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Combined Surgical and Concentrated Growth Factor Therapy in the Management of Stage II and III MRONJ Associated with Denosumab: A Report of Two Cases

Denosumab ile İlişkili Evre II ve III MRONJ'un Cerrahi ile Birlikte Konsantre Büyüme Faktörü Uygulamasıyla Tedavisi: İki Olgu Sunumu

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Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a significant complication associated with antiresorptive agents such as denosumab, particularly in oncology patients. This report describes two patients with prostate cancer who developed MRONJ during denosumab treatment. One patient exhibited stage 3 MRONJ in the mandible, while the other had stage 3 MRONJ in the maxilla. Following clinical and radiological evaluations, both patients underwent surgical intervention, and concentrated growth factor (CGF) was applied locally to promote postoperative healing. In the first case, mandibular sequestrectomy was performed with reconstruction using a pre-shaped plate. In the second case, premaxillary resection was carried out after infection control. Both patients experienced favorable outcomes with successful, complication-free wound healing. These cases highlight the potential benefits of CGF-assisted surgical treatment in denosumab-related MRONJ and underscore the importance of individualized treatment planning in the absence of standardized protocols.

Keywords: Osteonecrosis, denosumab, MRONJ, concentrated growth factor

Öz

İlaç ilişkili çene osteonekrozu (MRONJ), özellikle onkoloji hastalarında denosumab gibi anti-rezorptif ajanlarla ilişkili önemli bir komplikasyondur. Bu raporda, denosumab tedavisi sırasında MRONJ gelişen prostat kanseri tanısı olan iki hasta sunulmaktadır. Bir hastada alt çenede evre 3 MRONJ gözlenirken, diğerinde üst çenede evre 3 MRONJ mevcuttu. Klinik ve radyolojik değerlendirmelerin ardından her iki hasta da opere edildi ve ameliyat sonrası iyileşmeyi desteklemek amacıyla lokal olarak konsantre büyüme faktörü (CGF) uygulandı. İlk olguda mandibular sequestrektomi yapılarak önceden şekillendirilmiş plak ile rekonstrüksiyon gerçekleştirildi. İkinci olguda ise enfeksiyon kontrolü sonrası premaksiller rezeksiyon yapıldı. Her iki hastada komplikasyonsuz başarılı yara iyileşmesi ile olumlu sonuçlar elde edildi. Bu olgular, denosumab ilişkili MRONJ'de CGF destekli cerrahi tedavinin potansiyel faydalarını vurgulamakta ve standart bir protokol olmaması durumunda bireyselleştirilmiş tedavi planlamasının önemini ortaya koymaktadır.

Anahtar kelimeler: Osteonekroz, denosumab, MRONJ, konsantre büyüme faktörü

Introduction

Medication-induced osteonecrosis of the jaw was first described by Marx (1). After it was established that bisphosphonates and other antineoplastic and antiangiogenic agents could cause maxillofacial osteonecrosis, the American Association of Oral and Maxillofacial Surgeons (AAOMS) named this condition "medication-related osteonecrosis of the jaw" (MRONJ) in 2014 (2).

For individuals taking antiresorptive or antiangiogenic drugs and with no history of radiotherapy, open bone for more than eight weeks or lesions with fistulas suggest MRONJ (2). The most common risk factor is dentoalveolar surgery, with the majority of cases occurring after tooth extraction (3). Other risk factors include implant operations, oral infections, poor hygiene, and ill-fitting dentures (2).

Treatment options range from conservative methods to extensive surgery. Conservative options include maintaining oral hygiene,

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antibiotic therapy and minimally invasive sequestrectomy (4). Surgical excision and curettage are also commonly used methods (5). Additionally, the regenerative effects of locally applied platelet concentrates have been reported in various studies to support tissue regeneration. Concentrated growth factor (CGF) is a leukocyte-rich platelet concentrate that supports angiogenesis and tissue regeneration, offering potential benefits in immunocompromised individuals (6-10).

These case reports describe the surgical treatment of extensive osteonecrosis of the maxilla and mandible in two patients who were receiving denosumab for prostate cancer alongside CGF. Although our cases are related to oncologic patients, denosumab is also widely used in osteoporotic patients and may similarly lead to osteonecrosis of the jaws. What distinguishes this report is the combined use of surgical intervention and CGF in stage 2 and 3 MRONJ cases associated with denosumab in patients with prostate cancer. In this respect, our study may contribute to the management of MRONJ in osteoporotic patients.

In this case series, all procedures involving human subjects were conducted in accordance with our institution's ethical standards and the Helsinki Declaration. All patient identifiers were meticulously safeguarded, and a comprehensive informed consent process was duly implemented.

Case Reports

Case 1

A 78-year-old male patient presented at our clinic, complaining of pain and exposed bone in right mandible (Figure 1). Radiological examination revealed radiolucent areas with irregular borders in the parasymphyseal region of the mandible (Figure 2). The patient's medical history indicated a diagnosis of prostate cancer, for which he had been receiving monthly 120 mg denosumab injections for a total of 8 months. There was no history of systemic disease, metastasis, or other oncologic treatments. Denosumab therapy had been discontinued three months prior to surgery, based on consultation with the oncology department. Preoperative cone beam computed tomography (CBCT) showed necrotic bone margins. Prior to the planned sequestrectomy, during which MRONJ was initially suspected, a 3D-printed model of the mandible was prepared to assist surgical planning. To reinforce mandibular integrity and prevent intra-operative or post-operative fracture, a pre-shaped reconstruction plate was applied. Surgical debridement was performed under local anesthesia. Following this, CGF was prepared by centrifuging the patient's own venous blood using a specialized device (Medifuge®, Silfradent, Italy). For this procedure, six tubes of

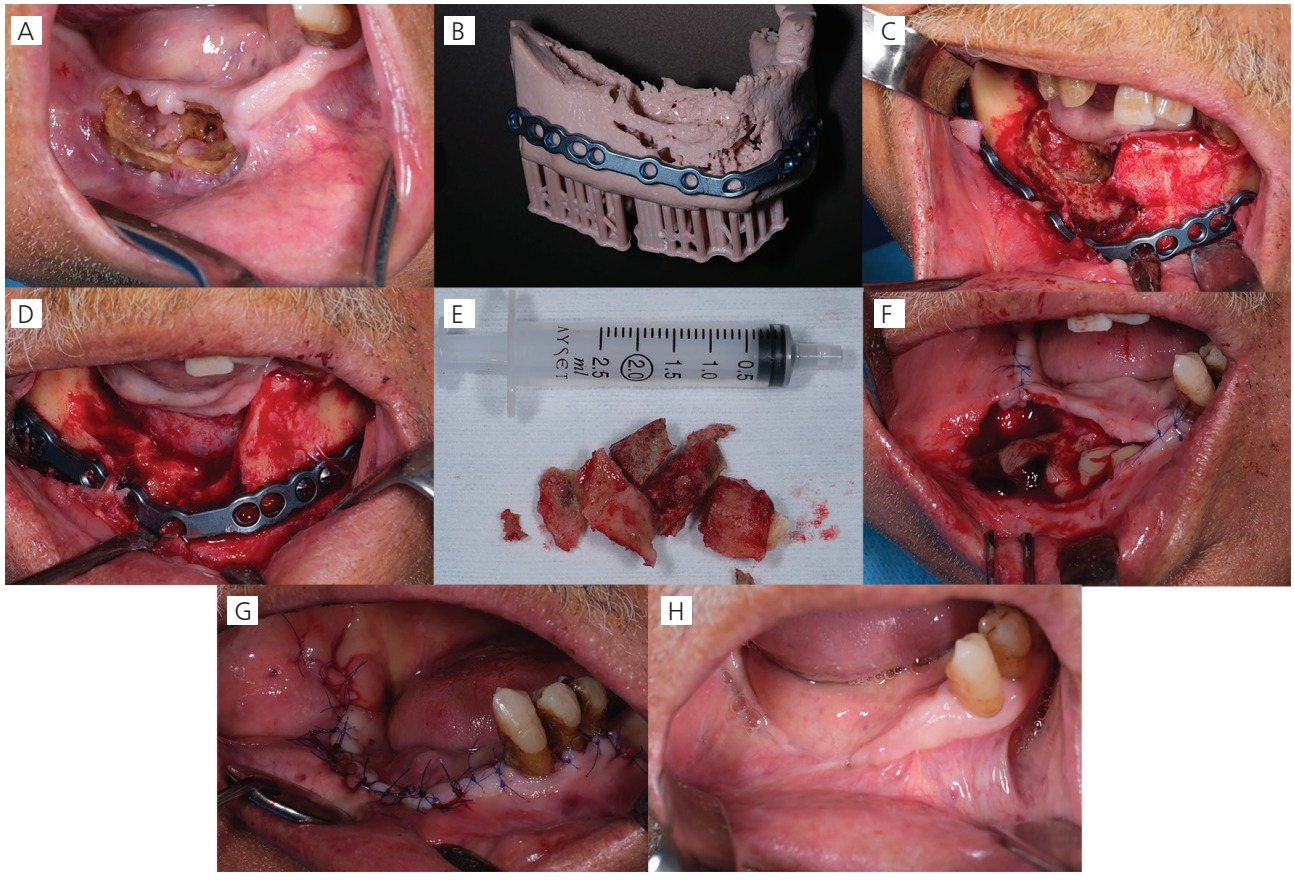

Figure 1. Clinical presentation of Case 1. **A)** Preoperative intraoral view, **B)** Pre-shaped reconstruction plate on 3D model, **C)** Intraoral view reconstruction plate and necrotic bone, mental nerve (white arrow), **D)** After sequestrectomy, mental nerve (white arrow), **E)** Necrotic bone fragments, **F)** Applied concentrated growth factor, **G)** Primary closure, **H)** Healing after 3 month

blood were collected. The obtained CGF was processed into membrane form and placed directly into the surgical site prior to primary closure. After adequate flap mobilization, the wound was closed primarily. The healing process was uneventful, with satisfactory soft tissue recovery observed at 8 weeks.

Case 2

A 64-year-old male patient attended our clinic, complaining of pain in the maxilla and halitosis following a tooth extraction at an external centre. On examination, non-healing tissue and purulent discharge were present at the extraction site. The patient had been receiving monthly 120 mg denosumab for six months due to prostate cancer. As in the first case, there was no history of systemic illness, metastasis, or other cancer therapies. Following oncology consultation, denosumab was discontinued, and a three-month drug holiday was observed prior to surgery. A pre-diagnosis of stage 2 MRONJ was made and amoxicillin and chlorhexidine mouthwash were prescribed to control the infection (Figure 3). Following oncology consultation, the patient's denosumab therapy was discontinued. A CBCT scan, performed 2 months after discontinuation of denosumab, revealed a broad demarcation line involving the nasal floor and the maxillary sinus (Figure 4). With a diagnosis of stage 3 MRONJ, premaxillary resection was performed under local anesthesia. Followed by CGF application using the same protocol as in Case 1. Six tubes of venous blood were collected, and the resulting CGF was processed into membrane form and applied to the surgical site before primary closure. After an uneventful eight-week healing period, a removable prosthesis was delivered to the patient.

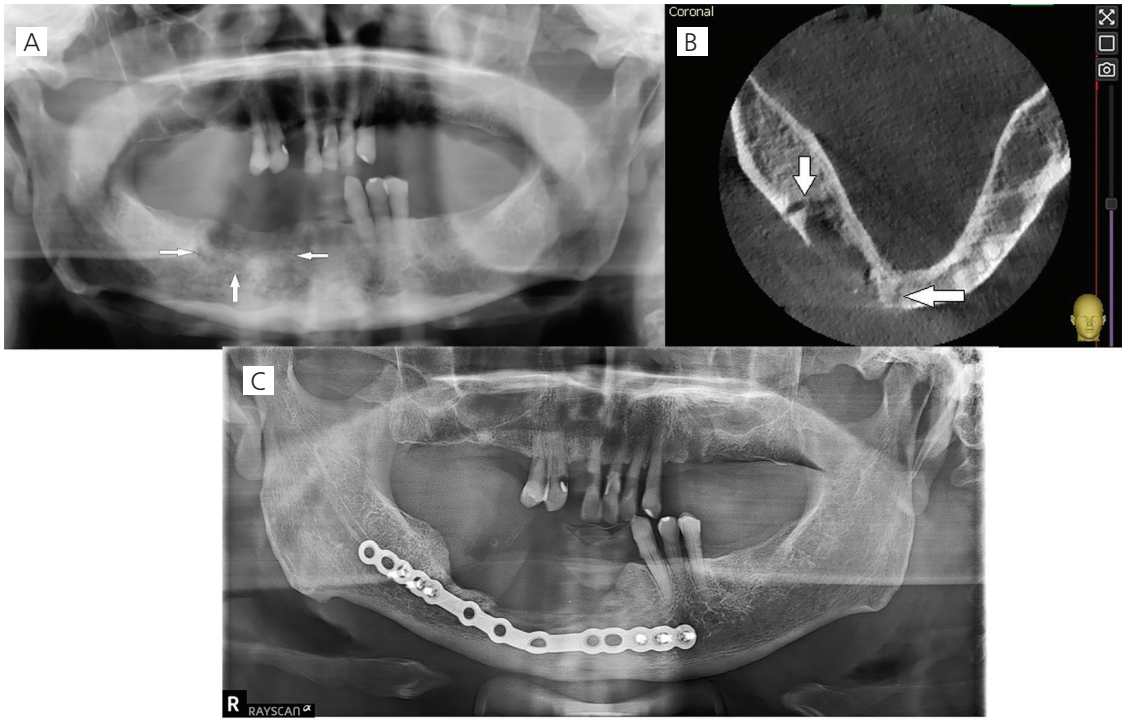

Figure 2. Radiological presentation of Case 1, **A)** Preoperative orthopantomography, **B)** Dental volumetric tomography axial seciton, **C)** Postoperative orthopantomography

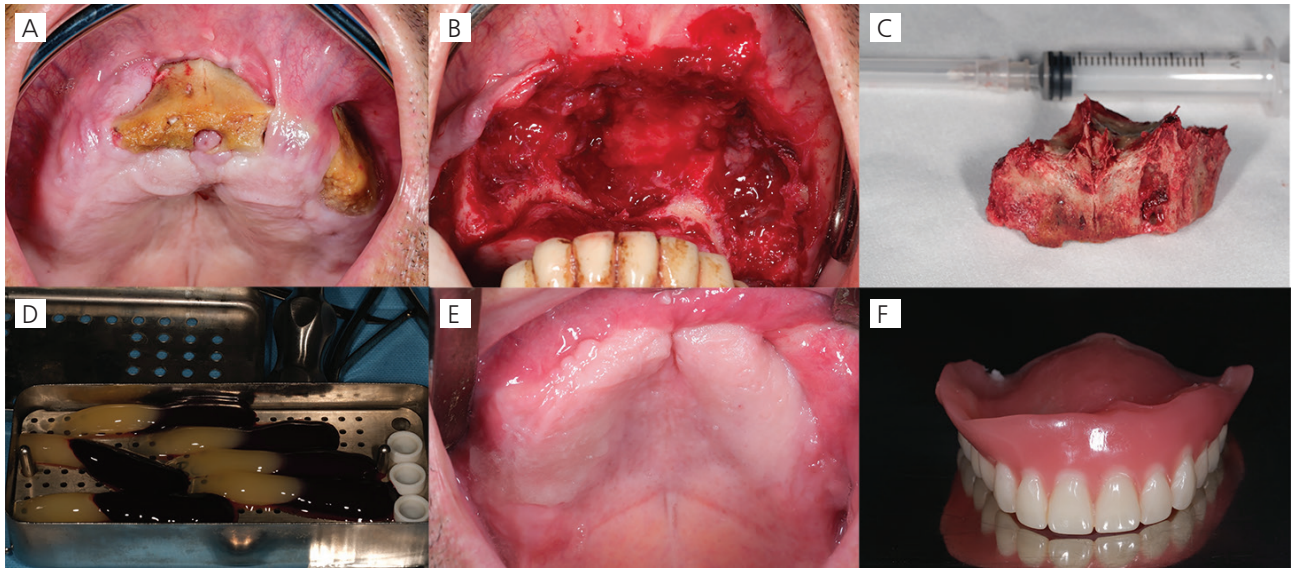

Figure 3. Clinical presentation of Case 2, **A)** Preoperative intraoral view, **B)** Intraoral view after lambo removal, **C)** Necrotic bone fragment, **D)** Concentrated growth factor, **E)** Healing after 8 weeks, **F)** Final prosthesis

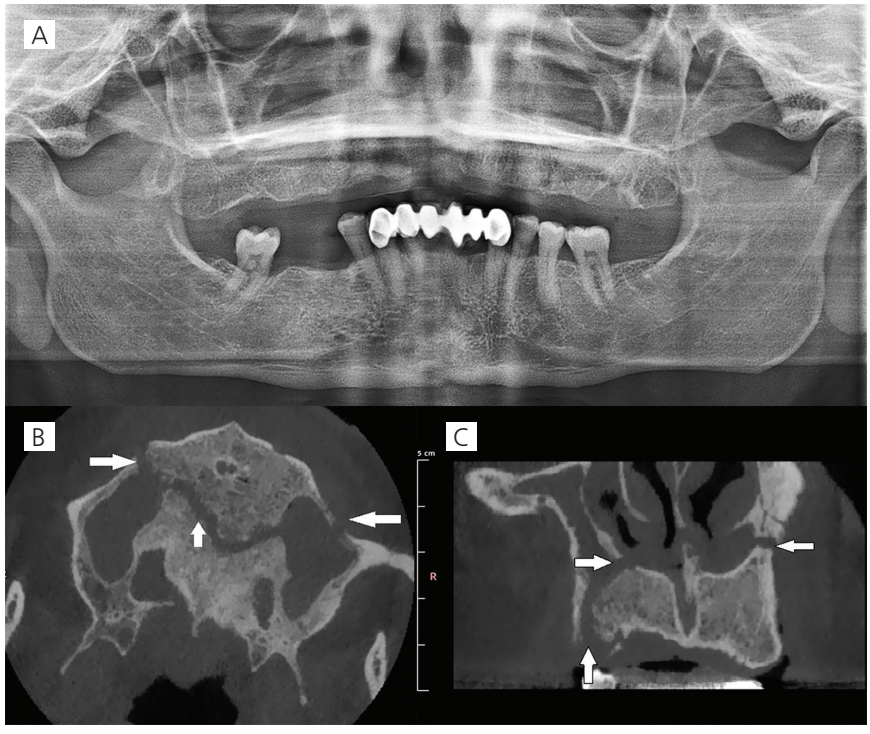

Figure 4. Radiological presentation of Case 2, **A)** Preoperative orthopantomography, **B)** DVT axial section, **C)** DVT sagittal section
DVT: Dental volumetric tomography

Discussion

MRONJ is a serious complication associated with the use of antiresorptive and antiangiogenic drugs. MRONJ is frequently observed in elderly female patients, particularly those using bisphosphonates or denosumab for osteoporosis or cancer (2). MRONJ is relatively uncommon in patients taking antiresorptive drugs for osteoporosis, with reported incidence rates ranging from 0.1% to 0.01%. An incidence rate of 0.052% has been reported in patients using denosumab. IV bisphosphonates used in oncology patients have been reported to cause MRONJ at a higher rate than denosumab (2). Another study reported a prevalence of MRONJ ranging from 0% to 27.5% after bisphosphonate use, whereas the risk of developing denosumab-induced MRONJ was up to 2% (7). Although denosumab is often considered to have fewer adverse effects, some recent studies have reported that it may pose a comparable or even higher risk of MRONJ than zoledronic acid (5).

While dentoalveolar surgery has been identified as the main risk factor, some studies have found that the impact of minor surgery is low. Chemotherapy, corticosteroid use and smoking are also risk factors (3). For individuals at risk of MRONJ, a pre-treatment clinical and radiological evaluation, elimination of infection, good oral hygiene and regular dental check-ups are recommended. This approach has been shown to significantly reduce the risk of MRONJ (7).

The AAOMS recommends interrupting drug treatment three months before and after invasive procedures, but this decision should be made jointly with the prescribing physician. In 2012, both the Italian Society of Maxillofacial Surgery and the Italian Society of Oral Pathology and Medicine recommended conservative surgery for early-stage lesions, as defined by the two associations. Surgical excision is recommended for advanced-stage lesions. Treatment protocols remain heterogeneous, and a universally accepted approach has yet to be established (5). While surgical treatment is generally considered more effective, it is not without limitations, as some patients may experience recurrence requiring additional interventions (8). In addition to surgery, other methods have been proposed, including low-dose laser therapy, fluorescent staining, ozone therapy, hyperbaric oxygen therapy, pentoxifylline and alpha-tocopherol (9).

Plasma-rich fibrin (PRF) stimulates the migration and proliferation of fibroblasts and osteoblasts, while L-PRF stimulates angiogenesis (7,8). CGF enables the formation of a denser fibrin matrix with a high concentration of growth factors (10). Studies have reported that the local application of CGF improves tissue regeneration in the surgical treatment of MRONJ (6).

Current literature suggests that CGF application may be beneficial in osteoporotic patients who develop MRONJ. In the treatment of early-stage MRONJ in osteoporotic individuals, the use of CGF in combination with conservative surgery has resulted in significant improvements in wound healing and bone regeneration (6). Borsani et al. (11) reported that CGF accelerates postoperative healing, while Yüce et al. (6) found that it enhances tissue integrity following sequestrectomy. However, these studies were mostly conducted in osteoporotic patients or early-stage MRONJ cases. In contrast, our study differs in that it demonstrates the supportive effect of CGF in the surgical treatment of stage 2 and 3 MRONJ in prostate cancer patients receiving denosumab. In this respect, our report represents one of the rare examples highlighting the effectiveness of CGF in advanced oncologic MRONJ cases.

Conclusion

These case reports demonstrate that stage 2 and stage 3 MRONJ cases resulting from denosumab use for cancer treatment can be managed surgically, and that the application of CGF may support healing. Although there is no standardized approach for the treatment of advanced-stage MRONJ, individualized, case-specific planning may enhance clinical success. Further advanced clinical and scientific studies are needed to better understand the pathophysiology of MRONJ and to determine the most effective treatment strategies.

Ethics

Informed Consent: All patient identifiers were meticulously safeguarded, and a comprehensive informed consent process was duly implemented.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K., M.E.D., B.B., Concept: M.K., M.E.D., Design: M.K., M.E.D., Data Collection or Processing: M.K., M.E.D., B.B., Analysis or Interpretation: M.K., M.E.D., B.B., Literature Search: M.K., M.E.D., B.B., Writing: M.K., M.E.D., B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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