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Treatment of Biphosphonate-Related Osteonecrosis of the Jaw (BRONJ) Combining Surgical Resection and PRGF-Endoret® and Rehabilitation with Dental Implants: Case Report

SUMMARY

***Background**: The first cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were reported in 2003. Since then number of possible treatments have been proposed. **Case report**: We report a case of a 50-year-old patient with bisphosphonate-related osteonecrosis of the jaw (BRONJ). The treatment included resection of necrotic bone and the application of plasma rich in growth factors (PRGF®-Endoret®). We closed the ulcer in the soft tissue and the treated bone was regenerated one year later. Finally the regenerated area was rehabilitated with dental implants. **Conclusion**: Resection followed by PRGF® -Endoret® was successful in promoting closure of the wound and the recovery of nerve function.*

Key words: Bisphosponates-Related Osteonecrosis (BRONJ), Medicament-Related Osteonecorosis (MRONJ), Nerve Injury, Platelet Rich Plasma, PRGF

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CASE REPORT (CR)
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Introduction

The first cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were reported in 2003[1]. A number of possible mechanisms of treatments have been proposed[2], including immunomodulation, infection, excessive reduction in bone turnover, impaired angiogenesis, and direct toxicity to soft tissue and bone[3,4].

We report the management of a patient with BRONJ. In addition to resection we used plasma rich in growth factors (PRGF®-Endoret®) because of its potential to stimulate healing of gingival ulceration and wound closure. The treated bone was regenerated one year later and dental implants were placed in the regenerated bone. No bone loss or negative effects were reported regarding the dental implants.

Case report

In 2010 a 50-year-old patient attended the Clinic with an ulceronecrotising lesion that affected the soft and hard tissue of the fourth quadrant, associated with the extraction of lower right first molar with history of treatment with intravenous bisphosphonates (zoledronate) for the breast cancer and with the presumptive diagnosis of medicament-related osteonecrosis of the jaw (MRONJ) due to bisphosphonates.

In April 2008, the lesion was treated in a hospital with a conservative treatment consisting of chlorhexidine mouthwashes, systemic antibiotics and hyperbaric oxygen until December 2009, without obtaining positive results at any time. During this time the patient developed constant acute pain in the area and hemimandibular paraesthesia (due to the affection of the inferior alveolar nerve). The patient also reported loss of sensation in the lower lip (Figure 1).

In March 2010, the patient attended the clinic. After clinical and radiographical evaluation the lesion was in stage 2 according to the classification of the American Association of Oral and Maxillofacial Surgeons (AAOMS). Once the case had been studied and the poor response to conventional treatment, the lesion was treated with Endoret (PRGF). To do so, the necrotic

bone fragments were excised paying the attention not to cause any trauma to the surrounding hard and soft tissues. For this reason, ultrasonic surgery was used for the excision of necrotic bone. In the same intervention the tooth in position 45 was extracted due to high degree of mobility. Once excised, a recently formed clot of Endoret (PRGF) was placed, prepared from fraction 2 in the bone socket and covered it with fibrin membranes (fraction 1 coagulated and retracted). Finally, a primary closure of the edges was performed with 5/0 monofilament and some PTFE 5/0 stitches in the area where the tissue was in poorer conditions, in order not to elongate the flap and cause the dehiscence of the sutures. To finish, the edges of the surgical wound were infiltrated with recently activated PRGF fraction 2 (liquid) (Figure 2).

Figure 1. (A) Pre-operative panoramic radiograph showing the presence of necrotic bone at the site of tooth extraction (lower right first molar), although it does not provide information on its extent. (B) Intraoral appearance of the lesion at the time of examination where we can see a large amountof necrotic bone exposed to the oral medium. (C) Cone-beam computerised tomography (CBCT) showing the lesion to extend apically up to the inferior dental nerve canal indicated with a pink dot in the image.

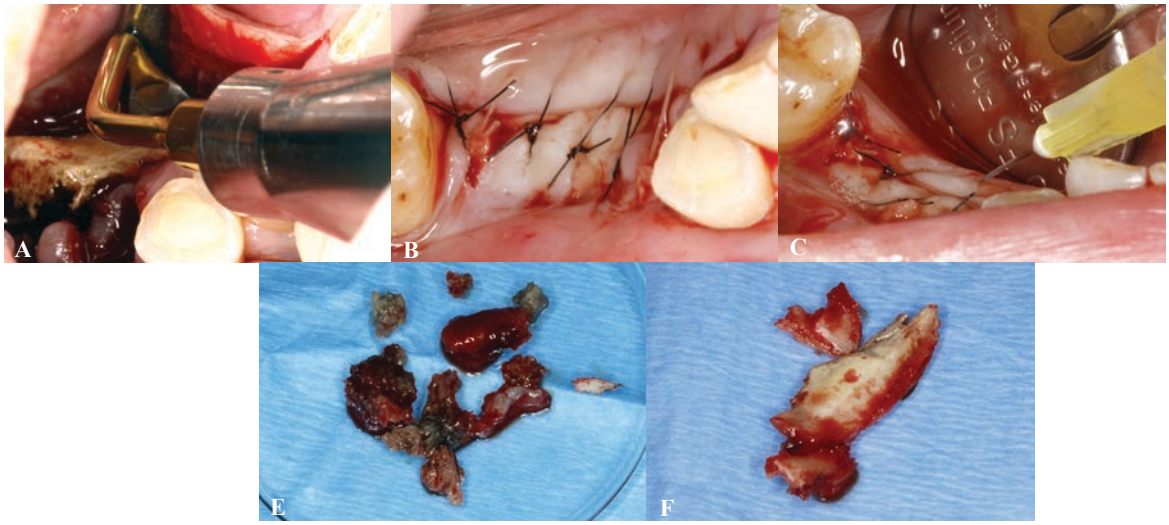

Figure 2. (A) Excision of necrotic bone with ultrasound surgery. (B) Primary closure of the surgical wound after the placement of Endoret (PRGF). (C) After this the incision margins were infiltrated with Endoret (PRGF) liquid (fraction 2 recently activated). (D) Soft tissue fragments that surrounded the bone sequestrum. (E) Bone fragments of necrotic tissue after the excision.

The bone fragments, once excised, were referred for the histopathological report and to confirm the presence of bisphosphonate-related osteonecrosis of the jaw (BRONJ). The patient was then followed up once a week.

Signs of epithelization at the surgical margins were observed. The suture that had lost tension was removed and another recently formed clot of Endoret (PRGF) fraction 2 was placed in the wound without any surgical manipulation of the site. Sutures were only used in the area of the wound with a larger opening to avoid losing the PRGF clot (Figure 3). Two weeks after the first surgery the soft tissue was well respecting the process of regeneration and closure. New tissue formed at the bottom of the defect can also been observed as shown in the Figure 4. In addition, the patient reported a complete absence of pain for the first time since the start of the necrotic process. Intake of painkillers was also stopped, that had become routine since 2008.

Four weeks after the first procedure, tissue at the bottom of the defect that is almost fully epithelised can be observed. At that time cone-beam computerised tomography (CBCT) was also performed to evaluate the radiographic changes. Complete elimination of the necrotic tissue can be observed, and new bone tissue appears to be starting to colonise the empty bonesocket from the lingual cortical wall (Figure 5).

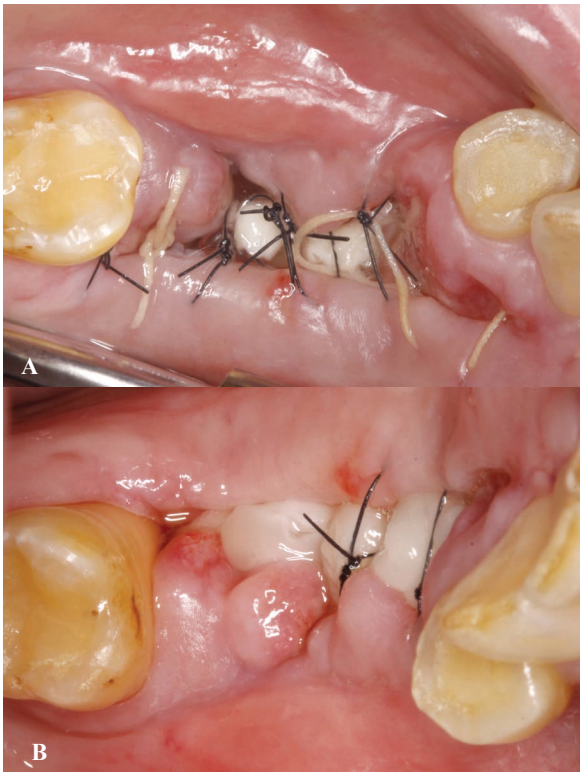

Figure 3. (A) Appearance of the lesion a week later. (B) Appearance once the suture has been removed and Endoret (PRGF) added again.

Figure 4. Appearance of the tissue after 2 weeks. We can see that there is tissue at the bottom of the defect.

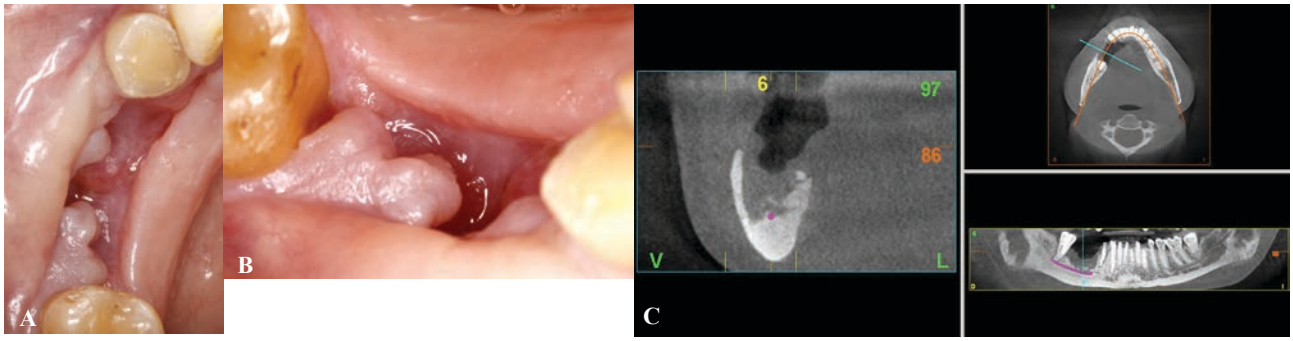

Figure 5. Appearance of the tissue after 4 weeks. The newly formed tissue at the bottom of the defect has matured and we can consider the closure of the surgical wound a success, as there is no bone exposed to the oral cavity. (C) CBCT images showing the complete excision of necrotic bone and the start of bone regeneration from the lingual cortical wall to the centre of the defect.

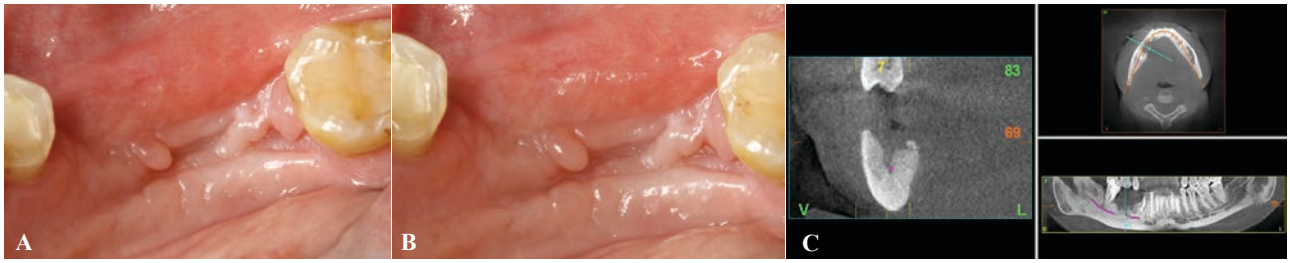

Figure 6. Clinical images of the regeneration of soft tissue a year after surgery. CBCT showing the complete regeneration of the tissue.

In the revision, one year after the procedure, the same image of regeneration in the soft tissue can be observed, accompanied by an almost complete bone regeneration of the defect, even observing the regeneration of the mandibular canal. The bone density measured in Hounsfield units in the area regenerated is similar to that of the preserved basal bone and the patient is asymptomatic (Figure 6).

After 31 months, CBCT carried out to plan the prosthesis shows sufficient bone volume and suitable bone quality for the insertion of two implants, so the surgery was performed and implants were placed and immediately loadded after 24 hours. In the same procedure tooth 47 was extracted as it presented a vertical fracture with infectious symptoms (Figure 7).

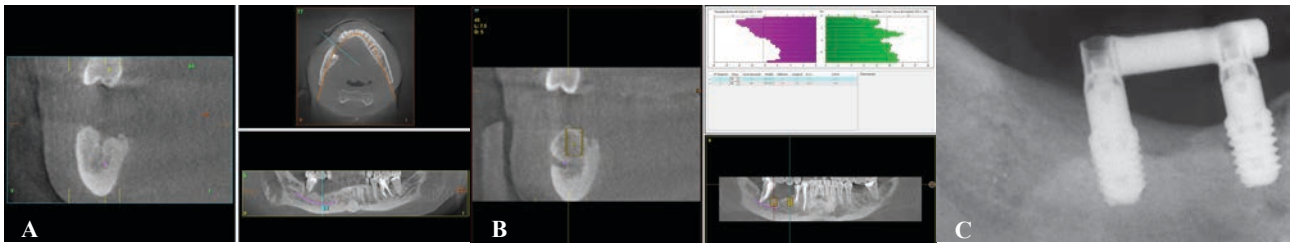

Figure 7. (A) CBCT image for treatment planning showing the 100% regeneration of bone volume. (B) Planning the position of the dental implants (C) Image of the immediately-loaded dental implants. The extraction socket of the lower right second molar can be observed. The post-extraction alveolus was treated with Endoret (PRGF) without any secondary effects or complications.

Figure 8. (A) CAD-CAM correcting the angle of screw chimneys, which were finally much more favourable. In addition, the cold micromilling seated on transepithelial abutments ensures a correct passive fit accompanied by excellent hermetism. (B) Image of the definitive prosthesis on the day it was placed. (C) Patient with the definitive prosthesis one year after loading.

After 4 weeks a CBCT was performed to evaluate the condition of the area corresponding to the dental extraction, and any type of adverse effects were found in the area treated with Endoret (PRGF) despite the patient's history.

After 3 months of implant insertion, the manufacturing of the definitive prosthesis began. This was done on Multi-Im abutments placed slightly at supragingival level (0,5 - 1mm) and using CAD-CAM to correct the angle of emergence of the screws, so they come out in the centre of the occlusal surfaces. The patients follow-up indicated an excellent healing, presenting satisfactory function and integration of the implants a year after the placement of the definite prosthesis. The area treated and regenerated after the existence of BRONJ has responded satisfactorily to the regeneration treatment and subsequent implant treatment (Figure 8).

Discussion and conclusions

This case report entails the use of Endoret(PRGF) in the treatment of medicament-related osteonecrosis of the jaw in conjunction with surgical resection of the necrotic bone. The described clinical treatment has been able to close the gingival ulcer and regenerate the alveolar bone defect.

Until now, treatments for MRONJ have been limited and results were inconclusive. Hyperbaric oxygen (HBO) has been proposed[7] but it cannot be recommended as the sole treatment[8]. Recently the use of platelet-rich plasma has been reported to have potential for the prevention and treatment of MRONJ, as shown by Mozzati et al.[9,10]. The mechanism of action of PRGF®-Endoret® in tissue regeneration has been widely studied. In the case of BRONJ, bisphosphonates inhibit bone resorption and angiogenesis by blocking the action of vascular

endothelial growth factor (VEGF). The application of PRGF®-Endoret® provides proteins and growth factors to the local milieu like angiogenic factors (VEGF and angiopoietin), and factors that promote osteogenic differentiation, which can activate and accelerate the regeneration of the involved tissues. Moreover, it has been recently demonstrated the cytoprotective effects of the Endoret(PRGF) against the damage that zoledronic acid (intravenous bisphosphonate) could cause to the alveolar osteoblasts and the gingival fibroblasts[11]. In our case, conservative treatment was unsuccessful. Resection followed by PRGF® -Endoret® was successful in promoting closure of the wound and the recovery of nerve function.

Rereferences

1. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg, 2003; 61:1115-1117.
2. Novince CM, Ward BB, McCauley LK. Osteonecrosis of the jaw: an update and review of recommendations. Cell Tiss Organ, 2009; 189:275-283.
3. European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP). EMEA/ CHMP assessment report on bisphosphonates and osteonecrosis of the jaw. EMEA/CHMP/291125/ 2009.
4. Otto S, Hafner S, Grotz KA. The role of inferior alveolar nerve involvement in bisphosphonate-related osteonecrosis of the jaw. J Oral Maxillofac Surg, 2009; 67:589-592.
5. Yu W, Wang J, Yin J. Platelet-rich plasma: a promising product for treatment of peripheral nerve regeneration after nerve injury. Int J Neurosci, 2011; 121:176-180.
6. Anitua E, Prado R, Orive G. A lateral approach for sinus elevation using PRGF technology. Clin Implant Dent Relat Res, 2009; 11:e23-e31.
7. Freiberger JJ, Feldmeier JJ. Evidence supporting the use of hyperbaric oxygen in the treatment of osteoradionecrosis of the jaw. J Oral Maxillofac Surg, 2010; 68:1903-1906.
8. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. J Oral Maxillofac Surg, 2009; 67:2-12.
9. Mozzati M, Gallesio G, Arata V, Pol R, Scoletta M. Platelet rich therapies in the treatment of intravenous bisphosphonate-related osteonecrosis of the jaw: a report of 32 cases. Oral Oncol, 2012; 48:469-474.
10. Mozzati M, Arata V, Gallesio G. Tooth extraction in patients on zoledronicacid therapy. Oral Oncol, 2012; 48:817-821.
11. Anitua E, Zalduendo M, Troya M, Orive G. PRGF exerts a cytoprotective role in zoledronic acid-treated oral cells. Clin Oral Investig, 2016;20 :513-521.

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