CASE REPORT OLGU SUNUMU

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Denosumab-Related Osteonecrosis of the Jaw with Actinomycosis Infection and Extensive Periosteal Reaction

Aktinomikoz Enfeksiyonu ve Yaygın Periost Reaksiyonu Gösteren Denosumab İlişkili Çene Kemiği Osteonekrozu

Elif ASLAN[a], Gözde IŞIK[b], Elif ŞENER[a], Başak DOĞANAVŞARGİL[c], Banu ÖZVERİ KOYUNCU[b], Hülya ÇANKAYA[a]

[a]Ege University Faculty of Dentistry, Department of Oral and Maxillofacial Radiology, İzmir, Türkiye
[b]Ege University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery, İzmir, Türkiye
[c]Ege University Faculty of Medicine, Department of Pathology, İzmir, Türkiye

ABSTRACT Medication-related osteonecrosis of the jaws (MRONJ) is a well-known side effect of bisphosphonate drugs used in the treatment of osteometabolic disorders and some types of cancer. However, development of MRONJ have also been reported in patients using denosumab, a monoclonal immunoglobulin G2 antibody inhibiting osteoclastic bone resorption. Even though denosumab is more advantageous than bisphosphonates due to its shorter half-life and lack of binding to the bone, MRONJ has accepted as a well-known side-effect of denosumab as it is in bisphosphonates. We reported clinical, radiographic, and histopathological findings of a female patient who developed osteonecrosis of the jaw following denosumab treatment and presented with actinomycosis infection and extensive periosteal new bone formation. Our case emphasized the importance of dental screening before initiating and during denosumab treatment in order to prevent and lower the risk of MRONJ development.

Keywords: *Actinomyces;* actinomycosis; denosumab; mandible; osteonecrosis

ÖZET İlaca bağlı çene kemiği osteonekrozu [medication-related osteonecrosis of the jaws (MRONJ)], metabolik kemik hastalıklarının ve bazı kanser tiplerinin tedavisinde kullanılan bisfosfonat grubu ilaçların bilinen bir yan etkisidir. Bununla birlikte osteoklastik kemik rezorpsiyonunu inhibe eden bir monoklonal immünglobulin G2 antikoru olan denosumab kullanan hastalarda da MRONJ gelişimi bildirilmiştir. Denosumab, yarılanma ömrünün daha kısa olması ve kemiğe bağlanmaması nedeniyle bifosfonatlara göre daha avantajlı olsa da günümüzde MRONJ bifosfonat grubu ilaçların yanı sıra denosumabın da bilinen bir yan etkisi olarak kabul görmektedir. Bu olgu raporunda, denosumab tedavisini takiben çene osteonekrozu gelişen ve aktinomikoz enfeksiyonu ile yaygın periosteal yeni kemik oluşumu saptanan bir kadın hastanın klinik, radyografik ve histopatolojik bulguları sunulmaktadır. Olgumuz, MRONJ gelişimini önlemek ve MRONJ gelişim riskini azaltmak amacıyla denosumab tedavisine başlamadan önce ve tedavi sırasında yapılması gereken dental muayenenin önemini vurgulamaktadır.

Anahtar Kelimeler: *Aktinomiçes;* aktinomikoz; denosumab; mandibula; osteonekroz

Medication-related osteonecrosis of jaws (MRONJ) is an antiresorptive and/or antiangiogenic drug-associated adverse effect characterized by the progressive destruction of the jawbones.[1] 90% of MRONJ cases are cancer patients using intravenous bisphosphonate or subcutaneous denosumab.[2] Denosumab is a monoclonal immunoglobulin G2 antibody suppressing bone turnover by selectively binding receptor activator of nuclear factor kappa-B and used in the treatment of osteometabolic disorders, osteoporotic patients with increased bone fracture risk, and some cancer types.[1,3] Although denosumab seems to

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Correspondence: Elif ASLAN
Ege University Faculty of Dentistry, Department of Oral and Maxillofacial Radiology, İzmir, Türkiye
E-mail: aslanelif090@gmail.com

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be preferable to bisphosphonates due to its shorter half-life, lack of binding to the bone, and effectiveness in the prevention of skeletal-related events, osteonecrosis has proven to be a well-known side-effect of denosumab.[1,3,4]

Actinomyces spp. are gram-positive, anaerobic, filamentous microorganisms, and the most frequent bacterial agents causing MRONJ-related infections.[4-6] It has been reported that MRONJ-associated actinomycosis occurs predominantly in cancer patients, and the presence of *actinomyces* spp. has been demonstrated in patients presenting with denosumab-associated osteonecrosis.[4,6]

In this case report, a metastatic breast cancer patient with denosumab-related MRONJ and actinomycosis infection is discussed along with the clinical, radiographic, histopathological findings, and seven-month postoperative follow-up.

CASE REPORT

A 53-year female patient was referred to our outpatient clinic with complaints of severe pain, chewing difficulty in her left mandible and an abscess formation in the mandibular right posterior region for a year. Medical anamnesis revealed breast cancer and liver metastasis. The patient had one month of radiotherapy and ten cycles of chemotherapy in 2019. She had used 120 mg of denosumab for 1.5 years. She was currently under the treatment of capecitabine and tamoxifen.

Intraoral examination showed exposed necrotic bone areas and alveolar sockets in the left posterior and anterior regions of the mandible, along with mobility in teeth #43, 44. An exposed bone area accompanied by an inflammatory pus formation was detected in the right mandible and a large extraoral fistula was noted in the submental region (Figure 1). The right submandibular lymph node was tender and increased in size. No prosthetic restoration or tooth extraction history was reported by the patient. Panoramic radiography and cone beam computed tomography images disclosed radix of tooth #38, persistent alveolar sockets, osteolytic-osteosclerotic areas, narrowing of inferior alveolar canals, and widespread periosteal reaction (Figure 2).

The patient was preliminary diagnosed as MRONJ, and was referred to the department of oral and maxillofacial surgery. Amoxicillin-clavulanate and ornidazole were prescribed for 2 weeks due to existing infection symptoms detected in osteonecrotic bone areas. In the two-week follow-up, pain and pus formation decreased, but the size of the extraoral fistula remained.

The patient was further referred to the department of plastic and reconstructive surgery due to widespread necrotic bone and fracture risk. Necrotic bone was removed by mandibular osteotomy, and the surgery sites were closed primarily. Histopathological examination with Haematoxylin&Eosin staining disclosed necrotic bone trabeculae and bone marrow, increased bone turnover, and bacteria accumulation along with *Actinomyces* filaments (Figure 3). Biochemical evaluation revealed increased alkaline phosphatase (143 U/L, normal range: 35-104 U/L) and C-reactive protein levels (16.89 mg/L, normal range: 0-5 mg/L). The final diagnosis was Stage 3 MRONJ.

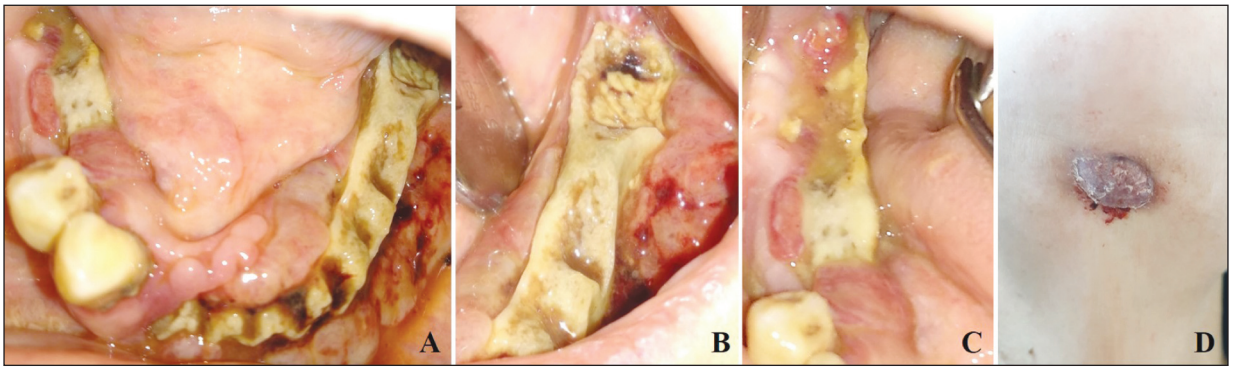

FIGURE 1: Clinical examination of the patient disclosing **(A, B)** widespread necrotic bone areas and persistent alveolar sockets in the mandibular anterior and left posterior regions, **(C)** inflammatory pus formation along with exposed necrotic bone in the mandibular right posterior area, and **(D)** an extraoral fistula in the submental region.

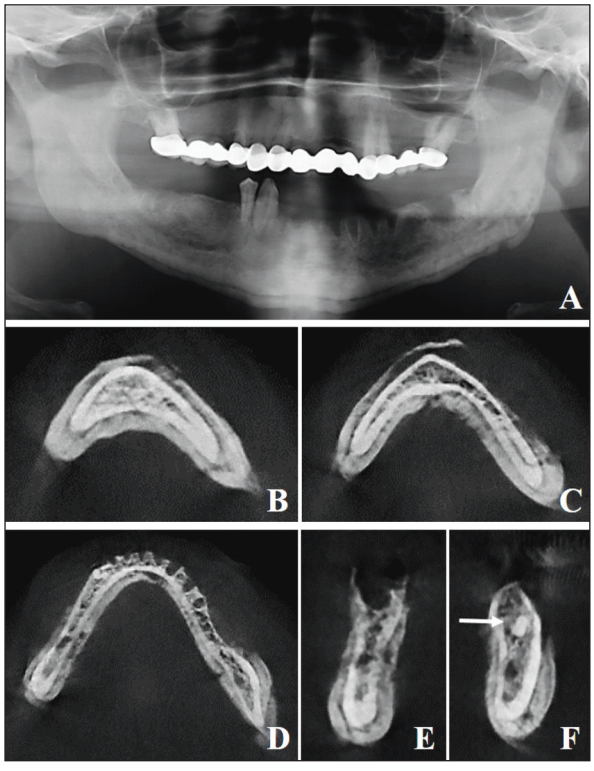

FIGURE 2: Radiographic evaluation of the mandible. **(A)** Panoramic radiography showing persistent alveolar sockets, osteolytic-osteosclerotic areas, narrowing of inferior alveolar canals, and widespread periosteal reaction along the mandible. Axial CBCT sections showing **(B, C)** extensive periosteal new bone formation and **(D)** persistent alveolar sockets. Coronal CBCT sections showing **(E)** thickening of cortical bone and **(F)** impacted radix of tooth #38 (arrow).
CBCT: Cone beam computed tomography.

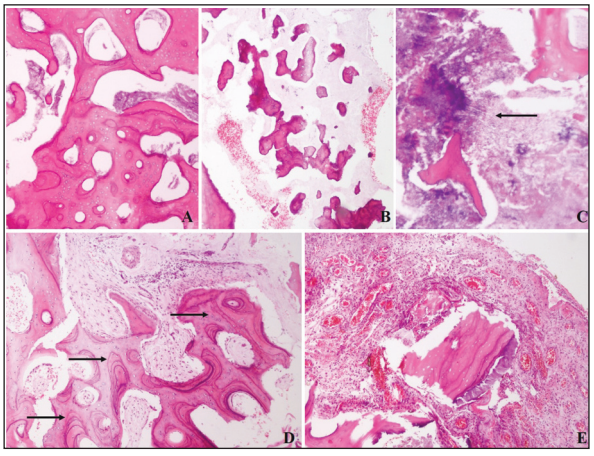

FIGURE 3: Photomicrographs showing the histopathological aspect of the patient. **A)** Osteonecrosis in lamellar bone with empty osteocyte lacuna (H&E, x 10). **B)** Total necrosis of newly formed bone and bone marrow (H&E, x 10). **C)** Bacterial growth among necrotic bone trabeculae along with Actinomyces filaments (arrow) (H&E, x 20). **D)** Increased sement-lines showing increased bone production turnover (arrows) (H&E, x 10). **E)** Necrotic bone fragments (sequestrum) under the ulcerated mucosal surface as one of the signs of a possible fistulisation (H&E, x 20).

At the postoperative 7th month, healing was detected in the right mandibular region and the extraoral fistula was decreased in size. However, incomplete healing and newly formed sequesters were noted in the mandibular anterior and left posterior regions (Figure 4). The size of the anterior sequestrum was 24.8x6.7 mm and 12x7.1 mm in the coronal and sagittal multi slice computed tomography (MSCT) sections, respectively. The left posterior sequestrum was measured as 14.2x7.2 mm in the coronal and 17.2x12.9 mm in the sagittal MSCT sections. A persistent widespread periosteal reaction was detected along with extensive deterioration in mandibular cortical bone, involvement of the in-

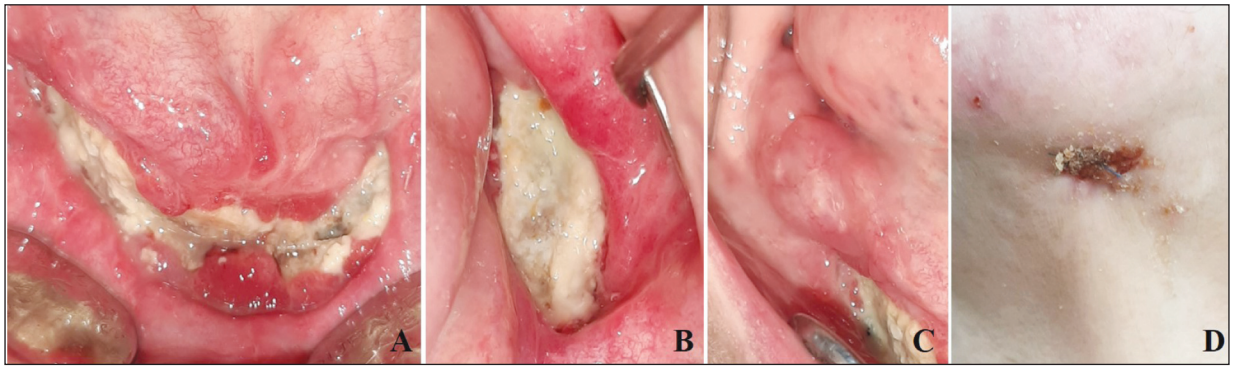

FIGURE 4: Clinical examination in the seven-month follow-up showing **(A, B)** incomplete healing and exposed bone areas in the mandibular anterior and left posterior regions, **(C)** healing with soft tissue closure in the right mandibular posterior area, and **(D)** reduction in the size of the extraoral fistula.

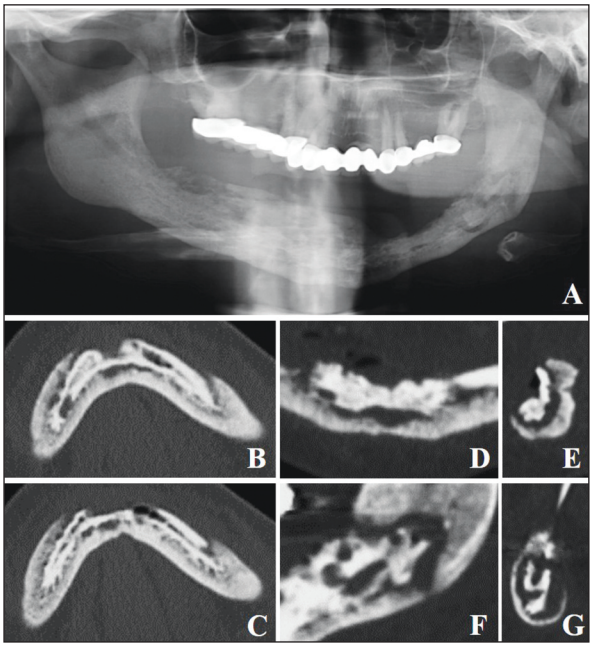

FIGURE 5: Radiographic evaluation in the seven-month follow-up appointment. **A)** Panoramic image showing osteolytic-osteosclerotic bone extending through the mandible, involvement of left inferior alveolar canal, and pathological fracture in the left mandibular angle. **B, C)** Axial MSCT sections revelaing widespread periosteal reaction along the mandible. **D)** Coronal and **(E)** sagittal MSCT sections showing the newly formed mandibular anterior sequestrum and extensive deterioration of mandibular cortical bone. **F)** Sagittal and **(G)** coronal MSCT images disclosing the newly formed sequestrum in the mandibular left posterior region. MSCT: Multi slice computed tomography.

ferior alveolar canal and pathological fracture in the left mandibular angle (Figure 5). The left submandibular lymph node was tender to palpation. The patient was consulted again with plastic and reconstructive surgery. Re-surgery and mini-plate application were determined by the relevant department.

Written informed consent was obtained from patient.

DISCUSSION

We presented a metastatic breast cancer patient with MRONJ in whom osteonecrosis lesions were detected at Stage 3. Noteworthily, the results of the study of Favia et al. revealed that patients with denosumab-related MRONJ tend to be frequently detected at Stages 2 or 3.[7] It has been thought that the lesser occurrence and slower separation speed of bone sequestrum observed in denosumab osteonecrosis may explain this insufficiency in early detection of denosumab-associated MRONJ.[8,9]

Tooth extraction has been identified as the most frequent local risk factor regarding MRONJ.[2,10] It is noteworthy that our case did not have a history of tooth extraction or use of removable dentures. Spontaneous exfoliation of teeth may point out periodontal disease and poor oral hygiene as possible risk factors for the present case, consistent with the previous studies reporting poor oral hygiene as a triggering factor for denosumab-associated MRONJ.[11,12] Although in some cases MRONJ lesions may develop spontaneously, it is not possible to propose such a statement in the present case since the patient's complete dental history prior to the development of MRONJ was not followed up by our hospital.[2]

MRONJ-related systemic risk factors include chemotherapy, concomitant corticosteroid use, smoking habit, and co-morbidities.[2,7] In the current case, chemotherapy and liver metastasis may have promoted the development of denosumab-associated MRONJ. Liver metastases is a potential systemic risk factor regarding the development and progression of MRONJ due to the negative effects of liver damage on wound healing.[13] However, to our knowledge, the correlation between liver dysfunction and the risk of MRONJ has not been fully investigated. Therefore, further studies are required to enlighten the effect of liver damage on the development of MRONJ.

The radiographic characteristics of denosumab-related MRONJ have not been fully identified.[6] However, it has been reported that patients under denosumab treatment tend to have larger sequestrums and more frequent periosteal new bone formation compared to patients receiving bisphosphonates.[8] Accordingly, we defined an unusual form of periosteal reaction with a diffuse pattern, which was similar to the cases Tagliamento et al. reported.[14] Atypical periosteal new bone formation in the present case might be explained by the actinomycosis infection, as well as different pharmacologic mechanisms of denosumab.[9] In contrast to the bisphosphonates, bone modeling, which plays an important role in periosteal expansion, remains non-inhibited in patients using denosumab.[8,15] Furthermore, denosumab is not effec-

tive in the suppression of angiogenesis.[8,15] However, in the present case, the extensive periosteal reaction might also be reasoned by the delayed consultation time with the dentist and the advanced stage of MRONJ.

Denosumab-related MRONJ may show spontaneous resolution following the discontinuation of denosumab, whereas surgical resection of sequestrum might be necessary in the advanced stages.[1,7,14] However, cancer patients may not make a complete recovery even after invasive surgical treatment, and recurrence mostly occur in this group of patients due to their concomitant antineoplastic therapies.[2,7] In line with this statement, incomplete healing and recurrence were detected in our case at the postoperative 7th month, and re-surgery was required. This can be explained by the severity and advanced stage of MRONJ, ongoing antineoplastic drug therapy, and liver metastasis which delay mature cancellous bone development.[13]

In the present case report, a Stage 3 denosumab-associated MRONJ with actinomycosis infection and unusual form of periosteal reaction was presented. Although the patient's complaints had been present for a year, the patient had not been consulted with a dental practitioner. The advanced clinical and radiographic symptoms of the patient and the postoperative recurrence and incomplete healing prove the importance of early diagnosis and intervention in MRONJ patients.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Hülya Çankaya;* ***Design:*** *Elif Şener, Banu Özveri Koyuncu;* ***Control/Supervision:*** *Hülya Çankaya;* ***Data Collection and/or Processing:*** *Elif Aslan, Gözde Işık, Banu Özveri Koyuncu;* ***Analysis and/or Interpretation:*** *Başak Doğanavşargil, Hülya Çankaya;* ***Literature Review:*** *Elif Aslan, Gözde Işık, Elif Şener, Hülya Çankaya;* ***Writing the Article:*** *Elif Aslan, Gözde Işık;* ***Critical Review:*** *Elif Şener, Banu Özveri Koyuncu, Hülya Çankaya.*

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