BISPHOSPHONATES RELATED OSTEONECROSIS OF JAW: A CASE REPORT FROM MIDDLE EAST

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ABSTRACT

Bisphosphonates which are used in bone diseases like osteoporosis, multiple myeloma and metastatic bone diseases can lead to the most lethal complication of osteonecrosis of the jaw which particularly involves the mandible. The pathophysiology of BRONJ is not clear. However, it is considered that it is due to the defect in osteoblast and osteoclast activity as a result of which bone remodeling and wound healing is affected. It is also believed that dental procedures can lead to the BRONJ. Because bone cells are highly networked, the importance of multicellular interactions during the onset of these risk factors cannot be overstated. As such, this perspective addresses current research on the effects of BPs, mechanical load and inflammation on bone remodeling and on development of BRONJ. Our investigation has led us to conclude that improved in vitro systems capable of adequately recapitulating multicellular communication and incorporating effects of osteocyte mechanosensing on bone resorption and formation are needed to elucidate the mechanism(s) by which BRONJ ensues.

Keywords: Bisphosphonates, Osteonecrosis, Jaw

Introduction

BRONJ is considered in those patients who have no history of being treated with radiotherapy of head and neck and non healing of devitalized bone in the oral cavity for minimum of eight weeks (Migliorati et al.;[1] Saia et al;[2] Ruggiero et al.[3]). Few other antiresorptive and antiangiogenic medications are also associated with osteonecrosis (Ruggiero et al.[3]) as in antiresorptive medications like Denosumab; resorption of osteoclast is affected along with its differentiation and activation (Qaisi et al).[4] In antiangiogenic medications like tyrosine kinase inhibitors bone remodeling and healing is affected which is repressed by these medications. Cases regarding these antiresorptive and antiangiogenic medications are published by the American association of oral and maxillofacial surgeons in 2014 in which nomenclature of BRONJ is replaced with medication-related osteonecrosis of the jaw (MRONJ) to incor-porate cases of osteonecrosis following exposure to other antiresorptive and antiangiogenic treatments. In many researches, it is concluded that sunitinib and imatinib which are tyrosine kinase inhibitors are associated with bone necrosis of jaw and are not related to the adjunct treatment with BPs (Ruggiero et al[3] and Viviano et al.[5]

BPs mitigates bone resorption by osteoclasts and remodeling as a whole. Disease which are associated with the loss of bones like osteoporosis, bone metastasis, malignancy associated hypercalcemia and Paget's disease are usually treated with BPs in which osteoclast activity and bone remodeling is affected resulting in bone resorption. (Feller et al.[6]; Zara et

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al.[7]; Manzano-Moreno et al.[8]; Heymann,[9]; Landesberg et al.[10]). An increase in BP prescriptions has led to an increased need to interpret the mechanism(s) by which BRONJ develops. Some researches explain that dental procedures like tooth extraction and infection also lead to the BRONJ (Ikebe,[11]; Otto et al,[12]; Abu-Id et al,[13]; Aragon-Ching et al).[14] In these two conditions, affected tooth is vulnerable to infection by bacteria because the sockets are unshielded. So the normal bone turnover is disturbed and the combined effects of BPs, mechanical load and infection may lead to the osteonecrosis. The combined effect of these risk factors have been described in some studies which collaborated the biological mechanism of mechanical and physical stimuli. This study is called mechanobiology (Epari et al).[15] Cellular responses are generated by biochemical signals which is the result of physical stimuli and this process is called mechanotransduction. There are four phases involved in mechanotransduction:1) mechanocoupling (which involves the stretching of bone cells and generation of fluid movement within the bone canaliculae by mechanical loads), 2) biochemical coupling (or the conversion of a mechanical signal into a biochemical reaction by way of cellular pathways), 3) transmission of the signal from the sensor to the effector cell and 4) the effector cell response (Huang and Ogawa,[16]; Duncan and Turner,[17]; Turner and Pavalko,[18]). It is verified by an organized review of case series, retrospective studies and clinical trials on BRONJ that our focus on tooth extraction and infection is valid. These studies are published between 2003 and 2014. As current research seeks to elucidate the mechanism(s) by which BRONJ develops, the study of the disease from a mechanobiology perspective will support this resolve. Although we have chosen to present experimental studies on the effects of cofactors on bone cell communication and functional activity. It is seen that, within 3198 cases of BRONJ, 61.7% were associated with tooth extractions, and 5% were associated with periodontal disease (inflammation) (Fliefel et al).[19]

Case Report

A 65-year-old female who had been taking oral risedronate (Actonel), a type of bisphosphonates, 35 mg once weekly for 4 years as a treatment of osteoporosis, presented with history of osteonecrosis involving the upper and lower jaw. The diagnosis of osteonecrosis was made by history, physical examination and findings on CT scan. The patient was suffering from pain and inflammation and infectious episodes which were treated with mechanical debridement, hydrogen peroxide, iodopovidone, and 1% chlorhexidine gel twice a week. At home, she disinfected the oral cavity after meals with H_2O_2, 0.2% chlorhexidine, and one or two applications of the same gel.

The patient initially suffered with pain and the symptoms progresses with temperature, swelling and the discharge of pus from the site of necrosis in the mandibular region. Clinical examination revealed severe skin erythema, swelling of face and neck and limited jaw range of motion. The involved skin is also tender on palpation. On oral examination, pus was seen discharging from the oral cavity from right mandible and the jaw is deviated to the affected site. Laboratory findings of blood showed a white blood cell count of 41,200/mm^3, C-reactive protein 29.9 mg/dL, and glycemia 175 mg/dL. Metronidazole (1.5 g/day) and ceftriaxone (4 g/day) were given to the patient as the treatment.

A plain (without contrast) computed tomography (CT) scan of the face was performed which showed multiple patchy mixed density areas of sclerosis and lucencies involving both jaws predominantly mandible, which was a complication of bisphosphonates therapy, (Fig.1 and 2).

When the patient condition became worst, she was shifted to the intensive care unit, where antibiotic therapy was started with ciprofloxacin (500 mg twice a day i.v.) and imipenem (1.5 g/day). Daily local medication was continued with hydrogen peroxide

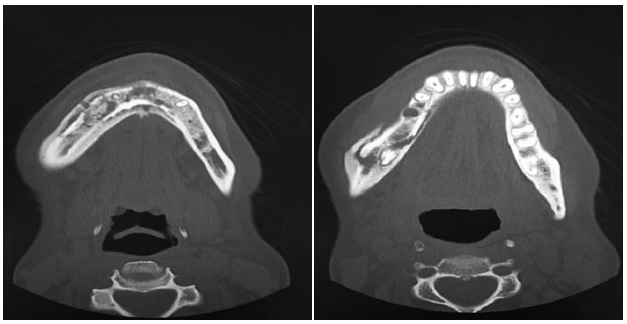

Figure 1: Non contrast CT scan axial view of face, showing patchy areas of sclerosis and lucencies involving mandible.

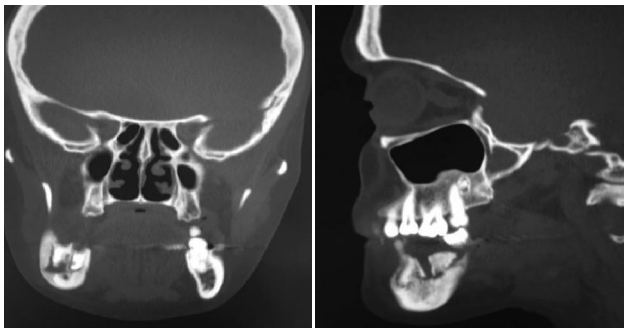

Figure 2: Non contrast CT scan coronal and saggital views of face, showing patchy areas of sclerosis and lucencies involving both jaws predominently mandible.

diluted with normal saline and local antibiotic (ceftazidime).

Discussion

BP which are used in many diseases like osteoporosis, multiple myeloma and metastatic bone diseases are associated with osteonecrosis of jaw particularly involving mandible. Osteonecrosis depends on the concentration and duration of BPs therapy.[20] In Bisphosphonate therapy, osteoclast activity is inhibited, proliferation of cells is decreased, and apoptosis rate is increased and is also leads to the decrease levels of vascular endothelial growth factor (VEGF) which describe its antiangiogenic effect.[21] Ortega et al reported that the Incidence of BRONJ increased from 0.15% to 12% of patients treated with bisphosphonates for osteoporosis.[22] BRONJ was first reported in 2003, recognized a few years after bisphosphonates approval for use.[23] The incidence of BRONJ is increasing because of BPs are highly recommended now a days for the treatment of osteoporosis.

It is seen that IV Bisphosphonate therapy is highly associated with BRONJ than oral Bisphosphonate therapy. Risk factors involved in the development of BRONJ are dento-alveolar trauma, duration of bisphosphonates exposure, and the type of bisphosphonates.[21,23] according to recent retrospective studies. Of these risk factors dentoalveolar trauma is strongly associated with BRONJ. Other associated risk factors are diabetes, positivity for hepatitis B virus, hepatitis C virus, human immunodeficiency virus, smoking, alcohol abuse, obesity, cardiovascular disease, and immunosuppressant therapy.

The signs and symptoms of BRONJ are skin erythema; swelling, altered sensation, tender skin, mobile tooth, ulceration and discharge of pus in advanced cases.[22,23]

In the early stages of osteonecrosis, the radiograph is negative and no significant changes are noted in panoramic and periapical radiograph.[21,24,23] Early or late radiographic changes may mimic osteomyelitis.

The treatment of choice in BRONJ patients are discontinuation of BPs, long term antibiotic combined with surgical debridement (Magopoulos et al).[25] BRONJ should be diagnosed in early stages so the management should be done accordingly and a good prognosis can be achieved.[20]

Oral examination and patient's history are the most effective way to diagnose BRONJ. So, the dentist should know the complication of dental procedures in patients receiving BPs in early stages of the disease.

Conclusion

Patients treated with bisphosphonates should be observed and monitored carefully, so the complications of BPs can be prevented and the BRONJ is managed in early stages of the disease. Special attention should be paid to patients with poor oral hygiene and poor general condition.

Conflict of interest: None

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