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Case Report

Surgical Treatment of Mandibular Stage III Medication-Related Osteonecrosis of the Jaw Combining Buccal Fat Pad and Platelet Rich Fibrin: A Novel Approach

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Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is more common in the mandible than in the maxilla. Since its management is challenging, identifying the proper treatment is important.

Aim: This clinical case report aimed to evaluate the surgical treatment of mandibular stage III medication-related osteonecrosis of the jaw using double-layer closure with platelet rich fibrin (PRF), buccal fat pad, and mucoperiosteal flap.

Patient and Methods: Surgically treated and followed-up mandibular medication-related osteonecrosis case in a patient who had received intravenous bisphosphonates injections for multiple myeloma.

The patient had complete removal of non-vital bone using fluorescence-guided surgery technique followed by meticulous wound closure optimized by fad pad and PRF use.

Results: Complete mucosal healing was achieved. No complications were noticed. Six months later, radiographic reossification signs were observed.

Conclusion: Removal of necrotic bone followed by closure with mucoperiosteal flap is reliable for mandibular medication-related osteonecrosis treatment. Use of PRF and buccal fat pad to optimize soft tissue healing can be effective in exposed bone coverage.

Keywords: *Bisphosphonate-Associated Osteonecrosis Of The Jaw; Mandible; Treatment; Adipose Tissue; Platelet-Rich Fibrin*

Abbreviations

MRONJ: Medication-Related Osteonecrosis of the Jaw; PENT-E: Pentoxifylline /Tocopherol

Introduction

Medication-related osteonecrosis of the jaw (MRONJ), first described by Marx in 2003, is an adverse drug effect associated to antiresorptive treatment especially bisphosphonates intravenous administration for cancer treatment including multiple myeloma or metastatic bone cancer [1]. MRONJ is defined as oral bone exposure or fistula that probes to bone persisting for longer than eight weeks in a patient who has been previously treated with antiresorptive or antiangiogenic agents.

The most common predisposing event is dental extractions. However, cases of spontaneous MRONJ have also been reported explained by recurrent micro trauma associated to altered bone turn over due to osteoclastic inhibition.

In spite of various clinical researches, bisphosphonates-related osteonecrosis of the jaw management is still challenging especially for stage III patients.

Several surgical protocols in addition to tissue repair promoters and adjuvant treatments were proposed. Therefore, the aim of this paper was to present a novel approach in the management of spontaneous stage III MRONJ and to assess the outcomes of double-layer closure with platelet rich fibrin (PRF), free buccal fat pad graft, and mucoperiosteal flap.

Case Presentation

A 44-year-old patient consulted the oral surgery department, Frahat Hached Teaching Hospital Sousse Tunisia with a chief complaint of pain and swelling in the right buccal area.

Medical history revealed antecedent of multiple myeloma management 5 years ago including thalidomide, dexamethasone and 18 zoledronate injections administration in addition to autogenic bone marrow stem cells transplantation. Complete remission was achieved with the absence of cancer recurrence according to his hematologist. Dental screening prior to initiation of antiresorptive therapy had been performed consisting of scaling and root planning, caries treatment and poor long-term prognosis teeth extraction.

On examination: extra oral exam showed face asymmetry with mild swelling in the left mandible, pain and induration on palpation associated to dysesthesia of the lower lip and chin.

Intra oral examination revealed edentulous posterior left mandible, vestibule swelling and productive fistula that probes to bone without bone exposure.

Panoramic radiograph showed large osteolysis in the posterior left region extending to the mandibular canal associated to a 2 cm sequestrum. Homolateral widespread osseous sclerosis was noticed (Figure 1).

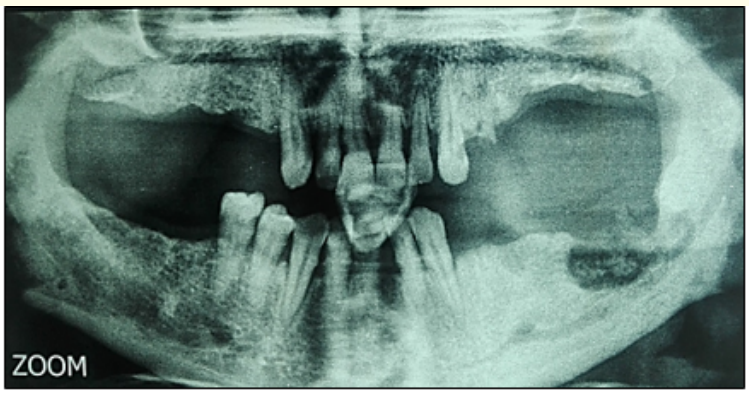

Figure 1: *Panoramic radiograph showing large osteolysis extending to the mandibular canal, a 2 cm sequestrum and homolateral osseous sclerosis.*

These findings were confirmed by the computed tomography (CT scan) revealing generalized thickening of the cortical plate and lamina dura, mixed sclerotic and lytic bone destruction extending beyond the region of alveolar bone and lingual area in addition to encroachment on the mandibular canal.

Based on medical history; clinical and radiographic findings the diagnosis of spontaneous stage III MRONJ was retained according to the Aaoms classification.

Treatment strategy consisted of medical treatment followed by surgical debridement and sequestrectomy.

To manage infection, one-month antibiotics were prescribed based on 2g amoxicillin and 1.5g metronidazole daily. The patient was also placed on 800 mg pentoxifylline and tocopherol 400 mg therapy per day for 8 weeks. Paracetamol and antiseptic mouth rinse were also prescribed.

Biological analyses showed vitamin D deficiency (16ug) treated by vitamin D supplementation.

During control appointments, site irrigation with betadine and saline solution was performed.

One month later we noticed pus discharge resolution, decrease of the swelling and persisting of lower lip dysesthesia.

Nevertheless, surgical intervention is still required. 200 mg per day of tetracycline was taken one week prior to the surgery to permit the fluorescence guided surgery. The patient was operated under local anesthesia.

Surgical steps (Figure 2) consisted of:

- Reflection of full-thickness mucoperiosteal flap revealing granulation tissue under the bony fragment.
- Removal of the sequestrum and necrotic bone basing on tetracycline fluorescence guided surgery and clinical parameters such as color and texture of the bone as well as bone bleeding.
- Bone curettage using piezo inserts with an integrated saline spray to maintain a low temperature and good vision of the surgical site and to avoid the use of an excessive force.
- Sharp bony edges smoothening.
- Use of both combined Platelet rich fibrin (PRF) and free buccal fat pad graft to promote healing: the free buccal fat pad flap has been harvested after incision in the posterolateral region of the maxilla, placed under the PRF membrane and covered by mucoperiosteal flap.
- Tension-free flap fixation with both periosteal and transmucosal sutures to prevent post-operative bone exposure.

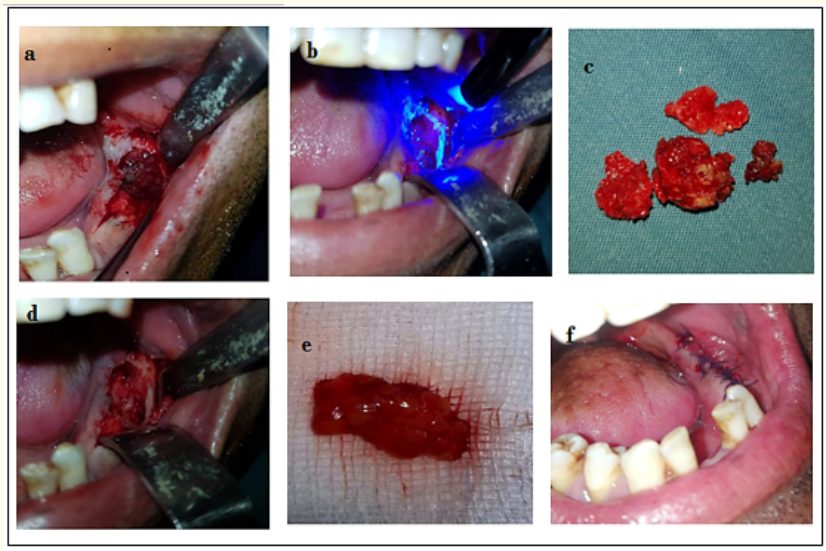

Figure 2: *Surgical steps: (a) Granulation tissue under the bony fragment (b) Tetracycline fluorescence guided surgery to distinguish necrotic and viable bone (c) Removal of the sequestrum and necrotic bone (d) Curettage of the infected site (e) Harvesting of the free fat pad graft (f) Tension-free flap fixation.*

Bone biopsy was taken for histological and microbiological assessment.

After two weeks routine control, complete wound healing, infection and inflammation resolution were achieved without any bone exposure (Figure 3).

At 8-month control, radiologic patterns showed osseous sclerosis regression, site re-ossification without any recurrence signs.

Figure 3: *Complete wound healing without bone exposure.*

Discussion

MRONJ typically develops in patients with cancer who received intravenous antiresorptive medications on a monthly dosing schedule. These injections associated to tooth extraction are the most commonly risk factors for MRONJ. Predisposing vitamin D deficiency has been recently described as an adjuvant risk factor. A survey including multiple myeloma patients revealed that 40% had vitamin D deficiency (36 nmol/L). In fact, an inverse association between serum vitamin D and MRONJ development in cancer patients has been reported [2].

Thus, identifying risk factors at first is crucial for MRONJ prevention and management.

Actually, bisphosphonates-related osteonecrosis of the jaw treatment remains challenging. With the lack of consensus treatment guidelines, different therapeutic approaches have been reported: treatments combination are commonly described such as hyperbaric oxygen (HBO), low level laser therapy bio stimulation, pentoxifylline administration, conservative surgery, extensive surgery with or without fluorescence guidance and platelet rich fibrin (PRF) application

Several studies recommended early and minimally invasive surgical management (debridement and sequestrectomy) throughout all stages of the disease to prevent the possibility of silent disease progression with the risk of large-scale bone loss. A recent cohort study [3] showed that patients who underwent surgery were 28 times more likely to have a positive outcome than patients who had received non operative therapy.

Conservative management might be a good option to preserve symptoms in patients either unwilling to undergo surgery or in those whose reduced general condition does not allow surgery.

Patients with stage I or II disease were more likely to have better outcomes than those with stage III disease.

These last years, tendency for minimally invasive surgery even for stage III MRONJ patients is growing, avoiding large bone resection, complex reconstructions and prosthetic rehabilitation.

Consequently, the use of tetracycline fluorescence guided surgery associated to piezzosurgery is recommended.

Still yet, combining early surgical intervention with adjuvant treatment is an attractive option.

In our case report we associated medical treatment based on long term antibiotics and Pentoxifylline/tocopherol (PENT-E) protocol on the pre-operative phase to tissue repair promoters like PRF membrane and free fat pad graft during the surgery.

Indeed, to guarantee complete healing, preoperative antibiotic treatment should be long term in order to effectively treat neighboring lightly infected bone, whereas surgery removes the irreversibly infected and necrotic bone. In 2011 Sebastian Hoefert., *et al*. [4] conducted a study comparing short- and long-term preoperative antibiotics (3 days versus 32 days). A higher success rate after prolonged preoperative therapy was noticed.

Adding (PENT-E) to the long-term antibiotic treatment is also promising. Very few studies have evaluated the efficacy of (PENT-E) in the management of MRONJ although they have shown its therapeutic benefit in the management of osteoradionecrosis.

Pentoxifylline and tocopherol are easily prescribed. Pentoxifylline may improve peripheral blood flow in MRONJ patients and induces anti-tumor necrosis factor alpha (anti-TNFα) effects. Tocopherol is a potent oxygen radical that reduces free radical damage generated during oxidative stress and protects cell membranes [5].

Hence, this long-term treatment associated to surgery could promote bone healing in MRONG patients.

Still yet complete mucosal wound healing could be promoted by adjuvant treatments.

Our novel surgical approach was based on a double-layer closure combing advantages of both PRF and free buccal fat pad graft.

Promising results with Platelet rich fibrin (PRF) as an adjuvant treatment have been reported. The rationale for its use is the addition of growth factors in suffering environment; it also helps in homeostasis and may have the ability of regulating the inflammation and stimulation of chemotactic agents as well as promoting both bone and soft tissues healing [6].

Free fat pad graft is also an excellent alternative to avoid post-operative bone dehiscence and handle soft tissue defect in MRONJ patients with consequent bone loss.

The use of fat pad graft has been widely reported in maxillofacial surgery and aesthetic medicine and its application is well documented.

However, few studies have been published concerning its use in MRONJ treatment. Some studies described pediculate fat pad for oro-antral communications in stage III maxillary MRONJ, but to our knowledge free fat pad grafts for mandibular MRONJ treatment haven't been reported yet.

To support our surgical approach, the buccal fat pad use as a free graft for intraoral defects has been a common procedure since its first publication in 1977 and the outcomes have been encouraging. Moreover, the free buccal fat pad can survive and heal very well even in the absence of blood supply [7]. Compared to muscle free flaps, harvesting of the graft from the buccal fat pad is a simple procedure with minor postoperative complications. In fact, the body and the buccal extension are easily accessible from the oral cavity.

Success of buccal fat pad graft has been attributed to its rich vascular supply, minor donor site morbidity, and the fast epithelialization during 3 - 6 weeks [8]. Low complications rate has been reported including distant dehiscence, necrosis, and mouth opening limitation.

The main healing mechanism of free fat grafts is by fibrosis epithelialization beginning at the 2nd week. The epithelium grew from borders at the graft interface. The fibrosis healing nature may transform thin tissue biotype to thicker biotype and improves the soft tissue quality and volume of the altered recipient site preventing bone exposure. Buccal fat pad also contains stem cells which can differentiate into different cell types promoting bone tissue healing [9].

Therefore, combining free fat pad graft to PRF is a reliable technique with promising results. Medical adjuvant treatment based on pentoxifylline and tocopherol therapy as well as vitamin D supplementation might enhance post-operative outcomes.

Still yet, only randomized clinical trials with a large sample size can evaluate the real impact of these techniques. Unfortunately, these studies are still lacking due to the rarity of this disease.

Conclusion

Bone curettage with total necrotic bone removal and tissue repair promoters including PRF and free fad pad graft as well as adjuvant medical treatment represent a new and innovative approach for MRONJ management that may allow less invasive surgical procedure with more comfortable postoperative recoveries.

Conflict of Interest

No conflict of interest.

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