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CASE REPORT

The role of fibrin rich platelets and leukocytes (L-PRF) in the medication-related osteonecrosis of the jaw: report of premaxilla necrosis

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Abstract:

Bisphosphonates (BPs), antiresorptive and antiangiogenic drugs are used to prevent metastatic bone cancers in prostate cancer, breast cancer and multiple myeloma and to treat osteoporosis and Paget's disease. Recently, in 2003 the first case of osteonecrosis of the jaws was induced, hitherto by bisphosphonates, but a few years later it was shown that other medications were also responsible for the development of this type of necrosis. Thus, in 2014 there was a change in the name for medication-related osteonecrosis of the jaws (MRONJ). Since then, the treatment for this type of necrosis is quite controversial in the world literature, and there is still no protocol for established treatment, be it clinical or surgical. The objective of this work is to demonstrate the efficacy of platelet and leukocyte-rich fibrin membranes (L-PRF) after curettage of necrotic bone tissue in the management of drug-related jaw osteonecrosis, since they have innumerable biological benefits such as large amount of growth factors and cytokines, hemostatic capacity, angiogenesis capacity, and has been shown to accelerate and improve results in hard and soft tissue wound healing. The patient presented MRONJ and have been treated with surgical necrotic bone debridement, placement of L-PRF in the affected site and primary closure. Patient were followed up clinically and radiographically until total mucosal coverage of the necrotic bone was achieved.

Keywords: Platelet-Rich Fibrin; Multiple Myeloma, Diphophosnates, Osteonecrosis, Maxilla.

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INTRODUCTION

Medication-related osteonecrosis of the Jaw (MRONJ) is a severe adverse drug reaction, consisting of progressive bone destruction in the maxillofacial region of patients being a side effects of the antiresorptive and antiangiogenic therapies[1]. Was first reported in 2003 after intravenous administration of zoledronate and pamidronate in patients with multiple myeloma and metastatic breast cancer[2].

The major cause of MRONJ occur is related to tooth extraction. However, in most cases it is not clear if the tooth extraction causes development of MRONJ. Nowadays it is proven that periodontitis and mucosal lesions such as pressure marks, smoking, and corticoids also represent risk factors[3].

The clinical manifestations of MRONJ has been classified by AAOMS since 2009 and has been modified in 2014. To be considered to have MRONJ the patients must present the following clinical characteristics: Current or previous treatment with antiresorptive or antiangiogenic agents; Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws[4].

The complex topic of management of this condition will depend on stage of the necrosis and patient's symptoms. There are no definitive guidelines as to how we should approach management of MRONJ. What we know is that non-surgical therapy is employed in mild disease or symptoms (prevention infection and symptom control). Surgical therapy on the other hand, is reserved for larger, more painful, progressive and infected areas of necrosis and where conservative management has failed[5].

Because of this, new alternative therapies has emerged, such as the use of laser therapy, hyperbaric oxygen, ozone therapy and platelet concentrates, being this last technique one of the newest and promising treatments for the management of MRONJ[6]. The Fibrin rich Platelets and Leukocytes (L-PRF) is a second-generation of autologous growth factors, wich encourages healing and is proposed to be associated with effective and early organization of bone substance and bone volume percentage. Moreover, L-PRF is a platelet concentrate with leukocytes in dense fibrin matrix, wich can be conveniently prepared from autogenous non anti-coagulated blood when centrifuged[7].

CASE REPORT

64-year-old male patient was referred to Department of Oral and Maxillofacial Surgery of the Erasto Gaertner Hospital with complaints of bone exposure in the premaxilla wich arrised after tooth extraction (Figure 1). Medical history showed that patient uses intravenous Zoledronic Acid (Zometa®) once a month due multiple myeloma since February 2017 and had teeth extractions five months before referring to our service. Computed Tomography (CT) examination revealed a poorly defined hypodensity area in the pre-maxilla region (Figure 2). With the help of anamnesis, clinical and CT examinations, MRONJ diagnosis was made wich caused by the treatment of multiple myeloma with

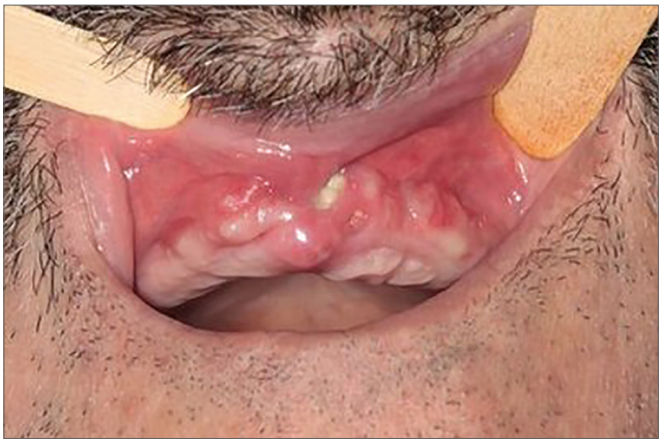

Figure 1. Maxillary osteonecrosis in a patient with multiple myeloma treated with Zometa® (Zoledronic Acid).

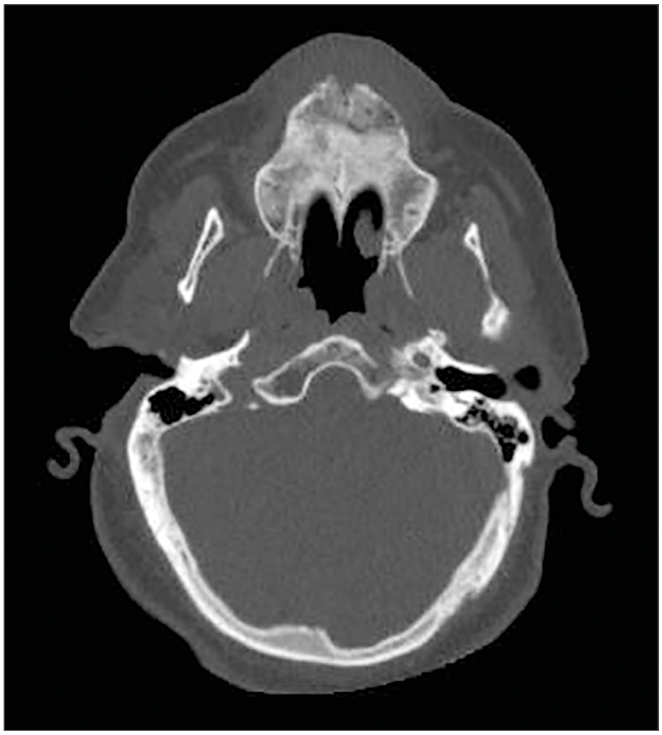

Figure 2. Computed tomography (CT) examination revealed osteonecrosis in the premaxil-lary region, with an ill-define hypodensity area.

zoledronic acid. As a medical treatment, mouthwash (0.12% Clorhexidine Gluconate) with a combination of Pentoxifylline and Tocopherol. Oral Clindamycin started as soon as the diagnosis was made advised for at least two weeks.

After consultations and consents, the patient was planned to undergo general anesthesia and L-PRF application after the lesion debridement. A large mucoperiosteal flap was elevated in the exposing bone tissue area. The area of the large necrosis was excised till a firm bone surface was left (Figure 3) and the application of L-PRF obtained from patient's blood that drawed preoperatively followed by primer wound closure (Figure 4). To prepare the L-PRF, 80mL of peripheral blood was collected from the antecubital vein into a 10 mL glass tube with no anticoagulant, and the blood samples were centrifuged at 2700rpm for 12 minutes. After centrifugation, 8 pieces of L-PRF were obtained from the middle of the tube (Figure 5). All membranes were arranged in layers covering the entire surgical bone bed (Figure 6). No suture removal was performed due to the use of absorbable suture and the Pentoxifylline and Tocopherol were not discontinued after surgical procedure. One month after the operation, it was determined that the mucosa in the area where osteonecrosis used to present was healthy but a small tissue dehiscence was observed, so follow-up period begun with monthly controls. Clinical and CT scans at the postoperative 2 years follow-up revealed healthy tissue, tissue dehiscence resolution (Figure 7 and 8) and patient's symptoms had passed. After that, the patient maintains semi-annual follow-ups.

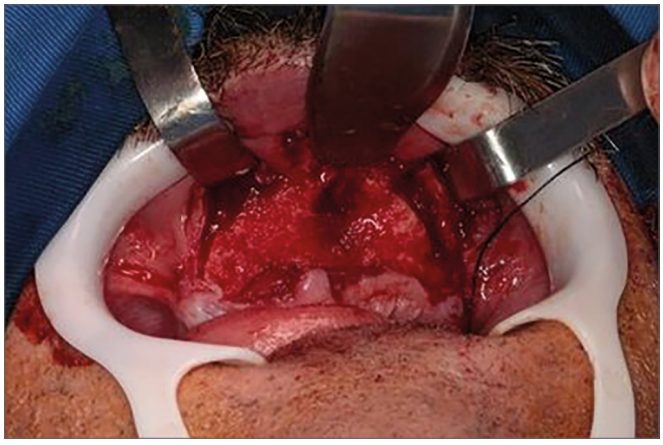

Figure 3. Surgical bed after curettage of necrotic bone with removal of anterior nasal spine.

Figure 4. PRF membrane after compression by using PRF box.

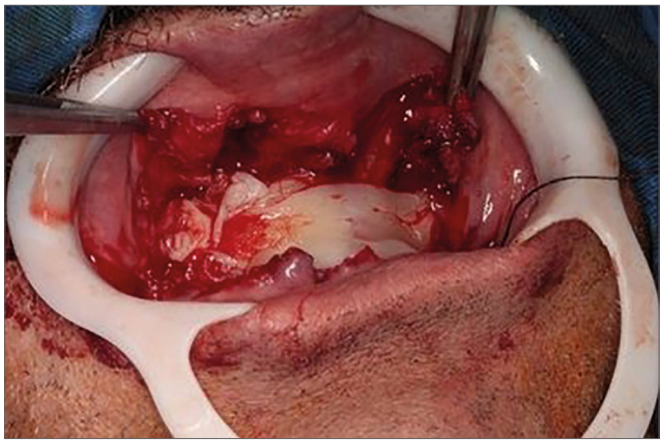

Figure 5. Application of fibrin rich in leukocytes and rich in platelets on the surgical bone bed.

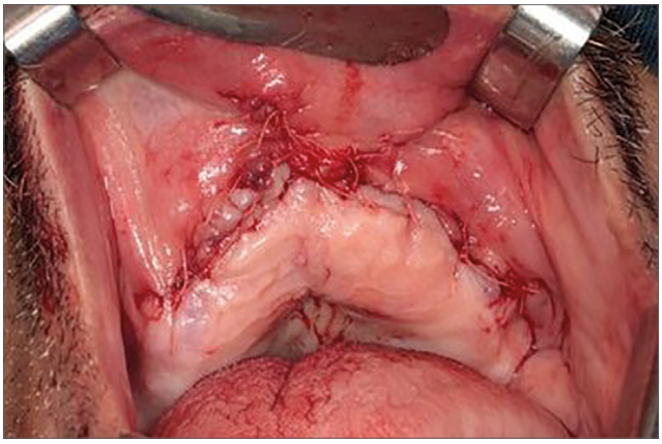

Figure 6. Immediate post-operative after closure with use of absorbable suture.

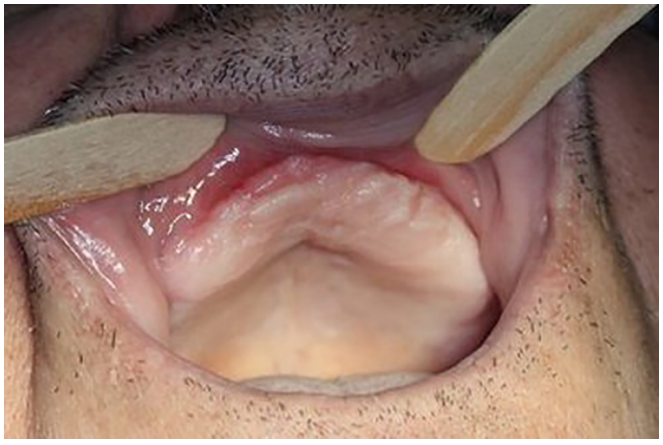

Figure 7. Post-operative with the formation of healthy tissue.

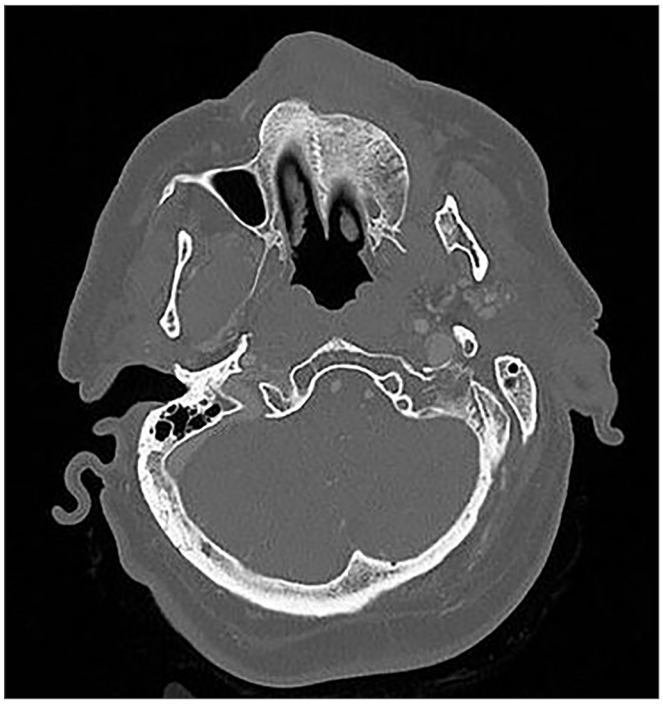

Figure 8. Computed Tomography (CT) of the patient showed the regeneration of the necrotic bone in 24 months follow-up.

DISCUSSION

Biphosphonates are currently the main class of medications used to treat osteoporosis and other diseases characterized by increased bone resorption[8]. Acting through two mechanisms of action related to antiosteoclastic and antiangiogenic activity alter the mechanism of bone tissue in several levels, inhibiting reabsorption and decreasing bone turnover[9,10,11,12]. Other drugs class has been utilized with similar indications than bisphosphonates, the monoclonal antibodies. Neutralizing the receptor activator of nuclear factor κB ligand (RANKL), a member of tumor necrosis factor receptor superfamily. This factor is produced by osteoblasts and activates the RANK receptor on osteoclast precursor cells and osteoclasts. The RANKL-RANK signaling pathway is essential for the differentiation, function, and survival of osteoclasts[13,14].

Nowadays the MRONJ staging is based on the Classification proposed by The American Association of Oral and Maxillofacial Surgeons (AAOMS) as showed in the Table 1 and its treatment still controversial because surgical procedures may induce disease progression and there is no a consensus regarding the best treatment[12,15,16,17,18,19].

Platelet-rich fibrin (L-PRF) for specific use in oral and maxillofacial surgery was first developed in France by Choukroun et al. L-PRF is a new generation of platelet concentrates that is not only inexpensive and autologous, but also does not require any biochemical modifications compared to other platelet concentrations. Act as a bioactive surgical additive to regulate inflammation, reduce the healing time and stimulation of chemostactic agents[5,6,15,20,21].

These concentrates allows the release of growth factors over a prolonged time (about 28 days), resulting in an acceleration in healing, reducing the risk of contamination, edema and postoperative pain, it helps in homeostasis, prevents tissue dehiscence and favors the remodeling and healing of both soft and hard tissues, increase tissue vascularization, overtaking one of the major factors in pathogenesis of MRONJ, the lack of vascularization. For these reasons, some researches propose applying L-PRF as a preventive measure in surgical interventions or as a treatment for cases of established MRONJ[6,12,18,19,22,23,24,25,26].

Dinca et al. performed removal of the bone sequestrations and curettage in the bone tissue until clear bleeding appeared from the subjacent bone. After that, bone cavities were filled out with L-PRF clots. No postoperative complications were observed and all the 10 patients were treated successfully without evidence of exposed bone.

CONCLUSION

The combined sequestrectomy and L-PRF has shown potential and good results for MRONJ healing but better communication from the prescribing physician to the dental surgeon is necessary to establish orientation and preventive treatment before initiation of the therapy with bisphosphonates or monoclonal antibodies.

Table 1. Staging and treatment strategies of BRONJ according to AAOMS[4].

Staging of BRONJ		Treatment modalities
Stage 0	No clinical evidence of necrotic bone, but non-specific clinical findings, radiographic changes, and symptoms	Systemic management, including the use of pain medication and antibiotics
Stage 1	Exposed and necrotic bone, or fistulae that probes to bone, in patients who are asymptomatic and have no evidence of infection	-Antibacterial mouth rinse -Clinical follow-up on a quarterly basis -Patient education and review of indica-tions for continued bisphosphonate therapy
Stage 2	Exposed and necrotic bone, or fistulae that probes to bone, associated with infection as evidenced by pain and erythema	-Symptomatic treatment with oral antibiotics -Oral antibacterial mouth rinse -Pain control -Debridement to relieve soft tissue irritation and infection control
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/nasal communication, or osteolysis extending to the inferior border of the mandible or sinus floor	-Antibacterial mouth rinse -Antibiotic therapy and pain control -Surgical debridement/resection for longer term palliation of infection and pain

Furthermore the L-PRF is encouraging results and open a new path in the treatment of this pathology.

REFERENCES

1. Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: clinical and practical guidelines. J Int Soc Prev Community Dent. 2016 Mar/Apr;6(2):97-104.
2. Poxleitner P, Engelhardt M, Schmelzeisen R, Voss P. The prevention of medication-related osteonecrosis of the jaw. Dtsch Arztebl Int. 2017 Feb;114(5):63-9.
3. Voss PJ, Poxleitner P, Schmelzeisen R, Stricker A. Semper-Hogg W. Update MRONJ and perspectives of its treatment. J Stomatol Oral Maxillofac Surg. 2017 Sep;118(4):232-5.
4. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw—2014 update. J Oral Maxillofac Surg. 2014 Oct;72(10):1938-56.
5. Bilimoria R, Young H, Patel D, Kwok J. The role of piezoelectric surgery and platelet-rich fibrin in treatment of ORN and MRONJ: a clinical case series. Oral Surg. 2018 Oct;11(2):136-43.
6. Cano-Durán JA, Peña-Cardelles JF, Ortega-Concepción D, Paredes-Rodríguez VM, García-Riart M, López-Quiles J. The role of Leucocyte-rich and platelet-rich fibrin (L-PRF) in the treatment of the medication-related osteonecrosis of the jaws (MRONJ). J Clin Exp Dent. 2017 Aug;9(8):e1051-e9.
7. Alzahrani AA, Murriky A, Shafik S. Influence of platelet rich fibrin on post-extraction socket healing: a clinical and radiographic study. Saudi Dental J. 2017 Oct;29(4):149-55.
8. Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. Osteoporos Int. 2008 Jun;19(6):733-59.
9. Brozoski MA, Traina AA, Deboni MCZ, Marques MM, Naclério-Homem MDG. Bisphosphonate-related osteonecrosis of the jaw. Rev Bras Reumatol. 2012 Mar/Apr;52(2):265-70.
10. Otto S, Kwon TG, Assaf AT. Definition, clinical features and staging of medication-related osteonecrosis of the jaw. In: Otto S, ed. Medication-related osteonecrosis of the jaws. Berlin: Springer; 2015. p. 43-54.
11. Aghaloo T, Hazboun R, Tetradis S. Pathophysiology of osteonecrosis of the jaws. Oral Maxillofac Surg Clin North Am. 2015 Nov;27(4):489-96.
12. Acikan İ, Aslan N, Durmuş H, Atalay Y, Atılgan S, Yaman F. Surgical treatment of bisphosphonate-associated osteonecrosis of the mandible: report of two cases. J Clin Exp Invest. 2015;6(1):61-4.
13. Then C, Von Tresckow E, Bartl R, Oduncu FS. Bisphosphonate and denosumab therapy: fields of application. In: Otto S, ed. Medication-related osteonecrosis of the jaws. Berlin: Springer; 2015. p. 17-26.
14. Maluf G, Pinho MCD, Cunha SRB, Santos PSS, Fregnani ER. Surgery combined with LPRF in denosumab osteonecrosis of the jaw: case report. Braz Dent J. 2016 May/Jun;27(3):353-8.
15. Gönen ZB, Asan CY. Treatment of bisphosphonate-related osteonecrosis of the jaw using platelet-rich fibrin. Cranio. 2017 Sep;35(5):332-6.
16. Coropciuc RG, Grisar K, Aerden T, Schol M, Schoenaers J, Politis C. Medication-related osteonecrosis of the jaw in oncological patients with skeletal metastases: conservative treatment is effective up to stage 2. Br J Oral Maxillofac Surg. 2017 Oct;55(8):787-92.

17. Del Fabbro M, Gallesio G, Mozzati M. Autologous platelet concentrates for bisphosphonate-related osteonecrosis of the jaw treatment and prevention. A systematic review of the literature. Eur J Cancer. 2015 Jan;51(1):62-74.
18. Longo F, Guida A, Aversa C, Pavone E, Di Costanzo G, Ramaglia L, et al. Platelet rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw: personal experience and review of the literature. Int J Dent. 2014;2014:298945.
19. Lopez-Jornet P, Perez AS, Mendes RA, Tobias A. Medication-related osteonecrosis of the jaw: is autologous platelet concentrate application effective for prevention and treatment? A systematic review. J Craniomaxillofac Surg. 2016 Aug;44(8):1067-72.
20. Dohan DM, Choukroun J, Diss A, Dohan SL, Dohan AJ, Mouhyi J, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006 Mar;101(3):e37-e44.
21. Bastami F, Khojasteh A. Use of leukocyte-and platelet-rich fibrin for bone regeneration: a systematic review. Regen Reconstr Rest. 2016 Apr;1(2):47-68.
22. Zumstein M, Berger S, Schober M, Boileau P, Nyffeler R, Horn M, et al. Leukocyte-and platelet-rich fibrin (L-PRF) for long-term delivery of growth factor in rotator cuff repair: review, preliminary results and future directions. Curr Pharm Biotechnol. 2012 Jun;13(7):1196-206.
23. Faot F, Deprez S, Vandamme K, Camargos GV, Pinto N, Wouters J, et al. The effect of L-PRF membranes on bone healing in rabbit tibiae bone defects: micro-CT and biomarker results. Sci Rep. 2017 Apr;7:46452.
24. Hartshorne J, Gluckman H. A comprehensive clinical review of Platelet Rich Fibrin (PRF) and its role in promoting tissue healing and regeneration in dentistry. Int Dent S Afr. 2016;6(5):14-24.
25. Kim JW, Kim SJ, Kim MR. Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study. Br J Oral Maxillofac Surg. 2014 Nov;52(9):854-9.
26. Dinca O, Zurac S, Staniceanu F, Bucur MB, Bodnar DC, Vladan C. Clinical and histopathological studies using fibrin-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw. Rom J Morphol Embryol. 2014;55(3):961-4.