J. Oral Diag. 2020;06:e20210005.

CASE REPORT

Surgical management combined with leukocyte and platelet rich fibrin (L-PRF) concentrate in the medication-related osteonecrosis of the jaws treatment - case report

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Abstract:

Medication-related osteonecrosis of the jaws (MRONJ) is described as an area of non-healing necrotic bone in the maxillofacial region for more than an eight-week period in patients who have received antiresorptive or antiangiogenic agents treatment, with no history of radiotherapy or metastatic disease to the jaws. A 68-year old woman medicated with oral sodium alendronate for a five-year period treating osteoporosis, presented with a painful necrotic bone exposure in the right mandible area close to the first premolar. Panoramic radiography revealed the presence of osteosclerosis and osteolysis in the area. Clinical and radiographic diagnosis was of MRONJ and antibiotic and analgesic therapy were prescribed before the surgery. Under general anesthesia, it was performed the necrotic bone curettage and use of peripheral ostectomy with a round burr in order to achieve bleeding-bone prior to the application of L-PRF membranes in the site. A two-year follow-up showed mucosa healing and at panoramic radiograph, no signs of sequestrum could be observed and no symptoms. Patient remain in clinical and radiographic follow-up with no recurrence. Therefore, the adjuvant therapy using L-PRF membranes is effective in many cases of MRONJ and should be considered as a therapeutic alternative.

Keywords: Osteonecrosis; Platelet-Rich Fibrin; Alendronate; Combined Modality Therapy

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Article received on April 8, 2021.
Article accepted on June 17, 2021.

DOI: 10.5935/2525-5711.20210005

1. INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) is described as an area of non-healing necrotic bone in the maxillofacial region for more than an eight-week period in patients who have received antiresorptive or antiangiogenic agents treatment, with no history of radiotherapy or metastatic disease to the jaws[1,2,3].

Bisphosphonates (BPs) are a class of drugs frequently prescribed in the treatment of several diseases causing bone resorption such as Paget's disease, osteoporosis and hypercalcemia associated with malignancy conditions. BPs mechanism of action consist of limiting osteoclastic activity and, therefore inhibiting bone resorption, besides exerting an antiangiogenic effect, which justify their use as an antineoplastic therapy[1-4].

MRONJ management should firstly focus on its prevention - including dental and adnexal structures evaluation before initiating the drug therapy using BPs or antiangiogenic agents, in order to reduce local risk factors such as periodontal disease or periapical pathology[1]. Whenever MRONJ can not be prevented, its management aims on controlling pain, infection and stabilizing the disease progression with necrotic bone removal and closure of the surgical site with the least traumatic method as possible. However, different approaches have been recommended in the literature, including the surgical removal of the necrotic bone through sequestrectomy and resection - despite the controversial discussion whether surgery could aggravate the necrotic condition due to local trauma - and less invasive modalities such as long-term antibiotic therapy, oral disinfectant mouthwashes, laser therapy, hyperbaric oxygen, ozone therapy and platelet concentrates[1-5].

The leukocyte and platelet rich fibrin concentrate (L-PRF) is a promising method on the MRONJ treatment as this physiological autogenous material induces healing acceleration and reduction of the contamination, edema and postoperative pain due to the release of growth factors in the receptor area. Furthermore, it favors homeostasis and soft and hard tissues remodeling and healing, whereas it eliminates the possibility of transmission of parenteral diseases, allergies or rejection immune reactions, once that it is collected from the patient's own blood[5,6].

Therefore, we report a successful case of MRONJ on a 68-year-old woman treated surgically with the adjuvant use of L-PRF and a two-year follow-up.

2. CASE REPORT

A 68-year-old woman was referred for evaluation of an one-year lasting painful mandibular bone exposure on the lower right premolar site with no history of local trauma, tooth extraction or tissue manipulation within this period. Medical history included the diagnosis of rheumatoid arthritis and osteoporosis - which was managed with oral sodium alendronate (suspended 6-months prior to consultation) for approximately a five-year period. The patient denied any tobacco or alcohol consumption. Extraoral clinical examination showed no alterations. Intraoral clinical examination revealed the presence of a circumscribed area of exposed necrotic bone on the alveolar region of the lower right premolar. There were no signs of spontaneous bleeding or suppuration (Fig. 1A). The panoramic radiography showed diffuse sclerosis of the alveolar bone and alveolar ridge sequestrum of the right mandibular bone area (Fig. 1B). Clinical and radiological diagnosis was of medication-related osteonecrosis of the jaw (MRONJ) Stage II, according to *Ruggiero et al.*[1], and antibiotic therapy with Amoxicillin/clavulanate (875 mg) in conjunction with Paracetamol (750 mg) and Nimesulide (100 mg), as well as mouth rinses (0.12% chlorhexidine gluconate) were

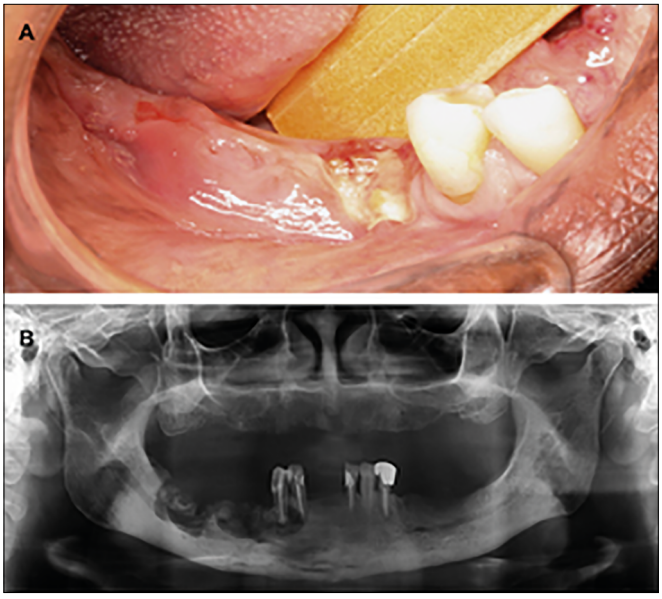

Figure 1. A - MRONJ clinical features showing an asymptomatic area of exposed necrotic bone on the alveolar region of the lower right premolar with no spontaneous bleeding or signs of infection. B - Initial panoramic radiography revealed the presence of diffuse sclerosis and sequestrum on the right mandibular body.

started preoperatively. Surgical treatment - under general anesthesia - included curettage of the necrotic bone and ostectomy with a round burr until vital bleeding-bone and rounded margins were achieved, with intensive saline solution irrigation to remove debris and clots, thereon the application of leucocyte-rich and platelet-rich fibrin (L-PRF) membranes and primary closure with absorbable sutures were performed (Fig. 2). Intravenous blood retrieval was performed prior to anesthetic induction in order to prevent its contamination with any type of drugs. Patient recovery was uneventful, and an immediate postoperative computed tomography showed no sequestrum and rounded margins of the mandibular bone (Figure 3A). The patient remained in clinical and radiological follow-up and there were no signs of local recurrence in a two-year follow-up (Figure 3B).

3. DISCUSSION

Medication-related osteonecrosis of the jaws has a slight predilection for adult females and rarely occurs in the pediatric population. The most common anatomical location for MRONJ is the mandible due its reduced vascularization compared to maxilla, and it presents as an area of exposed necrotic bone showing no healing progress over an eight-week period, and may occur spontaneously or induced by tooth extraction, local trauma,

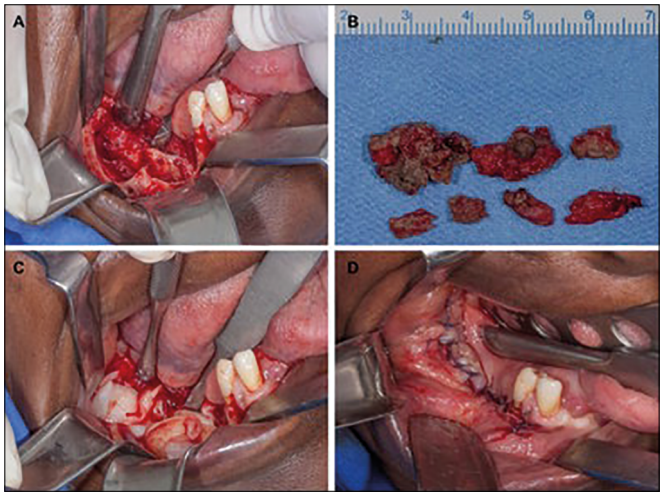

Figure 2. MRONJ surgical treatment with adjuvant use of leucocyte-rich and platelet-rich fi-brin. A - Surgery site after the resection of the necrotic bone and the use of a rotary in-strument in order to achieve vital bleeding bone and rounded margins of the right mandibu-lar bone. B - Seven fragments of necrotic bone were removed during surgery. C - L-PRF membranes placement - for its obtaining, approximately 60 mL of blood was collected in a 10 mL tube with no anticoagulant agent previously to the administration of IV medication and anesthesic induction. The samples were centrifuged at 2700 rpm for 12 minutes. D - Primary closure with absorbable sutures.

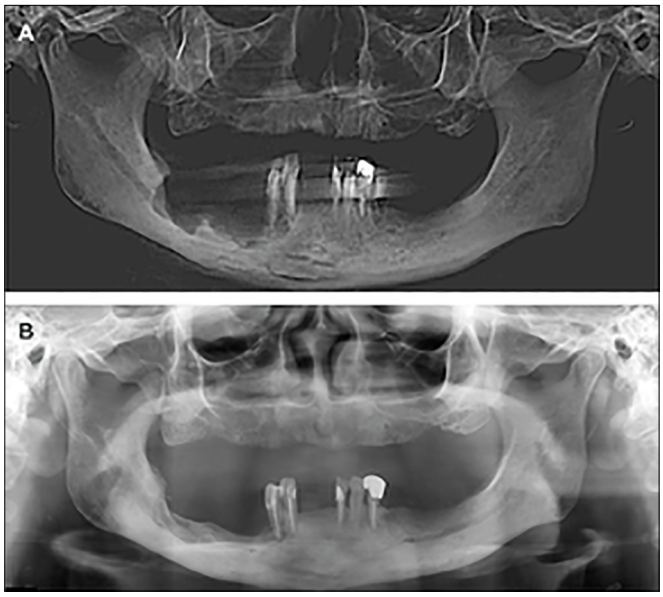

Figure 3. A- Panoramic reconstruction from an immediate post-surgery computed tomography showed the presence of regulated bone margins and no fragments of necrotic bone in the right mandible body. B - At a two-year panoramic radiograph follow-up, sclerosis of the mandibular bone – neoformed bone – with no signs of osteolysis or sequestrum could be observed.

poor oral hygiene, actinomyces infections and tissue manipulation[1-6]. Patients receiving oral BPs such as alendronate, for osteoporosis also are at risk for developing MRONJ, especially when the duration of the therapy is longer than four years, however, it seems less-likely to occur than those treated with IV antiresorptive therapy[1].

MRONJ stages suggested by Ruggiero *et al.*[1] divided the disease into 4 stages according to their clinical presentation - in which each subsequent stage shows worsening in the course of the disease, thus defining their indicated treatment. Nevertheless, clinical features of each stage should not be confounded and therefore, misdiagnosed with other diseases such as alveolar osteitis, sinusitis, gingivitis and periodontitis, caries, periapical pathology, odontalgia, atypical neuralgias, fibro-osseous lesions, sarcoma, chronic sclerosing osteomyelitis, and temporomandibular joint disorders[1-5]. Thereby, it is important to be aware of the patient's systemic conditions, medications in-use as well as the clinical and radiographic signs in order to establish MRONJ diagnosis.

The present case reports a stage II medication-related osteonecrosis of the jaws, which features an exposed and necrotic bone with painful symptoms, occurring spontaneously on the right lower premolar region in an elderly woman - who was prescribed oral alendronate for osteoporosis treatment over a five-year

period. Despite the fact that dental extraction stands as the procedure at higher risk of developing MRONJ followed by dental implant installation, the disease is also reported to occur as an spontaneous act in fewer cases[7].

The promising treatment using L-PRF on the management of MRONJ should be considered as a novel and non-invasive therapeutic option, especially because there is currently no consensus regarding the correct approach to this condition[6]. L-PRF - a three-dimensional fibrin scaffold obtained from blood puncture and centrifugation contains growth factors - platelet-derived growth factor, epidermal growth factor, transforming growth factor-beta, vascular endothelial growth factor – released for at least a seven-day period. These factors accelerate cell proliferation and bone healing, playing an important role in stabilizing the progression of osteonecrosis[7]. The study performed by Kim *et al.*[8] demonstrated the effectiveness of L-PRF on the MRONJ treatment, similar to the present case, as the disease was more frequently observed in women (n= 34) diagnosed with osteoporosis (n= 31), in use of Alendronate (n= 19) and the mandible was mostly affected (n= 22) with few cases occurring as a spontaneous act (n = 5). Furthermore, stage II was the most prevalent (n = 18) and all patients, prior to the application of L-PRF, underwent antibiotic and analgesic treatment and thorough oral hygiene, surgical debridement, as well as a sequestrectomy and ostectomy until a bleeding-bone bed was obtained. The treatment resulted in the complete remission in 77% (n= 26), partial remission in 18% (n= 6) and accounted for only 2 cases with no resolution - both were being treated with Zoledronate and had received chemotherapy.

In addition, the study conducted by Park *et al.*[9], 25 patients were treated using L-PRF and the same profile could be observed as the previous study by Kim *et al.*[8] and the present case - stage II (88%) MRONJ mostly occurring in the mandible (60%) of females (88%) with osteoporosis (88%), medicated with Alendronate (60%) and few cases happening spontaneously (20%). However, full resolution of the therapy using L-PRF was only achieved in 36%, with most cases showing partial remission of the lesion (52%).

Healing criteria suggested after MRONJ treatment include mucosal coverage, signs of infection/inflammation, symptoms/pain and radiographic signs in the bone observed in orthopantomography or computed tomography[10]. In the present case, after a two-year follow-up, the patient did not complain about pain, clinically there were no signs of bone exposure and a panoramic radiography revealed osteosclerosis of the mandible, but with no sequestrum or progression of the necrotic process.

4. CONCLUSION

Patients in use of bisphosphonates or antiangiogenic agents are at risk of developing MRONJ. This risk is higher in females diagnosed with osteoporosis medicated with Alendronate for more than a four-year period, with most lesions located in the mandible, not unusually happening spontaneously. The adjuvant therapy using L-PRF membranes is effective in many cases and can therefore be considered as a therapeutic alternative.

ETHICS

We state that we have followed the Helsinki declaration and that written permission was obtained from the patient included in the present report.

CONFLICTS OF INTEREST

None.

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