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BISPHOSPONATE INDUCED OSTEONECROSIS OF JAW – A CASE REPORT

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ABSTRACT Osteonecrosis of the jaw (ONJ), is the death or necrosis of a bone caused by an insufficient blood supply.[1,2,6] It is also called as avascular necrosis, aseptic necrosis or ischemic necrosis of bone. It is a clinically devastating condition that can affect the quality of life of patients. ONJ can be induced by medication such as anti-resorptive agents such as bisphosphonates (BPs) and antiangiogenic drugs, so is termed as medication related ONJ (MRONJ).[1,2,3,4,8,9] The management of MRONJ can be conservative or invasive, depending upon the stage of the disease, size of the lesions ,contributing drug therapy and presence of comorbidities.[4,7] We report a case of bisphosphonate induced osteonecrosis of jaw managed successfully with conservative treatment.

KEYWORDS : Necrosis of bone, Bisphosphonate induced, Devastating condition

INTRODUCTION:

Osteonecrosis of the jaw (ONJ) is described as a bone infarction due to decreased blood supply. [2,4,7] ONJ is characterized with symptoms which include pain, limited movements of the jaw leading to disarticulation which makes the oral hygiene and feeding difficult in turn affecting the quality of life. A vascular ONJ is commonly associated with radiation therapy in treatment of cancers.[1,2,4] Medication induced ONJ is found in usage of bisphosphonates and anti - angiogenic agents. These compounds were originally authorized for the management of skeletal complications of malignancy, including advanced breast cancer and multiple myeloma.[1,2,4,7] They are also a drug of choice for management of other bone disorders including osteoporosis, cancer-induced hypocalcaemia, Paget's disease, osteogenesis imperfecta , primary and secondary hyperparat hyroidism, and other conditions that leads to bone fragility. [1,2,4,5,7] We report a case of bisphosphonate induced osteonecrosis of jaw in a 53 years female who was under treatment for breast cancer.

CASE REPORT:

A 53 years old female patient reported to the Department of oral medicine and radiology with a complaint of non-healing socket in left lower back tooth region that had developed 5 months back. Extraction of grossly decayed tooth was done before 5months and it had not healed since then. She had pain in the region which was localised intermittent in nature and became more severe on eating. The pain was relieved on taking medication.

Patient had a history of breast cancer diagnosed before 3 years and was under chemotherapy. Tamoxifen (20mg) and Bisphosphonate (4 mg) were given in the form of injection once in 3 months cycle for a period of 3 years duration. Vitamin D3 supplements were also given. Patient also had a history of diabetes for 5 years and under medication for the same.

On inspection, a non-healing defect was evident in left side posterior alveolar ridge region (Fig 1). The defect extended from distal surface of 34 to retro molar region measuring approximately 2 x 2 cm which is devoid of mucosal coverage and the surrounding area appeared blanched. On palpation, the exposed bone was tender with secondary changes like bleeding, pus discharge. A single left submandibular lymph node approximately 1x1 cm size was evident which tender and mobile, soft in consistency was. Based on the history of the treatment of breast cancer with bisphosphonate and presence of painful non-healing extraction socket a provisional diagnosis of Bisphosphonate induced osteonecrosis of jaw was made. The differential diagnosis included metastatic tumor and primary bone malignancy.

The OPG revealed non healing extraction socket in relation to 36, 37 regions. Mixed radiolucent and radiopaque lesion in 36, 37 and 46, 47 regions with generalized sclerosis of the alveolar margin (Fig 2). Axial CT - Bone window shows sclerotic and lytic lesion evident in the left side posterior mandibular region in relation to 36, 37 regions with perforation of buccal and lingual cortical plates (Fig 3). Soft tissue window setting reveals soft tissue thickening adjacent to lesion suggestive of soft tissue inflammation (Fig 4).A final diagnosis of bisphosphonate induced osteonecrosis of jaw was given.

The patient was referred to medical oncology to obtain fitness to undergo sequestrectomy and surgical debridement of mandible under general anaesthesia but patient was not deemed fit[4]. Conservative treatment was done. Patient was asked to stop bisphosphonates and continue with tamoxifen. Patient was advised to take Pentoxifyllin - 400 mg twice daily for 2 weeks and Tocopherol - 1000 IU for two weeks. Patient was given 0.12 % Chlorhexidine mouth wash for 1 month and Tab. Flagyl - 400 mg twice daily for 5 days. Patient was reviewed after 15 days, 1 month and 3 months. She remained asymptomatic and wound closure occurred except for the posterior most regions. The patient on further follow up developed metastasis cancer to the hip and spine and was under palliative treatment but the oral symptoms did not recur.

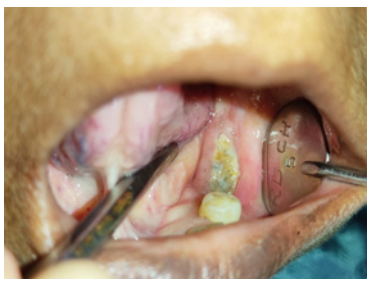

Fig 1: Intra oral photograph depicting non healing defect in left lateral alveolar ridge region

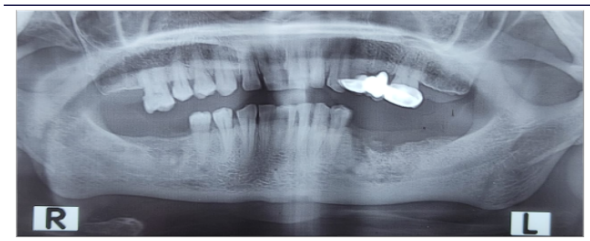

FIG 2: Diffuse, poor defined radiolucency with ragged border in region of distal surface of 34 to posterior most region of mandible.

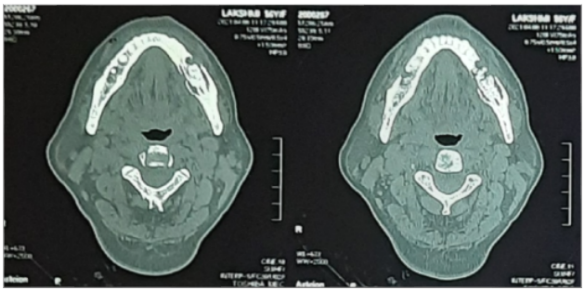

FIG 3: In axial CT - bone window shows sclerotic and lytic lesion evident in the left side posterior mandibular region in relation to 36,37 region with perforation of buccal and lingual cortical plates - suggestive of ON

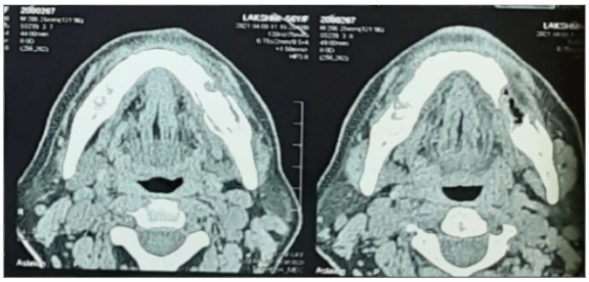

FIG 4: On axial CT - soft tissue window setting reveals soft tissue thickening adjacent to lesion was detected-suggestive of inflammation

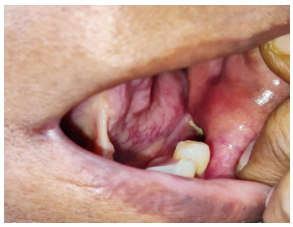

FIG :5 POST OPERATIVE PICTURE

DISCUSSION:

Medication induced Osteonecrosis of the jaw (ONJ) can be caused by two pharmacological agents: antiresorptive and antiangiogenic agents. [1]

Bisphosphonates are antiresorptive have been used since 1960 for the treatment of conditions such as bone metastases, multiple myeloma, lung cancer, calcium metabolism disorders, breast cancer and Paget's disease. Their therapeutic use has increased for the treatment and prevention of osteoporosis and osteopenia.[1,2]

Bps can be divided into Nitrogen-containing bisphosphonates (NBPs) and non-Nitrogen-containing bisphosphonates (NNBPs). Pamidronate and zoledronic acid are examples of NBPs and Etidronate and Clodronateare examples of NNBPs. Risk is higher with zoledronic acid than with pamidronate.[1]In our case zoledronic acid was used in treatment of breast cancer.

The pathophysiology of medication induced osteonecrosis of jaw was not completely elucidated. There are several suggested hypothesis that could explain its unique localization to the jaws: Inflammation or infection, micro trauma, altered bone remodeling or over suppression of bone resorption, angiogenesis inhibition, soft tissue BPs toxicity, peculiar biofilm of the oral cavity, terminal vascularization of the mandible, suppression of immunity, or Vitamin D deficiency[1,2]

Risk factors that contribute for development of necrosis in those taking high cumulative dosage of medication are local factors such as micro trauma and dental treatments like extraction.[3,6,10] Dentoalveolar surgery is considered to be a major risk factor for developing MRONJ. Denture use and pre-existing inflammatory dental disease, such as periodontal disease or periapical pathology, are also well recognized risk factors in patients with cancer exposed to bisphosponates.[1,2,3,5,7,11]

The diagnostic criteria for MRONJ developed by American Association of Oral and Maxillofacial Surgery in 2007 and various proposals for modification of the classification were received and finally in 2014 the AAOMS proposed a change in nomenclature in favour of the term medication related osteonecrosis of the jaws (MRONJ).[1,2,4]

According to AAOMS diagnostic criteria 2014[2,3,4,11]

AT RISK CATEGORY - No apparent necrotic bone in patients who have been treated with either oral or IV bisphosphonates

STAGE 0 - No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms

STAGE 1-Exposed and necrotic bone, or fistulae that probes to the bone in patients who are asymptomatic and have no evidence of infection

STAGE 2-Exposed and necrotic bone, or fistulae that probes to the bone, associated with infection as evidenced by pain and erythema in the region of the exposed bone, with or without purulent drainage

STAGE 3-Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one or more of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla) resulting in pathologic fracture, extra-oral fistula, oral-antral/oral-nasal communication or osteolysis extending to the inferior border of the mandible of sinus floor [2,3,4,11] In our case, patient was in stage 2 with symptomatic exposed necrotic bone.

Imaging modalities are confirmatory to arrive to the diagnosis of osteonecrosis of jaw. OPG shows unexplained bone loss not attributed to periodontal inflammation with a change in trabecular bone pattern.[2,4,7] In early stages of OPG shows diffuse sclerotic bone, ill-defined radiolucency, or a mix of a radiopaque and radiolucent lesion in addition to a non healing extraction socket as in our case. For detailed examination; advanced modalities such as CT and MRI have been used.

CT reveals diffuse osteosclerosis, bone resorption, degenerated cortical bone, periosteal reaction, and bone fistulas are findings that reveal the spread and the extent of such lesion.[4,7,8] The main advantage of MRI over other imaging modalities is the ability to assess the degree of extent of the lesion in bone and soft tissues, which helps in planning for surgical debridement and resection.[4,7]In our case CT investigation shows sclerotic and lytic lesion in the left posterior mandible with perforation of the buccal and lingual cortical plate with surrounding soft tissue inflammation near the non healing extraction socket which was confirmatory for osteonecrosis of mandible**.**

Management protocol for MRONJ is challenging and remains a controversial. However, the treatment protocol is case-dependent and requires treatment according to the condition stage and symptoms.[4,9,10]

AAOMS treatment strategies as follows (2014)[11]:

At risk- No treatment indicated patient education
Stage 0 - Systemic management, including use of pain medication and antibiotics
Stage 1 - Antibacterial mouth rinse clinical follow-up on a quarterly basis patient
education and review of indications for continued bisphosphonate therapy
Stage 2 - Symptomatic treatment with oral antibiotics oral antibacterial mouth

rinse pain control, debridement to relieve soft tissue irritation and infection control.

Stage 3 - antibacterial mouth rinse antibiotic therapy and pain control surgical debridement or resection for longer-term palliation of infection and pain[11]

Literature review on management of osteonecrosis showed that surgical debridement resulted in worsening of symptoms and delay in wound closure.[12] Migliorati etal , stated that in surgical intervention it is difficult to attain a viable bone margin due to the global effect of bisphosphonate on bone. Aggressive surgeries also caused wide necrotic areas. [13] Even in use of tissue flaps to cover the exposed bone resulted in fistula around the flap with complete dehiscence. Though our patient was categorized for treatment with surgical debridement she was managed successfully by conservative measures. [14]

Recently therapies which helps in management of ONJ are the uses of autologous bone marrow stem cells, allogenic mesenchymal stem cells to regenerate the damaged bone.Low-level laser therapy followed by surgical approach are also used but the uses of adjuvant therapies are not well supported.[4,5,7].

CONCLUSION:

The patho-physiology of MRONJ is not completely understood despite the strong association between jaw necrosis and bisphosphonates. [4]Hence, an effective and appropriate therapy for the condition is still to be decided. Potential preventive measures should be followed before initiating bisphosphonate therapy and follow up should be mandatory in patients who are under bisphosphonate treatment.[10]

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