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OLGU SUNUMU/CASE REPORT

Mandibular osteomyelitis developing due to a failed root canal treatment in a patient with multiple myeloma

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Summary
Hundreds of patients with bisphosphonate-associated osteonecrosis have been reported worldwide, and in several of those individuals, evidence of osteomyelitis has been found. However, to our knowledge, osteomyelitis without osteonecrosis has not been reported in patients treated with bisphosphonates. This case report describes a patient with multiple myeloma in remission who was treated with bisphosphonates and osteomyelitis developed due to insufficient root canal treatment. The patient had bone marrow transplantation after the elimination of ongoing inflammation.
Key words: Mandibular osteomyelitis, multiple myeloma, root canal treatment

Özet
Multipl miyelomlu bir hastada başarısız kanal tedavisine bağlı olarak gelişen mandibular osteomiyelit
Dünyada bifosfonat kullanımana bağlı olarak osteonekroz gelişen yüzlerce hasta bildirilmiştir ve bunların pek çoğunda osteomiyelit bulgusuna rastlanmamıştır. Ancak bildiğimiz kadarıyla bifosfonat kullanan hastalarda osteonekroz olmaksızın osteomiyelit gelişimi bildirilmemiştir. Bu vaka raporunda, bifosfonat ile tedavi edilip remisyon dönemine girmiş multipl miyelomlu bir hastada yetersiz yapılan kanal tedavisine bağlı olarak osteonekroz olmaksızın gelişen mandibular osteomiyelit sunulmaktadır. İnflamasyonun tedavi edilmesinden sonra hastaya kemik iliği transplantasyonu uygulanmıştır.
Anahtar kelimeler: Mandibular osteomiyelit, multipl miyelom, kök kanal tedavisi

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Introduction

Multiple myeloma is a B-cell malignancy of neoplastic plasma cells that usually produce a monoclonal immunoglobulin protein (1). The disease is contained primarily within the bone marrow. Clinical manifestations of multiple myeloma are the direct consequences of marrow infiltration by plasma cells, production of the monoclonal protein in blood or urine, and immune deficiency. Bone destruction is a prominent clinical feature in almost all patients with multiple myeloma (2). If treatment is required, the best approach for patients in good condition is high-dose chemotherapy with stem cell support (3).

Bisphosphonates (BPs) are the main component of supportive care, which are essential in the treatment of patients with myeloma. BPs are the most effective and potent inhibitors of osteoclastic resorption and they exert direct and indirect effects on osteoclast activity via molecular mechanisms that have not yet been fully defined (4). Recently, osteonecrosis of the jaw has been found to be associated with treatment with BPs (5-8). Patients with multiple myeloma have an increased susceptibility to the development of infections due to the hypogammaglobulinemia associated with this type of cancer. Thus far, the association of osteomyelitis with BP treatment has not been established. To our knowledge, this is the first report describing osteomyelitis without osteonecrosis in a patient with multiple myeloma who was treated with BPs.

Case Report

A 54-year-old man was referred from the Department of Hematology to the Department of

Periodontology at Başkent University for the treatment of dull pain inside his left cheek and pain referred to the corner of the ramus of the mandibular jaw. He did not complain of dental pain, and neither periodontal destruction nor mucosal irritation was detected. The patient had been diagnosed to have stage IIIA immunoglobulin A (IgA) multiple myeloma 5 months prior to his admission to our service. He had undergone 3 courses of standard combination chemotherapy (vincristine, doxorubicin and dexamethasone) administered at 20-day intervals. In addition, a monthly intravenous infusion of zoledronate 4 mg (a third-generation bisphosphonate) had been prescribed. To evaluate the degree of cytoreduction, the patient underwent bone marrow aspiration; laboratory analyses to determine the levels of lactic dehydrogenase, creatinine, C-reactive protein, and β-2 microglobulin; a complete blood count; serum protein electrophoresis; a 24-hour urine collection to test for Bence-Jones proteinuria; and serum immunofixation electrophoresis at the end of the combination chemotherapy regimen (3). Efficient cytoreduction was achieved, and autologous bone marrow transplantation was planned. Six weeks after the last dose of chemotherapy, when the patient was in good clinical condition, he underwent routine oral examination for transplantation. At that time, his hematologic and biochemical test results, including serum immunoglobulin levels were within the normal range, and he was receiving monthly treatment with BPs.

The patient was determined to be physiologically healthy. After an initial examination, he was referred to our Department of Radiology to undergo computerized tomography for imaging of the left mandibular posterior region, the results of which revealed no pathologic formation. Panoramic and periapical radiographs were obtained. The patient had bridge restorations at teeth 37, 36 and 35. The prostheses were removed, and an exposed devitalized glassy bone with a yellowish discoloration appeared on the lingual side of tooth 37 under the crown (Figure 1). Teeth 37, 36 and 35 were subjected to endodontic treatment. Although tooth 37 has 3 root canals, only 2 of those canals were fully filled in this patient, and a radiolucent area was noted around the mesial root of tooth 37 (Figures 2A, 2B). That tooth was extracted after the patient received antibiotic prophylaxis with amoxicillin-clavulanate potassium 1000 mg twice daily for 1 week. Conservative nonaggressive debridement of the bone sequestra and curettage of the soft tissue were performed. Devitalized bone and granulation tissue were removed from the cavity, and gingival tissue for biopsy was obtained from the lingual surface of the adjacent gingival margin. Treatment with a chlorhexidine digluconate mouthwash 0.2% was recommended for 2 weeks. Obtained tissue specimens were sent to pathological examination.

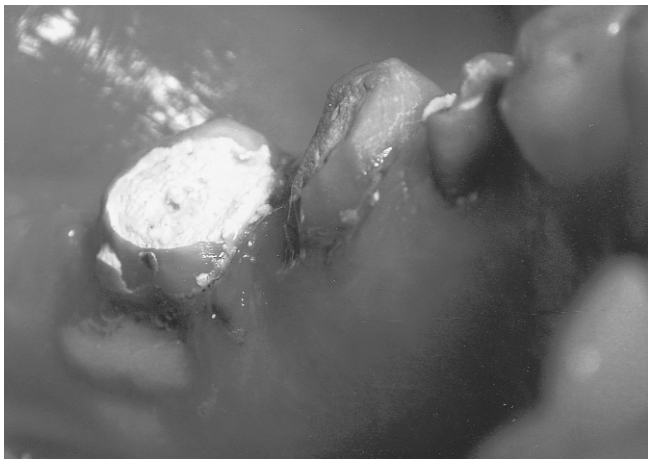

Figure 1. After removing the prosthesis, the lingual aspect of the suspected tooth (#37) with exposed devitalized glassy bone with a yellowish discoloration

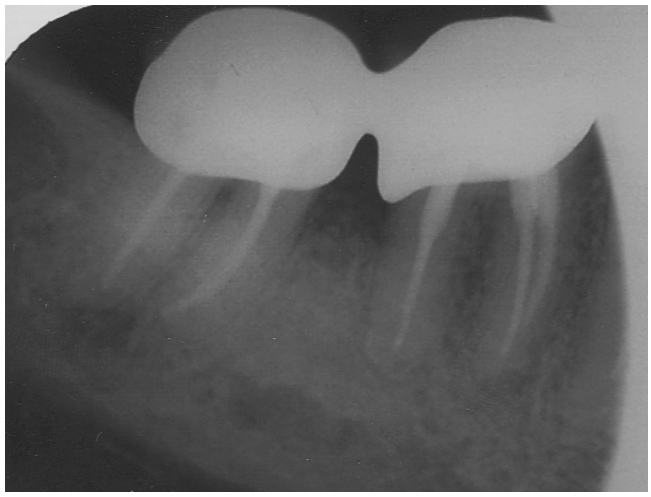

Figure 2A. Periapical radiograph of the tooth (#37)

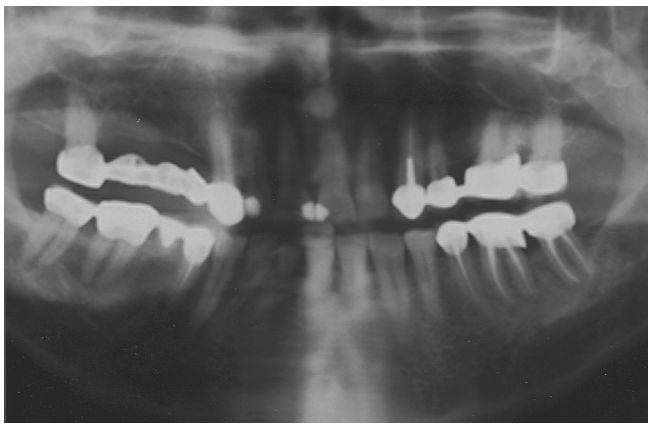

Figure 2B. Panoramic radiograph of the jaw

Ten days after the extraction, wound healing was uneventful (Figure 3). The patient experienced no pain around the cheek or mandible. He was referred to our Department of Radiology to undergo examinations that would establish whether the infected bone and tissue were removed. Magnetic resonance imaging (MRI) was performed to provide detailed information. To be sure that all the infected tissue was removed from the cavity swab sample was collected from the oral cavity for microbiological evaluation.

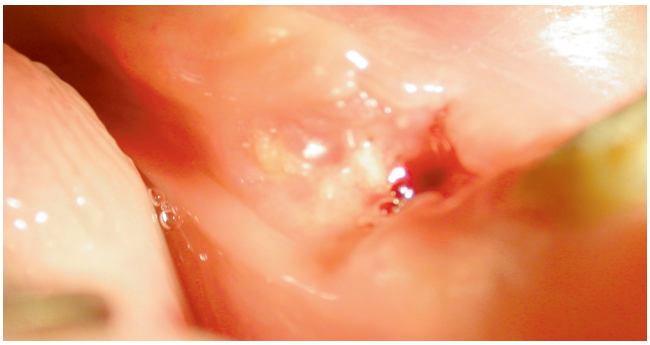

Figure 3. Wound healing, 10 days after extraction

The histopathologic diagnosis was osteomyelitis with active chronic inflammation and bone resorption (Figures 4A, 4B). Two types of α-hemolytic streptococci were identified in the culture. MRI revealed bone marrow edema and infection in the medulla from the angle of the mandible to tooth 36. The buccal and lingual cortical bone was healthy. The results of MRI confirmed the diagnosis of osteomyelitis (Figure 5).

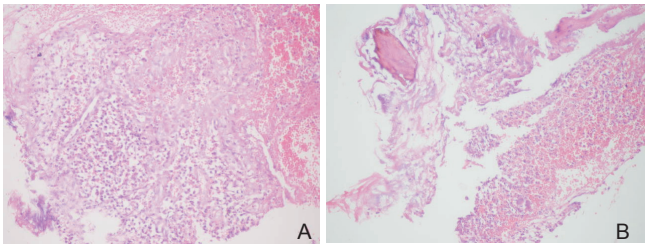

Figure 4. Histogical sections. **A.** Mixed inflammation (H&E x 200), **4.** Mixed inflammation and bone destruction. (H&E x 200)

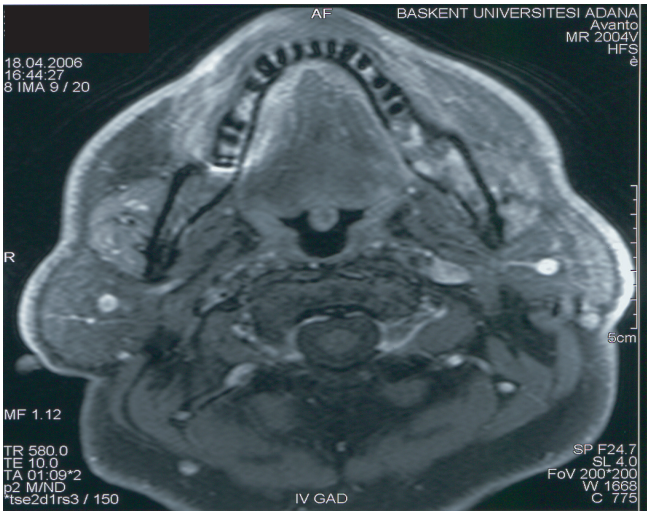

Figure 5. Magnetic resonance imaging view

Bone marrow transplantation was performed with no complications.

Discussion

BPs, which inhibit bone resorption, have been approved for the treatment of bone involvement in patients with multiple myeloma. They can block the development of osteoclasts from monocytes, induce osteoclast apoptosis, prevent the migration of osteoclasts to the bone surface, and inhibit the production of bone-resorbing cytokines by bone marrow stromal cells (9). BPs appear to have an antimyeloma effect in vivo (9). Recently, osteonecrosis has been found to be associated with BP therapy (5-8,10). The term "osteonecrosis of the jaw" (ONJ) refers to the death of jaw bone as a result of impaired blood supply to the affected areas. Cancer and its treatment have been described as risk factors for developing osteonecrosis. Osteonecrosis is an adverse effect of both radiotherapy and chemotherapy. Tooth extraction that serves as a trigger event for osteonecrosis is a common observation in the reports of many authors (5,6,8,11). Trauma, improper restorations and the presence of a prosthesis appear to be predisposing factors for developing ONJ, which can also occur after a secondary inflammation. In many patients with ONJ, the results of panoramic radiographs at the site of osteonecrosis are within normal limits, especially in the early stages of the disease (12). In a study by Badros et al. neither MRI nor conventional radiology revealed any abnormalities at the sites of osteonecrosis. In that study, treatment with BPs was terminated in all patients in whom ONJ was diagnosed, and the authors reported that several patients with ONJ also exhibited evidence of osteomyelitis (12).

Patients with multiple myeloma have an increased risk of developing infections. Neutropenia, chemotherapy and a decrease in the production of normal levels of immunoglobulins produce a major suppression of the immune system in patients with myeloma (13). It has been reported that patients with multiple myeloma and ONJ may have a concurrent infection. In one study, microorganisms were isolated in 7 of 17 patients with myeloma and associated ONJ treated with BPs, and the most common organism was actinomycosis. It has been stated that if osteoclastic recovery is incomplete and enhanced debris is present, a fertile bacterial medium

may develop (14). Therefore, it might be very difficult to decide whether osteomyelitis of the jaw is associated with BP treatment, especially when osteomyelitis of the jaw occurs without osteonecrosis.

Our patient was in good clinical condition at the time of his admission for oropharyngeal evaluation. He had no history of a recent neutropenic episode or a systemic infection. His serum levels of immunoglobulins were within normal limits. He had received his last treatment with combination chemotherapy 6 weeks prior to his admission, and he was receiving monthly treatment with BPs. In this patient, clinical view of alveolar bone after the extraction was not necrotic. The results of histologic examination of surgically removed bone revealed active chronic inflammation consistent with osteomyelitis without necrosis, a finding that conflicts with information in some previous reports (12).

Bamias et al. have shown that the length of the exposure to BPs is strongly associated with the development of ONJ and seems to be an important risk factor for the development of ONJ-related complications (10). Badros et al. stopped using BPs to treat patients in whom ONJ had been diagnosed (12), but Lenz et al. did not recommend the withdrawal of BP treatment after a diagnosis of ONJ (15). Talamo et al. focused their research on the cumulative effect of treatment with BPs (16).

To our knowledge, this is the first report of osteomyelitis without ONJ in a patient who was treated with BPs. Our patient was treated with those agents after having improper root-canal treatment. After extraction of the tooth following antibiotic prophylaxis, wound healing was uneventful, and the treatment regimen for multiple myeloma was delayed but not cancelled.

We strongly recommend that all patients with a systemic disease undergo dental examination. Undiagnosed or uncontrolled periodontal or dental infections or potential sources of infections in the mouth could be a trigger for a secondary infection and could contribute to the development of more complex and advanced disorders that affect treatment outcomes. Contrary to this, systemic diseases and drug administrations could be a trigger for asymptomatic dental/periodontal diseases.

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