BISPHOSPHONATE INDUCED OSTEONECROSIS OF THE JAW IN RENAL SARCIODOSIS – A CASE REPORT

ABSTRACT

The therapeutic use of Bisphosphonates has increased in the last decade. The long-term use of bisphosphonates has led to a challenging complication related to jaws knows as Bisphosphonate-induced osteoradionecrosis of the jaw (BIONJ). In this paper we report a case of BIONJ in a renal sarcoidosis patient with clinical implications and management.

Key words : Bisphosphonates, sarcoidosis, osteonecrosis, jaws.

INTRODUCTION

Bisphosphonates are widely used in the treatment of malignant tumors, bone metastasis, primary bony pathogenesis like multiple myeloma, Paget's disease, Rheumatoid arthritis, Fibrous dysplasia, Osteogenesis imperfect, hypercalcemia of malignancy and osteoporosis [1, 2, 3, 4].

Bisphosphonates are analogues of pyrophosphate; their primary mechanism of action is inhibition of osteoclastic resorption of bone. They have an increased affinity and bind with hydroxyapatite present in the bone particularly in areas where there is rapid turnover and resorption there by increase the bone density, calcium deposition and mineralization. The therapeutic action of Bisphosphonates as an antiresorptive agent is used in the treatment of metastatic disease and osteoporosis. They also have antiangiogenic property through which it decreases circulating vascular endothelial growth factor (VEGF). Thus, bone metabolism, which involves bone resorption and deposition is jeopardized [2].

The Bisphosphonates in clinical use are, Zolendronate, Pamidronate as intraveneous drugs and Alendronate Risedronate, Ibandronate, Etiodronate, Tiludronate as oral drugs [4]. Zoledronate is proved to be more effective in managing hypercalcemia of malignancy and skeletal related complications. The intravenous bisphosphonates have higher risk of developing osteonecrosis of jaw it approximately affects 1/10000 patients whereas with oral bisphosphonates, it is 0.7 per 10000 persons /year [3]. The half-life of Bisphosphonates is 10 years [2]. The average duration of incidence of BIONJ is 9-14months [4].

Incidence of BIONJ in mandible compared to maxilla is in the ratio of 2:1. Mandible accounts for 68% and maxilla 28% and 4% occur in both jaws. It is reported that 31 % of cases, present with asymptomatic bone exposure and 69% with bone exposure, pain, intra oral or extra oral draining sinuses. Spontaneous bone exposure can occur in the patients who

have optimal dental health and this particularly occurs in the lingual cortex of mandible [2]. Marx and Stern in 2003 first described, long term use of Bisphosphonate's leads to a potential complication known as Bisphosphonate induced osteonecrosis of the jaw [2,3]. American association of Oral & Maxillofacial Surgeons(AAOMS) in 2014 favored the term Medication related osteonecrosis of jaw (MRONJ) as osteonecrosis of jaws was associated with the use of other antiresorptive and antiangiogenic medications. These include anti-resorptive human monoclonal antibodies Denosumab and anti-angiogenic tyrosine kinase inhibitor's(5) . MRONJ is current or previous treatment with antiresorptive or antiangiogenic agents with exposed bone or bone that can be probed through an intra oral or extra oral fistula in the maxillofacial region that has persisted for longer than 8 weeks with no history of radiotherapy to the jaws or obvious metastatic disease to the jaws [6].

The antiresorptive agents like Denosumab is an antibody against RANKL and inhibits osteoclast function. It is used for the treatment of osteoporosis, skeletal related events due to metastatic disease. When compared to Bisphosphonates the Denosumab do not bind to bone and its effect diminishes by 6 months of completion of treatment (6) .

CASE REPORT

A 68-year-old male patient presented to Department of Oral and Maxillofacial Surgery with a chief complaint of pain and pus discharge in the left upper jaw since three months. His medical history revealed diabetes, hypertension and was diagnosed with sarcoidosis of kidneys 8 year back, during which he had developed hypercalcemia and renal calculi. To reduce the serum calcium level, he was given four IV doses of Zoledronic acid and to maintain same, he was advised sodium Alendronate 70mg Tab orally one per week with Methyl prednisolone 10mg Tab.

The patient visited local dentist, where his medical history was not evaluated and extractions in all the four quadrants was performed. Six months following extraction he noticed greyish black area in the upper left extraction area with pus discharge. Patient was referred from the nephrologist to us for further management.

On examination in the left upper posterior region there was 1cm * 1cm exposed necrotic bone, and obliteration of the buccal vestibule with multiple draining sinus [figure 1]. In the right upper jaw, the alveolar mucosa was erythematous. In left lower jaw there was exposed bone on the lingual surface in extracted region. The panoramic radiograph showed necrotic bone measuring 1x1 cm in left upper quadrant, necrotic bone measuring 0.5x0.5 cm in right upper quadrant and osteolytic area in left lower extracted region [figure2].

CBCT showed fragments of detached alveolar bone in the region of 24-26, continuity of the sinus floor was lost. There was irregular radiolucency involving the alveolar bone in relation to 45,46,47 and 14,15 regions [figure 3]. A provisional diagnosis of BIONJ was made based on history, clinical and radiographic features.

Under local anesthesia with antibiotic coverage, necrotic bone in the left upper quadrant was removed. Healing was uneventful [figure4]. The other areas are under regular checkup once in three months with one year of follow up the other areas are asymptomatic.

DISCUSSION

Sarcoidosis is an immune mediated disease with multiorgan association. It affects mainly pulmonary system up to 90%. It can also affect skin, eyes, nose, muscle, heart, liver, spleen, brain and joints. Renal sarcoidosis is rare. Hypercalcemia and hypercalciuria are the complications of renal sarcoidosis. Hypercalcemia is present in 10-17% of patients with

sarcoidosis. The cause is unknown. it is characterized by noncaseating epithelioid granuloma. The activates macrophages in the granuloma express 1 alpha –hydroxilase, this leads to increased levels of 1,25 dihydroxy vitamin D which accelerates absorption of calcium from the intestine and increased resorption of calcium from the one leading to hypercalcemia. [6]. The medical management in sarcoidosis is glucocorticoids to reduce inflammation. In this case bisphosphonate was used to treat hypercalcemia induced due to sarcoidosis of kidney [7].

The risk factors for MRONJ are: local risk factors are periodontal disease, acute dental infection, dental implant treatment, trauma from ill-fitting dentures, anatomical factors like presence of tori, exostoses, knife edge ridges, poor oral hygiene, xerostomia. Systemic risk factors include: chemotherapy for malignant tumors along with corticosteroids, underlying comorbidities like diabetes, cardiovascular diseases, sarcoidosis, renal dialysis other factors to considerate are; advanced age, obesity and presence of tobacco and alcohol [8] .

Dixon et al demonstrated alveolar crest remodels at 10 times the rate of tibia, 5 times the rate of mandible at the inferior border and 3 to 5 times the rate of mandible at the level of canal. Bisphosphonates readily accumulates at higher concentration in the alveolar bone and hence predisposes to BIONJ. On axial loading of mandibular molars, stress concentration is on the lingual cortex and not the inferior borders of mandible. This occurs in the Bisphosphonate induced avascular bone and the overlying thin mucosa easily gives away exposing the underlying bone [2,4].

Dental evaluation should be done before starting Bisphosphonate therapy, the unsalvageable teeth, local anatomic structures like tori, mylohyoid ridge, which are covered by thin mucosa, impacted teeth exposed to oral cavity should be removed at least 4-6 weeks before starting bisphosphonates to allow complete healing, Periodontal therapy, root canal therapy, Oral

prophylaxis, fluoride application should be considered. In denture wearers regular examination and soft relining is considered [3].

The radiographic signs of bisphosphonate toxicity include generalized sclerosis in the alveolar bone and lamina dura, widening of PDL space, tooth mobility unrelated to alveolar bone loss and dry bone pain without an appropriate dental etiology.

Clinical staging, Imaging & Treatment of MRONJ According to American Association of Oral & Maxillofacial Surgeons (6,8,9,10,11) .

Stage	Clinical condition	Imaging features	Treatment
At risk	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates	No specific radiographic changes	No treatment indicated, patient education.
Stage 0	No clinical evidence of necrotic bone, but nonspecific clinical findings & symptoms.	Alveolar bone loss or resorption, sclerotic alveolar bone, thickening & sclerosis of lamina dura, thickening or obscuring of periodontal ligament.	Pain medication and antibiotics
Stage 1	Exposed & necrotic bone or fistulas that probe to the bone in	Same as stage 0, changes in trabecular pattern, disorganized, poor	Antibacterial mouth rinse, clinical follow up

	patients who are asymptomatic and have no evidence of infection	corticomedullary Differentiation.	on quarterly basis, patient education
Stage 2	Exposed & necrotic bone or fistulas that probe to the bone associated with evidence of infection with or without purulent drainage	Mixed diffuse osteosclerosis, osteolysis from alveolar bone to jaw bone, thickening of mandibular canal, periosteal response, maxillary sinusitis & sequestration.	Symptomatic treatment with oral antibiotics, oral antibacterial mouth rinse, pain control debridement to relieve soft tissue irritation and infection control
Stage 3	Exposed & necrotic bone or fistulas that probe to the bone in patients with pain, infection & in or more of the following: exposed & necrotic bone extending beyond the region of	Osteosclerosis/osteolysis of the surrounding bone, pathologic mandibular fracture and osteolysis extending to the maxillary sinus floor.	Antibacterial mouth rinse, antibiotic therapy and pain control, surgical debridement or resection for long term palliation of infection and pain.

	alveolar bone(inferior border & ramus in mandible, maxillary sinus & Zygoma in maxilla)resulting in pathologic fracture ,extra oral fistula, oral antral or oronasal communication or osteolysis extending to inferior border of the mandible or sinus floor.		

Adjuvant therapies like Pentoxyfyline, Vitamin E and Teriparatide are used in the management of MRONJ. The role of HBO in MRONJ still remains unclear though presented to improve the leukocyte function. During IV bisphosphonate therapy invasive dental procedures are contraindicated. The goal is to keep optimum dental and oral health. Scooletta et al developed a protocol for extraction of teeth in intravenous bisphosphonate treated patients. Extraction was performed under antibiotic coverage without a vestibular split thickness flap, followed by piezo assisted minimal alveoloplasty and placing autologous platelet rich factors into the extraction socket with primary closure. There was a favorable outcome [12]. In case of BIONJ after superficial curettage, the exposed bone covered with two

layers of platelet rich growth factors, which acts as a barrier membrane and may hassen the healing [13].

The aim of management of MRONJ is to alleviate pain, control infection in hard and soft tissue, prevention of progression and occurrence of bone necrosis and this involves multidisciplinary approach. The case presented belongs to stage 2. The treatment protocol adopted which included removal of the expose bone along with antibiotic's, analgesics and chlorhexidine mouth wash appears to be appropriate.

CONCLUSION

BIONJ is a potential complication in patients receiving bisphosphonates. Thorough dental and medical history evaluation is mandatory before dentoalveolar surgery.

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