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ABSTRACT

Bisphosphonates (BPs) have been widely used in medical practice as anti-resorptive agents owing to their anti-osteoclastic action. These compounds are also used for their analgesic action and their potential anti-tumor effect. Patients treated with BPs develop ostenecrosis of jaw or maxillary bone after minor local trauma labeled as bisphosphonate related osteonecrosis of jaw (BRONJ). The etiopathogenic mechanism of this pathological condition is poorly understood. In the present case report, a case with follow up of left maxillary osteomyelitis due to BPs is presented.

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INTRODUCTION:

Bisphosphonates (BPs) are a class of drugs derived from pyrophosphates, endogenous inorganic regulators of mineralization, by substituting the oxygen atom in the basic pyrophosphate chain with a carbon, this leads to osteoclast inhibition.[1] Historically, bisphosphonates date back to the middle of the 19th century, where their use was mainly industrial. Their biological characteristics were first reported in 1968. In the early 1990s bisphosphantes were employed as a diagnostic agent in various disorders of bone and calcium metabolism. Currently oral bisphosphantes are used widely in the treatment of osteoporosis. Intravenous regimes are designed to treat the complications of metastatic disease and primary osteolytic pathology of bone.[2]

Bisphosphonates appear to express their effects at three levels: tissue, cell and molecular. Two broad theories have been articulated to explain the pathogenesis in BRONJ. One is bisphosphonate induced osteoclast induced inhibition and other is its antiangiogenic mechanism.[2] The effects of BPs include the reduction of bone loss and the risk of pathological fracture; these drugs are thus administered to patients suffering from destructive bone lesions resulting from osteoclast-induced resorption; they are mainly used to treat and prevent malignant hypercalcemia, skeletal related events associated with bone metastases secondary to solid cancer, and in the management of the lesions of multiple myeloma, Pagets disease, primary and secondary hyperparathyroidism and osteoporosis.[1] IV bisphosphonates are primarily used and effective in treatment and management of cancer-related conditions. These include hypercalcemia of malignancy, skeletal related events associated with bone metastases in the context of solid tumors such as breast cancer, prostate cancer, lung cancer, and in the management of lytic lesions in the setting of multiple myeloma. IV bisphosphonates are effective in preventing and reducing hypercalcemia, stabilizing bone pathology and preventing fractures in the context of skeletal involvement. While they have not been shown to improve cancer specific survival, they have had significant impact on the quality of life for patients with advanced cancer that involves skeletal system.[3]

Bisphosphantes are thought to concentrate in the jaws due to the associated physiology of this part of the skeleton. The greater degree of vascularization and the daily remodeling that occurs around the periodontal ligament of the teeth. In addition the chronic nature of invasive dental disease, and the treatment it requires occurs in a location where adjacent bone is minimally protected by a thin mucosal covering. This serves to explain why bisphosphonates related osteonecrosis (ON)

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manifest itself mostly in the jaws and not other sites of skeleton.[2] Bisphosphonate related osteonecrosis of the jaw (BRONJ) adversely affects the quality of life and produces significant morbidity in afflicted patients.[3] In this case report, we describe a case of BRONJ in left maxillary region.

CASE REPORT:

A 76 year old male reported to department of oral and maxillofacial surgery with complain of pain and pus discharge in upper left front and back region of upper jaw since two and half months. Patient gives history of pain and pus discharge in upper left front and back region (22-27) since three months following which he underwent extraction of teeth, but pus discharge and pain continued following extraction. Patient had past history of prostate cancer surgery twice (2004 & 2007) and angioplasty in 2004. Patient has been taking anti-hypertensives, oral bisphosphonates (alendronate), calcium tablets since 2007. Intraoral examination showed exposed necrotic bone of 4.5 * 3 cm in 25, 26, 27 region with inflamed surrounding mucosa. (Fig 1)

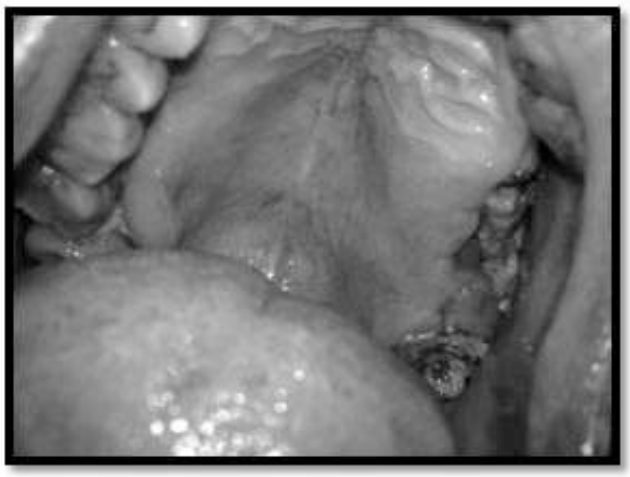

Fig 1: intra oral view of exposed necrotic bone

CT scan of maxilla showed generalized cortical thinning, irregular and patchy osteolysis, osteolytic pattern involving left maxillary arch and floor of left maxillary sinus. Left maxillary sinus was completely opacified with soft tissue. Sequetrectomy and saucerisation (Fig 2 & 3) was

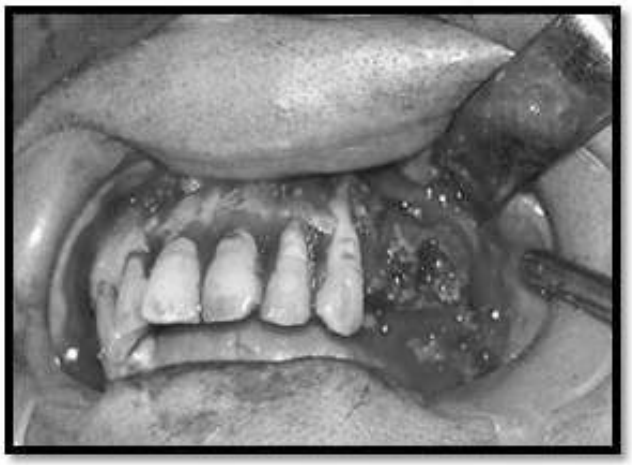

Fig 2: exposure of necrotic bone after reflection

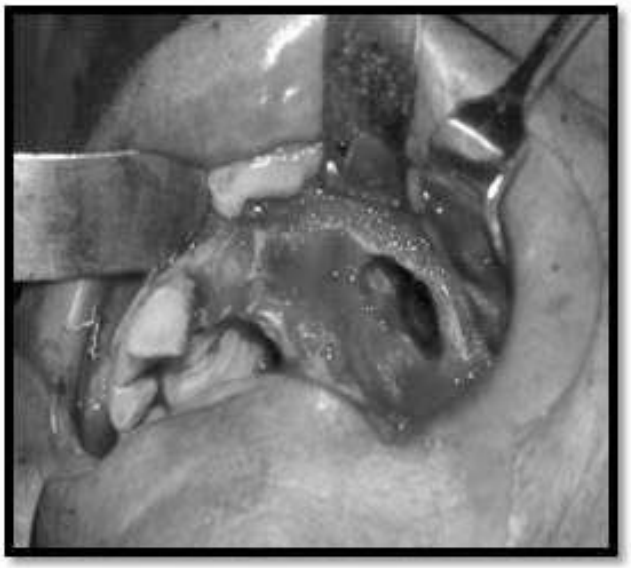

Fig 3: after sequestrectomy saucerisation & extraction of 21, 22, 23, 28

done along with extraction of 21, 22, 23, 28 followed by primary closure (Fig 4).

Fig 4: primary closure

Histopathology report showed granulation tissue, large number of extravasated red blood cells, chronic inflammatory cells and dead bone with empty lacunae in H & E stained section (Fig 5). Postoperatively patient was rehabilitated by obturator (Fig 6).

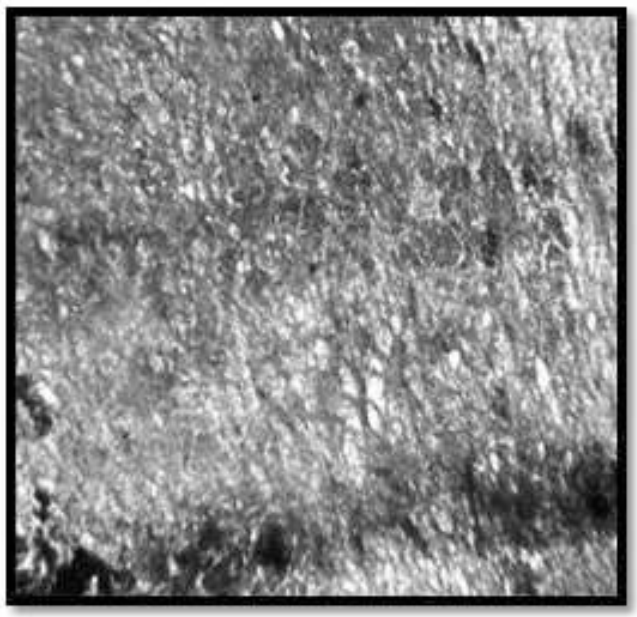

Fig 5: histopathology of specimen

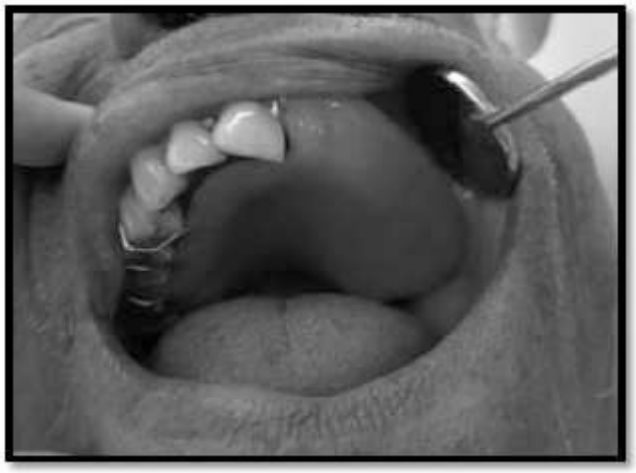

Fig 6: obturator in place

Bisphosphonates are stable analogs of pyrophosphates, which are naturally occurring modulators of bone metabolism. They are potent inhibitors of osteoclast – mediated bone resorption and have cytotoxic effects on mature osteoclasts and inhibit the formation of osteoclasts from precursors.[4] Hence they are used as antiresorptive medicines to maintain or increase bone density and strength in diseases like osteoporosis, hypercalcemia, Paget's disease, bone metastasis, multiple myeloma, primary hyperparathyroidism, osteogenesis imperfecta, and numerous other conditions that feature bone fragility. Bisphosphonates can be given by oral or IV administration. IV bisphosphonates are used extensively to treat osteolytic bone lesions related to multiple myeloma, and bone metastasis of solid cancers, breast cancer or prostate cancer.[4] An increased risk of osteonecrosis in the jaw bones is noted since 2003, causing large and therapy resistant bone exposures of the maxilla and mandible in patients with a history of bisphosphnate administered orally or by IV route. Marked inhibition of bone resorption is seen, particularly when administered by IV infusion.[4]

The exact origin of BRONJ is not known but many hypothesis seem to explain the pathogenesis under as:

- On bone remodeling: it is noted that bisphosphonate causes bone remodeling suppression. The jaw bones have high rate of remodeling than other bones hence rapid remodeling of jaw and suppression of remodeling leads to osteonecrosis.

- On osteocytes: in normal bone osteocytes at the end of their life cycle are removed and replaced with new ones. This process will be absent when bone remodeling is suppressed by bisphosphonates. Healthy osteoytes have canaliculi by which they communicate with adjacent osteocytes as well as exchange nutrients through blood supply. So, once the osteocytes, die the nutrition is also cut off leading to necrosis of bone. It is also noted bisphosphonates attached to the bone act as cytotoxic agents to the ostocytes thereby leading to their death and later their necrosis.

- On antiangiogenesis: bisphosphonate have antiangiogenic property as they suppress capillary regeneration, epithelial growth factor and angiogenesis. The normal healing mechanism in

jaw bone following extraction or invasive dental treatments is disturbed as the blood clot will not form due to angiosuppression by bisphosphonate. Bone remodeling is also inhibited as osteoclasts are suppressed by bisphosphonates leading to delay in wound healing process and BRONJ ultimately.[5]

In order to standardize the criteria for BRONJ the Amercian Association of Oral and Maxillofacial Surgeons (AAOMS) in 2007 has come up with three following criteria:[6]

- Current or previous treatment with bisphosphonate
- Exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks
- No history of radiation therapy to the jaws.[5,7]

The present case report is of 76 year old male who was taking oral bisphosphanates followed by prostate cancer surgery and patient had undergone extraction of teeth in upper left quadrant due to pain and pus discharge. But pain and pus discharge did not subside following extraction. Clinically there was bare necrosed bone in upper left maxillary region. Criteria given by AAOMS in 2007 for BRONJ were present in this case suggesting osteonecrosis post bisphosphonate therapy. Post operatively patient had satisfactory healing with no exposed bone. Patient was kept on follow up for six months. Healing after six months was satisfactory (Fig 7). Opening present in buccal vestibule was closed by means of an obturator.

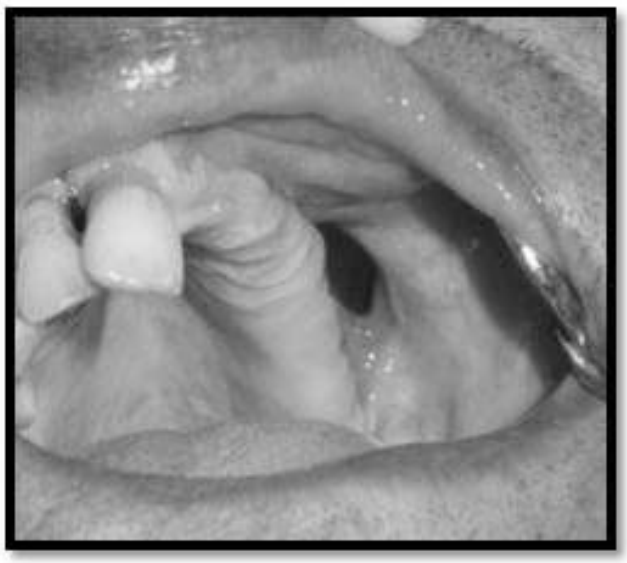

Fig7: follow up after 6 months

CONCLUSION:

Bisphosphonate related osteonecrosis of the jaws is a clinical and pathological entity that is not yet fully understood; the true incidence of this adverse effect is almost certainly underestimated.[1] Although the definitive role of bisphosphonates remains to be elucidated, the alteration in bone metabolism together with surgical insult or trauma appear to be key factors in the development of osteonecrosis.[4]

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