at the extraction site with mild osteolytic areas in relation to 45 46 region. [Fig. 2,3]A definitive diagnosis of Stage 2 Bisphosphonate related osteonecrosis of jaw was given.

The patient was terminally ill and the informed consent from the oncologist was to manage lesion conservatively. Thus, emperical antibiotics (Tab Augmentin 625 1-1-1 x 5 days and Tab metrogyl 400 1-1-1 x 5 days) along with analgesic (Tab zerodol p 1-1-1 x 5 days) were given systemically. For Topical application, Quadra gel (chlorhexidine gluconate 1%w/w,lignocaine 2%w/w, metronidazole 1%w/w) was prescribed.Fabrication of custom made tray (silicon based soft splint) was planned to retain medicament for longer period.Alginate impression was made and silicon based tray was fabricated. Topical medicament was thus advised to use thrice daily for 10 minutes. [Fig. 4,5]In subsequent visits, the lesion showed improvement with reduction in size. [Fig. 6] Further followup was not made as the patient expired soon after.

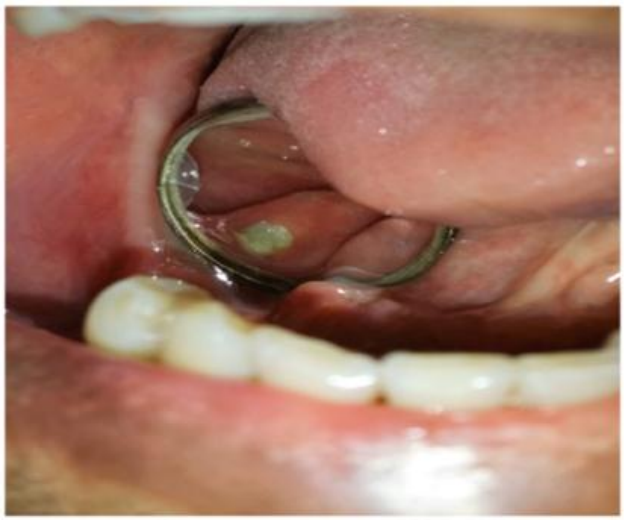

Fig. 1: well defined yellowish white sloughing of alveolar mucosa with bone exposure in the lingual alveolar ridge in relation to edentulous 45 46 region.

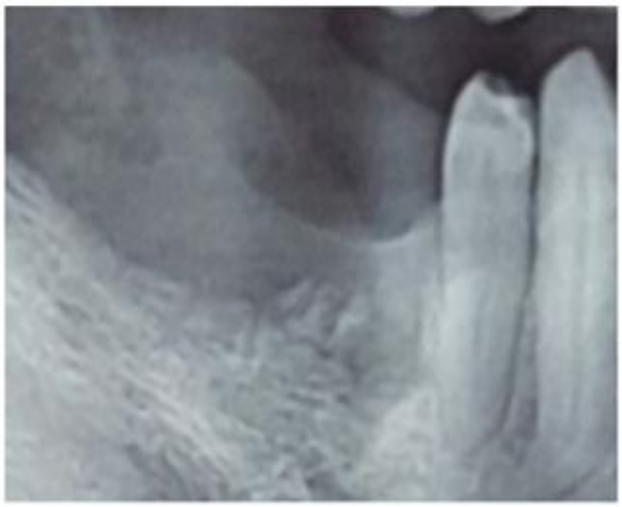

Fig. 2: Little ossification at extraction site with osteolytic changes wrt 45 region.

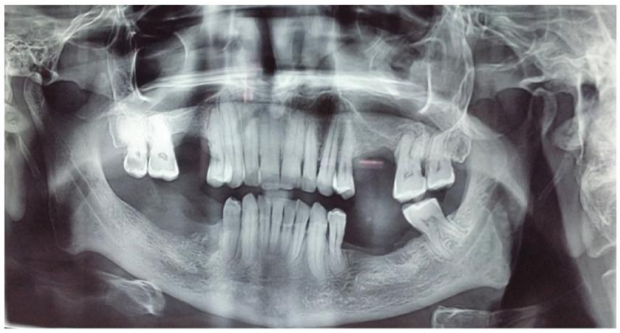

Fig. 3: Little ossification at extraction site with osteolytic changes wrt 45 region.

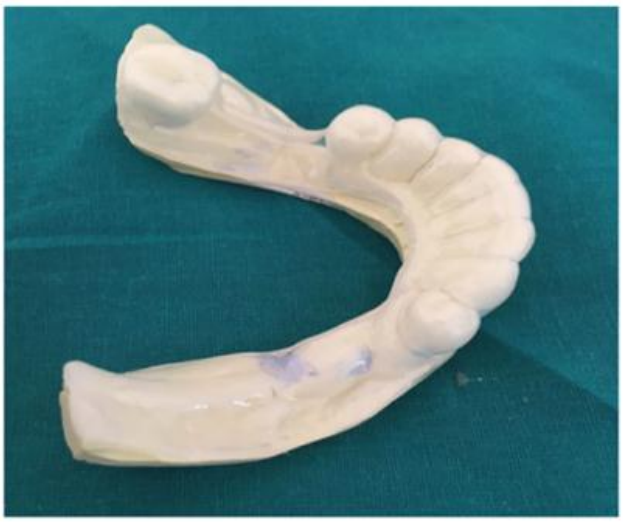

Fig. 4: Primary impression of lower arch made with alginate.

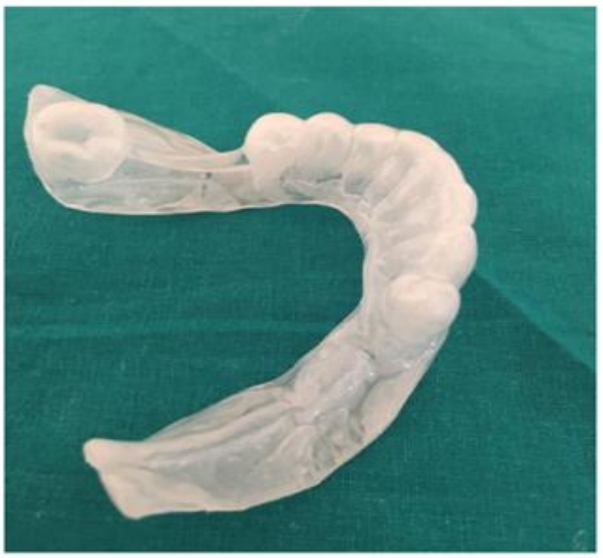

Fig. 5: Silicon based splint as custom tray for topical application of medicament.

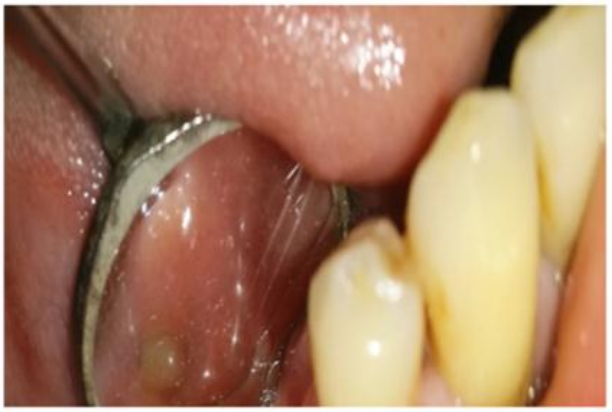

Fig. 6: Lesion reduced in size with bony exposure.

Discussion

Bisphosphonates are effective inhibitors of osteoclast mediated bone resorption. It slows down remodelling process and increase bone mineral density and thus reduces pathologic fracture. Hence it is used in primary and secondary osteoporosis, hypercalcaemia, multiple myeloma, bone metastases and Paget's disease.[3] Until recently the only significant adverse events associated wereupper gastrointestinal intolerance and an acute phase reaction with flu-like symptoms. In 2003, the first cases of BRONJ were reported by Marx et alin association with zoledronic acidand pamidronate.[4] The incidence of BRONJ in bone malignancy cases, treated with intravenous bisphosphonates, is about 1–12%.

Pathogenesis of BRONJ can be due to a defect in jaw bone physiologic remodelling secondary to profound inhibition of osteoclast function. This inhibits the normal bone turn over creating microdamage from normal mechanical loading or injuries after extraction which cannot be repaired. Antiangiogenic properties of bisphosphonates also affect local bone blood supply which contribute to apparent ischemic changes. Not all patients under bisphosphonates are affected by BRONJ is being explained by genetic variation in drug metabolism and skeletal homeostasis which may confer resistance to developing BRONJ. The unique environment of oral cavity and bisphosphonates being deposited in bones with significant turn over rate make mandible and maxilla more favourable for developing BRONJ.[5]

BRONJ is considered as sterile necrosis of jaw. Clinically presented with pain in initially erythematous region which progresses to ulceration and bone exposure. Associated tooth mobility and mucosal swelling may be evident. Purulent discharge with fistula if secondarily infected.

Radiographically not evident until significant bone involvement is present. Early stages usually present as little or no ossification at site of extraction. Later intraoral periapical radiograph shows mottled bone pattern and sequestrum formation similar to osteomyelitis. Widening of periodontal ligament space with osteosclerotic lamina dura can be evident. Panoramic imaging reveals osteolytic changes to inferior border of mandible with pathologic fracture.

Computerized Tomography (CT) and Cone Beam Computed Tomography (CBCT) scans can provide more accurate three dimensional information about the extent of the necrosis and is often useful for planning surgical debridement procedures. However it has not proved helpful with early identification in asymptomatic individuals.

Magnetic Resonance Imaging (MRI) has the ability to detect marrow edema which may be an early sign of bone ischemia and necrosis but it is associated with a high rate of false positive results.

Radionucleotide bone scans are the most sensitive modality for detecting changes in bone vascularity and may be helpful if vascular changes prove to be part of the early phase of BRONJ. It is presented as increased uptake in osteonecroticregions.[6]

The microscopic examination of debrided specimens of exposed bone will typically reveal necrotic bone with associated bacterial debris and granulation tissue. Microbial cultures from areas of exposed bone will usually isolate normal oral microbes and therefore are not always helpful. However in cases where there is extensive soft tissue involvement, microbial culture data may define co-morbid oral infections and facilitate the selection of an appropriate antibiotic regimen.

Carboxy-terminal collagen crosslinks (Ctx) is a telopeptide that can be used as a bioarker in the serum to measure the rate of bone turn over. It is usedto assess risk for developing BRONJ. Ctx< 100 pg/ml is associated with a high risk for developing BRONJ.[7]

Treatment for BRONJ depends on staging of the lesion. [Table 1]

In asymptomatic (Stage 0,1) patients, periodic oral rinses and close clinical follow up is sufficient. Symptomatic (stage 2,3) patients should be administered with antibiotic therapy like flucloxacillin or clindamycin along with surgical debridement & Segmental osteotomies if required.

Laser therapy at low intensity has shown better results by improving reparative process, increasing osteoblastic index, and stimulating lymphatic and blood capillaries growth. Applicability of "drug holidays" to minimize long-term bisphosphonate exposure is also been under discussion.[8]

Table 1: AAOMS staging criteria for osteonecrosis of jaw.

Category	Criteria
At risk	Clinically normal, asymptomatic patients who have received antiresorptive therapy
Stage 0	No clinical evidence of exposed bone, but presence of non-specific symptoms or clinical and/or radiographic abnormalities
Stage 1	Exposed and necrotic bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone associated with pain and/or signs of infection in the region of bone exposure with or without purulent drainage
Stage 3	Exposed and necrotic bone in patients with pain, infection, and at least one of the following: exposure and necrosis extending beyond the local alveolar tissues; radiographic evidence of osteolysis extending to the inferior mandibular border or the maxillary sinus floor; pathologic fracture; oro-antral, oronasal or oro-cutaneous communication

Conclusion

Bisphosphonates are inevitable treatment modality for bone metastasis. BRONJ is relatively rare but well know ncomplication at maxillofacial units around the world. It is important to undergo dental checkupand management of poor prognosis teeth before induction of bisphosphonates therapy. Dental surgeons need to be cautious in treatingpatient under bisphosphonate therapy.In case of treating BRONJ patients, it is essential to obtain informed consent documentation. Our case has been approached with drug delivery using custom made tray to retain medicament for longer period and thus increase efficacy of medicament.[9] It is hoped that documentation of this case report will prompt research to further investigate on conservative management approaches of BRONJ in debilitating patients.

Conflict of Interest: None.

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