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Osteonecrosis of the Jaw in the Absence of Antiresorptive or Antiangiogenic Exposure: A Series of 6 Cases

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Abstract

Purpose—Medication-related osteonecrosis of the jaws (MRONJ) is a well-described complication of anti-resorptive and antiangiogenic medications. Although osteonecrosis can be associated with other inciting events and medications, such as trauma, infection, steroids, chemotherapy, and coagulation disorders, these are rarely reported in the literature.

Materials and Methods—This is a six case series of MRONJ associated with medications other than anti-resorptive or antiangiogenic drugs.

Results—Patient demographics, incitingevent, location, stage, imaging findings, and outcome are reported.

Conclusion—With the continued development and clinical use of new biologic medications for diseases such as cancer and rheumatoid arthritis, it is important to continue to evaluate their effects on the oral cavity. The degree of risk for osteonecrosis in patients taking these new classes of drugs is uncertain but warrants awareness and monitoring.

Although valuable in clinical practice, antiresorptive therapies and bisphosphonates (BPs), and denosumab in particular, increase the risk of osteonecrosis of the jaw (ONJ).[1–5] Since 2003, the number of ONJ cases has increased substantially. ONJ can range from minor bone exposure that is mostly asymptomatic to more severe cases with extensive bone exposure, pain, infection, jaw fracture, and fistulas.[4,6,7] Several professional associations have produced position papers to describe the clinical symptoms, radiographic findings, and recommended management of patients with ONJ.[6–10] As knowledge and understanding of the pathogenesis and spectrum of presentation of ONJ have increased, modifications to the nomenclature, staging, and medications associated with the disease have been implemented. The most recent American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper includes BPs, denosumab, and antiangiogenic drugs as agents related to the presence of ONJ.[6] Currently, medication-related ONJ (MRONJ) is defined as exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial

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region for at least 8 weeks with a history of antiresorptive or antiangiogenic medication in the absence of radiation therapy to the jaws.

With the national focus on MRONJ and the effect on patients' quality of life, clinicians have turned their attention toward identifying at-risk patients on antiresorptive medications and recommending preventative measures. However, there is growing evidence that suggests the development of ONJ in patients without a history of antiresorptive exposure.[11,12] Recent pharmacologic therapies used in the treatment of rheumatoid arthritis (RA) also have been implicated in the development of ONJ.[13,14]

Although disease-modifying antirheumatic drugs are linked to adverse effects on bone metabolism, early research has shown possible negative effects of these medications on osseous healing.[15] Moreover, reports have described necrotic exposed bone in the oral cavity in patients treated with other medications, including steroids, methotrexate, and chemotherapeutics, or as a result of infection, coagulation disorders, or trauma.[14,16–24] Currently, MRONJ related to BPs and denosumab has been well described in the literature.[6] However, when patients present with clinically exposed, necrotic bone and radiographic findings similar to classic MRONJ, it is important to report and compare these findings to identify a new population of potentially at-risk patients for whom preventative measures can be taken. This report presents 6 cases of ONJ without relevant antiresorptive exposure (Table 1).

Report of Cases

CASE 1

An 83-year-old woman with a history of RA, hypertension, hyperlipidemia, and distant history of smoking (40 yr previously) presented with a poorly healing site in the right posterior maxilla. Her dental history included placement of 2 maxillary crowns and scaling and root planning in the right upper quadrant. Two weeks later, she reported a small area of exposed bone and was started on a 3-week course of antibiotics. The area continued to be exposed and painful, with difficulty eating for 8 weeks, after which she was referred for hyperbaric oxygen therapy by her primary physician. Her medication history was noteworthy for methotrexate use for 5 years to treat her RA.

On examination, she had a small area of denuded bone that was visible along the buccal aspect of the upper right second molar and upper right first molar, which exhibited Class II mobility and deep periodontal pocketing. There was gingival erythema, minimal purulent drainage, and tenderness around the buccal and palatal areas of the exposed bone. On radiographic examination (high-resolution cone-beam computed tomographic [CBCT] scan), caries destruction and resorption of the upper right second molar and upper right first molar were seen with widening of the periodontal ligament around the distobuccal root of the upper right first molar. There also was severe localized bone loss between the upper right second molar and upper right first molar extending into the furcation of the upper right first molar. Substantial thickening of the mucoperiosteal lining along the walls and floor of the right maxillary sinus with blockage of the osteomeatal complex also was seen.

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The patient was diagnosed with stage III ONJ of the right posterior maxilla owing to the extension into the right maxillary sinus. She was managed with conservative therapy, including a prolonged course of antibiotics. At her 3-month follow-up, the denuded bone had sequestered and detached from the maxilla, where the site had completely healed. At this time, hyperbaric oxygen therapy was suspended. Approximately 6 months later, she presented with increased pain and erythema at the same site. The teeth (upper right second molar and upper right first molar) were treated with endodontics and sectioned at the gingival level. The area of exposed bone and root surface healed, and the patient has been symptom free for more than 2 years (Fig 1).

CASE 2

A 42-year-old woman with a history of RA presented with poor wound healing and bone spicules extruding from a previously extracted tooth. Approximately 5 months previously, she had undergone a right maxillary tooth extraction (upper right second premolar) that failed to heal. She was started on Peridex rinses and antibiotic therapy that provided some relief from her symptoms.

Her medication history included daily prednisone etanercept for 2 years, tramadol, diclofenac, Cymbalta (duloxetine HCl; Eli Lilly, Indianapolis, IN), and trazadone for her RA. On examination, she presented with a mildly erythematous gingiva and exposed bone along the buccal aspect of the socket of the upper right second premolar.

CBCT scan depicted irregular trabeculation of the alveolar ridge and extraction socket in the area of the tooth. Given her history and constellation of clinical findings, a diagnosis of ONJ stage II was given. After a period of antibiotic therapy and chlorhexidine local wound care, ONJ staging was modified from II to I. After continuing with conservative therapy, including local wound care with chlorhexidine, for almost 1 year, a bony sequestrum was easily debrided from the site, which began to heal. Complete healing with gingival tissue completely covering the site of the previously exposed bone was achieved after 18 months. Since then, she has been symptom free with no clinical or radiographic evidence of ONJ (Fig 2).

CASE 3

A 52-year-old woman presented for evaluation of exposed bone in the left upper quadrant between the upper left first molar and upper left second molar. Her medical history was noteworthy for non-Hodgkin lymphoma treated with chemotherapy, including steroids, followed by stem cell transplantation. She subsequently developed osteoporosis secondary to long-term steroid use. This was managed with hormone replacement therapy and vitamin D, but no BPs. Her social history was noteworthy for smoking (15–pack-year history).

Her oral symptoms began approximately 1 year previously, when she developed a pocket between the upper left first molar and upper left second molar while undergoing chemotherapy, but failed to see a dentist during this time. She developed a foul taste with left cheek swelling. She was seen for scaling and root planing and a bone recontouring procedure. On examination, there was a 6- to 7-mm pocket with gingival recession and bone that could be probed through a deep pocket between the upper left first molar and upper left

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second molar (along the buccal and palatal aspects), although frank bone exposure was absent. There was no evidence of infection or other areas of bone exposure. CBCT scan showed sclerotic bone with thickening of the left sinus mucosa near the upper left first molar and upper left second molar.

She was diagnosed with stage II ONJ of the left posterior maxilla owing to the presence of bone that could be clinically probed. This was conservatively managed with a prolonged course of amoxicillin in addition to improved oral hygiene, local wound care with chlorhexidine, and routine nonsurgical oral prophylaxis. She was lost to follow-up for 2 years and returned with new foul taste and pain in the same area. She had continued the chemotherapeutic medications, which then included rituximab, a chimeric monoclonal antibody against the protein CD20 found mostly on the surface of B cells, and bendamustine, a nitrogen mustard alkylating agent. On examination, her periodontal pocket was increased to 9 to 10 mm with deep bone exposure. There was no purulence, but bleeding on probing was present. CBCT scan visualized a craterlike defect between the furcation areas of the upper left first molar and upper left second molar with localized severe bone loss and mildly sclerotic surrounding trabecular bone. There was near opacification of the right and left maxillary sinuses. At this time, she was diagnosed with stage III ONJ. She was treated with conservative therapy, including amoxicillin, local wound care with chlorhexidine, and nonsurgical prophylaxis (Fig 3).

CASE 4

A 70-year-old woman presented with a small opening in the gingiva on the left edentulous maxillary alveolar ridge with bleeding and sensitivity. She had no history of recent extractions or trauma, osteoporosis, cancer, or antiresorptive therapy. She had a history of osteoarthritis and previously received multiple local hip steroid injections. Her other medications included Elavil (amitriptyline; AstraZeneca, London, England), Celebrex (celecoxib; Pfizer, New York, NY), Flonase (fluticasone; GlaxoSmithKline, Middlesex, UK), hydrochlorothiazide, Claritin (loratadine; Bayer, Leverkusen, Germany), Micardis (telmisartan; Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT), and Crestor (rosuvastatin calcium; AstraZeneca, London, UK). She also had been given amoxicillin for the bleeding and pain in the upper right alveolar ridge. On examination, the left posterior maxilla showed an open area in the attached gingiva with bleeding. Although there was no frank bone exposure, bone could be probed through the opening in the gingiva.

CBCT scan depicted a large osteolytic defect in the posterior left maxilla with sequestrum formation and trabecular sclerosis to the midline. Owing to the extent of the sequestrum, she was given the diagnosis of stage III ONJ. She was instructed on local oral wound care with chlorhexidine and her symptoms subsided. She has been maintained without increased exposure or healing. Approximately 6 months later, the sequestrum exfoliated (Fig 4).

CASE 5

A 66-year-old woman presented with a history of the lower left second molar extraction 2 years previously. She had swelling and pain 2 to 3 weeks later, underwent antibiotic therapy, and incision and drainage. The area seemed to be healing well, but then the gingiva opened

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and bone was exposed. The site continued to drain and cause pain. Approximately 6 months later, an extraoral fistula appeared in the left submental area, which was draining serosanguinous fluid. She had been taking oral cephalexin for almost 2 years. Her medical history was noteworthy for hypertension, anemia, gastroesophageal reflux disease, and RA. Her medications included prednisone, hydrochlorothiazide, and Plaquenil (hydroxychloroquine; Concordia Pharmaceuticals, Ontario, Canada). She had a history of alendronate orally, which she received for 2 years, and stopped more than 2 years previously, before the tooth extraction. She also had previously taken adalimumab and etanercept for her RA. On examination, she had an extraoral fistula on the left submental area. Intraorally, exposed bone in the extraction site for the lower left second molar and erythema, edema, minimal purulence, and tenderness to palpation were observed.

CBCT visualized extensive sclerosis of the anterior and posterior mandible with irregular lytic lesions of the cortical and trabecular bone in the anterior lingual mandible. Partial sequestrum formation was seen in the left anterior mandible. She was diagnosed with stage III ONJ. She has been managed conservatively with local intraoral and extraoral wound care with chlorhexidine. She has no pain or active infection, but still has exposed bone in the left posterior mandible and scarring on the submental area (Fig 5).

CASE 6

A 41-year-old woman presented with pain, bleeding, and exposed bone in the buccal right maxillary area adjacent to the upper left first premolar. She had previously undergone a pulpectomy procedure on the upper left second premolar approximately 1 year previously and did not return for the completion of the endodontic therapy. The pain had increased during the past several months before she presented for evaluation. Her medical history was noteworthy for fibromyalgia and a history of multiple bone fractures. She took no medications other than occasional ibuprofen or aspirin. On examination, exposed bone was present on the buccal alveolar ridge adjacent to the root of the upper left second premolar. The upper left first premolar had Class II mobility with erythema and edema of the gingiva around the upper left first premolar and upper left second premolar with tenderness to palpation. CBCT displayed a sequestrum of the buccal cortical plate in the area of teeth the upper left first premolar and upper left second premolar, with the superior margin extending to the apical third of the root of the upper left second premolar. A second small, round sequestrum of alveolar bone was noted at the palatal aspect of the alveolar crest between the upper left canine and upper left first premolar with moderate periodontal bone loss along the root surface of the upper left first premolar and apical inflammation of the upper left second premolar.

A diagnosis of stage II ONJ was given. The patient was managed with local oral wound care with chlorhexidine and the buccal sequestrum exfoliated without difficulty. She has healed well and has remained symptom free (Fig 6).

Discussion

ONJ is a well-known adverse effect of antiresorptive medications such as BPs, especially when administered intravenously for primary or metastatic bone cancer.[6,7] During the past

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several years, other antiresorptive medications such as denosumab have been associated with ONJ.[3,6,25,26] Interestingly, case reports have reported on ONJ-like lesions without exposure to BPs or other antiresorptive drugs.[11,14,27,28] This prompted the AAOMS to amend the position paper to include antiangiogenic medications associated with ONJ, alone and in combination with BPs.[6,11,28–37]

This report described 6 cases of ONJ between 2012 and 2015 of approximately 100 patients with MRONJ associated with antiresorptive medications. All patients were self-referred or were referred from their dentist or physician to address the symptomatology or exposed bone. In the 6 present cases, there were no antiresorptive or antiangiogenic medications, although 1 case had a short and distant history of oral BP use. However, ONJ has been reported in patients not receiving BPs, denosumab, or antiangiogenics. These cases are rare and are associated with glucocorticoids, infection, trauma, chemotherapy, and coagulation disorders.[14,16–24] Diseases such as RA and the medications used to treat it can present a risk for impaired healing and can present lesions clinically and radiographically identical to ONJ. The present inciting events are similar to those for MRONJ and include extractions, periodontal disease, trauma, implants, or even spontaneous or unknown.[4,6,38,39] However, less common medications or disease processes are associated with these cases, including methotrexate, etanercept, prednisone, adalimumab, rituximab, and distant local steroid injections. To the best of the authors' knowledge, this is the first report of ONJ associated with etanercept, adalimumab, and rituximab.

RA was the primary disease affecting 3 of the 6 patients in this case series. RA is a prevalent inflammatory autoimmune disease affecting mostly women younger than 60 years, causing considerable join pain, destruction, and restriction of movement.[40] The pathophysiology involves blood vessels, lymphocytes, and synovial cells that lower the pain threshold and activate T and B cells in response to inflammatory mediators.[41] Because tumor necrosis factor (TNF) plays a major role in RA-associated inflammation, it is not surprising that anti-TNF–targeted therapies have been developed to treat the disease. Several of these were being used by the present patients, including adalimumab, a monoclonal antibody against TNFα, and etanercept, a soluble TNF-receptor fusion protein.[40–42] Although the ONJ appearance in these patients was clinically and radiographically similar to that seen in patients on antiresorptive medications, whether the ONJ pathogenesis is the same in these 2 patient populations is unclear. TNF receptors or inhibitors do not exhibit direct inhibition of osteoclasts the way BPs or denosumab do. However, TNFα does stimulate osteoclast development and function directly, and stimulates bone marrow stromal cells to increase the macrophage colony-stimulating factor and osteoblasts to decrease osteoprotegerin production.[43,44] TNFα-inhibiting biologics prevent the function of TNFα through lysis or apoptosis of macrophages with membrane-bound TNFα.[45,46] Interestingly, etanercept decreases the ratio of M1 to M2 macrophages, which attenuated orthodontic root resorption in mice.[46] Moreover, changing the M1-to-M2 ratio with interleukin-17 led to an increase in ONJ incidence compared with mice receiving zoledronate alone.[47]

Interestingly, a more conventional therapy for RA, methotrexate, was associated with ONJ in 1 case in this series. However, another patient was taking methotrexate and etanercept. This is surprising, especially because methotrexate has been used for many years without reports

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of ONJ. Methotrexate is a commonly used antimetabolite and antifolate drug in the treatment of cancer and RA.[48–50] At chemotherapeutic doses, methotrexate has been shown to inhibit bone formation and mineralization and could be associated with increased bone resorption, as shown by increased osteoclast density.[51–53] The literature did report on 1 case of ONJ associated with methotrexate, but it was in a patient previously treated with BPs.[13]

Interestingly, all the patients in this case series were women and were peri- or postmenopausal, with the expected decrease in estrogen levels. This estrogen deficiency could have altered bone homeostasis, even if such effects probably were not so severe to prompt the diagnosis of osteopenia or osteoporosis in most of these patients. Thus, the combination of a systemic disease that increases inflammatory signals, such as RA, could have altered alveolar bone homeostasis because of estrogen deficiency, agents that compromise immune response, and a local instigating factor, such as dental infection or local trauma, to create the perfect storm that led to ONJ in our patients, even in the absence of antiresorptive medications. Whether the intra-articular hip injections had any direct effect on the oral tissues of case 4 is not certain and could be unrelated. Rare cases of oral ulcerative bone sequestration in the jaws have been reported[7] and this patient could present such a case.

The aim of this case series was to highlight the fact that despite the awareness of the role antiresorptive medications in ONJ pathophysiology, other pharmacologic and nonpharmacologic factors can have similar clinical effects. By highlighting these cases, the authors add to the growing body of literature on emerging classes of drugs that have been linked to an increased risk of ONJ. The degree of risk for osteonecrosis in patients taking these new classes of drugs is uncertain but warrants awareness and close monitoring. The authors hope this information will bring awareness to clinicians and allow early detection of this disease process so that appropriate measures can be taken to halt progression and lead to disease resolution.

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References

1. Fizazi K, Carducci M, Smith M, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. Lancet. 2011; 377:813. [PubMed: 21353695]
2. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol. 2011; 29:1125. [PubMed: 21343556]
3. Lipton A, Fizazi K, Stopeck AT, et al. Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: A combined analysis of 3 pivotal, randomised, phase 3 trials. Eur J Cancer. 2012; 48:3082. [PubMed: 22975218]
4. Marx RE, Sawatari Y, Fortin M, et al. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg. 2005; 63:1567. [PubMed: 16243172]

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5. Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. J Clin Oncol. 2010; 28:5132. [PubMed: 21060033]
6. Ruggiero SL, Dodson TB, Fantasia J, 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; 72:1938. [PubMed: 25234529]
7. Khan AA, Morrison A, Hanley DA, et al. International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. J Bone Miner Res. 2015; 30:3. [PubMed: 25414052]
8. Yoneda T, Hagino H, Sugimoto T, et al. Bisphosphonate-related osteonecrosis of the jaw: Position paper from the Allied Task Force Committee of Japanese Society for Bone and Mineral Research, Japan Osteoporosis Society, Japanese Society of Periodontology, Japanese Society for Oral and Maxillofacial Radiology, and Japanese Society of Oral and Maxillofacial Surgeons. J Bone Miner Metab. 2010; 28:365. [PubMed: 20333419]
9. Migliorati CA, Casiglia J, Epstein J, et al. Managing the care of patients with bisphosphonate-associated osteonecrosis: An American Academy of Oral Medicine position paper. J Am Dent Assoc. 2005; 136:1658. [PubMed: 16383047]
10. Hellstein JW, Adler RA, Edwards B, et al. American Dental Association Council on Scientific Affairs Expert Panel on Anti-resorptive Affairs. Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis: Executive summary of recommendations from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc. 2011; 142:1243. [PubMed: 22041409]
11. Fleissig Y, Regev E, Lehman H. Sunitinib related osteonecrosis of jaw: A case report. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012; 113:e1.
12. Baur DA, Weber JM, Collette DC, et al. Osteonecrosis of the jaws unrelated to bisphosphonate exposure: A series of 4 cases. J Oral Maxillofac Surg. 2012; 70:2802. [PubMed: 22520563]
13. Alsalleeh F, Keippel J, Adams L, et al. Bisphosphonate-associated osteonecrosis of jaw reoccurrence after methotrexate therapy: A case report. J Endod. 2014; 40:1505. [PubMed: 25146044]
14. Horie N, Kawano R, Kaneko T, et al. Methotrexate-related lymphoproliferative disorder arising in the gingiva of a patient with rheumatoid arthritis. Aust Dent J. 2015; 60:408. [PubMed: 25302816]
15. Annussek T, Kleinheinz J, Thomas S, et al. Short time administration of antirheumatic drugs—Methotrexate as a strong inhibitor of osteoblast's proliferation in vitro. Head Face Med. 2012; 8:26. [PubMed: 23021595]
16. Lambade P, Lambade D, Saha TK, et al. Maxillary osteonecrosis and spontaneous teeth exfoliation following herpes zoster. Oral Maxillofac Surg. 2012; 16:369. [PubMed: 22069058]
17. Meer S, Coleman H, Altini M, et al. Mandibular osteomyelitis and tooth exfoliation following zoster-CMV co-infection. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006; 101:70. [PubMed: 16360610]
18. Woodmansey KF, White RK, He J. Osteonecrosis related to intraosseous anesthesia: Report of a case. J Endod. 2009; 35:288. [PubMed: 19166792]
19. Almazrooa SA, Chen K, Nascimben L, et al. Case report: Osteonecrosis of the mandible after laryngoscopy and endotracheal tube placement. Anesth Analg. 2010; 111:437. [PubMed: 20495140]
20. Farah CS, Savage NW. Oral ulceration with bone sequestration. Aust Dent J. 2003; 48:61. [PubMed: 14640160]
21. Schwartz HC. Osteonecrosis of the jaws: A complication of cancer chemotherapy. Head Neck Surg. 1982; 4:251. [PubMed: 6896046]
22. Sung EC, Chan SM, Sakurai K, et al. Osteonecrosis of the maxilla as a complication to chemotherapy: A case report. Spec Care Dentist. 2002; 22:142. [PubMed: 12449457]
23. Glueck CJ, McMahon RE, Bouquot JE, et al. A preliminary pilot study of treatment of thrombophilia and hypofibrinolysis and amelioration of the pain of osteonecrosis of the jaws. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998; 85:64. [PubMed: 9474617]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

24. Pogrel MA, Miller CE. A case of maxillary necrosis. J Oral Maxillofac Surg. 2003; 61:489. [PubMed: 12684969]
25. Aghaloo TL, Dry SM, Mallya S, et al. Stage 0 osteonecrosis of the jaw in a patient on denosumab. J Oral Maxillofac Surg. 2014; 72:702. [PubMed: 24397946]
26. Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on denosumab. J Oral Maxillofac Surg. 2010; 68:959. [PubMed: 20149510]
27. Marino R, Orlandi F, Arecco F, et al. Osteonecrosis of the jaw in a patient receiving cabozantinib. Aust Dent J. 2015; 60:528. [PubMed: 25474298]
28. Koch FP, Walter C, Hansen T, et al. Osteonecrosis of the jaw related to Sunitinib. Oral Maxillofac Surg. 2011; 15:63. [PubMed: 20401503]
29. Guarneri V, Miles D, Robert N, et al. Bevacizumab and osteonecrosis of the jaw: Incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. Breast Cancer Res Treat. 2010; 122:181. [PubMed: 20361252]
30. Brunello A, Saia G, Bedogni A, et al. Worsening of osteonecrosis of the jaw during treatment with Sunitinib in a patient with metastatic renal cell carcinoma. Bone. 2009; 44:173. [PubMed: 18849018]
31. Ayllon J, Launay-Vacher V, Medioni J, et al. Osteonecrosis of the jaw under bisphosphonate and antiangiogenic therapies: Cumulative toxicity profile? Ann Oncol. 2009; 20:600. [PubMed: 19188135]
32. Christodoulou C, Pervena A, Klouvas G, et al. Combination of bisphosphonates and antiangiogenic factors induces osteonecrosis of the jaw more frequently than bisphosphonates alone. Oncology. 2009; 76:209. [PubMed: 19212145]
33. Hoefert S, Eufinger H. Sunitinib may raise the risk of bisphosphonate-related osteonecrosis of the jaw: Presentation of three cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010; 110:463. [PubMed: 20692189]
34. Bozas G, Roy A, Ramasamy V, et al. Osteonecrosis of the jaw after a single bisphosphonate infusion in a patient with metastatic renal cancer treated with Sunitinib. Onkologie. 2010; 33:321. [PubMed: 20523097]
35. Smidt-Hansen T, Folkmar TB, Fode K, et al. Combination of zole-dronic acid and targeted therapy is active but may induce osteonecrosis of the jaw in patients with metastatic renal cell carcinoma. J Oral Maxillofac Surg. 2013; 71:1532. [PubMed: 23642545]
36. Kim DW, Jung YS, Park HS, et al. Osteonecrosis of the jaw related to everolimus: A case report. Br J Oral Maxillofac Surg. 2013; 51:e302. [PubMed: 24094895]
37. Santos-Silva AR, Belizario Rosa GA, Castro G Junior, et al. Osteonecrosis of the mandible associated with bevacizumab therapy. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013; 115:e32.
38. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic. J Oral Maxillofac Surg. 2003; 61:1115. [PubMed: 12966493]
39. Migliorati CA, Schubert MM, Peterson DE, et al. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone: An emerging oral complication of supportive cancer therapy. Cancer. 2005; 104:83. [PubMed: 15929121]
40. Aaltonen KJ, Virkki LM, Malmivaara A, et al. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One. 2012; 7:e30275. [PubMed: 22272322]
41. Takeuchi T. Revolutionary change in rheumatoid arthritis management with biological therapy. Keio J Med. 2011; 60:75. [PubMed: 21979826]
42. Tracey D, Klareskog L, Sasso EH, et al. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. Pharmacol Ther. 2008; 117:244. [PubMed: 18155297]
43. Harre U, Kittan NA, Schett G. Autoantibody-mediated bone loss. Curr Osteoporos Rep. 2014; 12:17. [PubMed: 24407713]
44. Braun T, Zwerina J. Positive regulators of osteoclastogenesis and bone resorption in rheumatoid arthritis. Arthritis Res Ther. 2011; 13:235. [PubMed: 21861862]
45. Teitelbaum SL. Bone resorption by osteoclasts. Science. 2000; 289:1504. [PubMed: 10968780]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

46. He D, Kou X, Luo Q, et al. Enhanced m1/m2 macrophage ratio promotes orthodontic root resorption. J Dent Res. 2015; 94:129. [PubMed: 25344334]

47. Zhang Q, Atsuta I, Liu S, et al. IL-17-mediated M1/M2 macrophage alteration contributes to pathogenesis of bisphosphonate-related osteonecrosis of the jaws. Clin Cancer Res. 2013; 19:3176. [PubMed: 23616636]

48. Scott DL. Biologics-based therapy for the treatment of rheumatoid arthritis. Clin Pharmacol Ther. 2012; 91:30. [PubMed: 22166850]

49. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: A systematic literature research. Ann Rheum Dis. 2009; 68:1100. [PubMed: 19060002]

50. King TJ, Georgiou KR, Cool JC, et al. Methotrexate chemotherapy promotes osteoclast formation in the long bone of rats via increased pro-inflammatory cytokines and enhanced NF-kappaB activation. Am J Pathol. 2012; 181:121. [PubMed: 22642908]

51. Friedlaender GE, Tross RB, Doganis AC, et al. Effects of chemotherapeutic agents on bone. I. Short-term methotrexate and doxorubicin (Adriamycin) treatment in a rat model. J Bone Joint Surg Am. 1984; 66:602. [PubMed: 6707039]

52. Wheeler DL, Vander Griend RA, Wronski TJ, et al. The short- and long-term effects of methotrexate on the rat skeleton. Bone. 1995; 16:215. [PubMed: 7756050]

53. Halton JM, Atkinson SA, Fraher L, et al. Mineral homeostasis and bone mass at diagnosis in children with acute lymphoblastic leukemia. J Pediatr. 1995; 126:557. [PubMed: 7699533]

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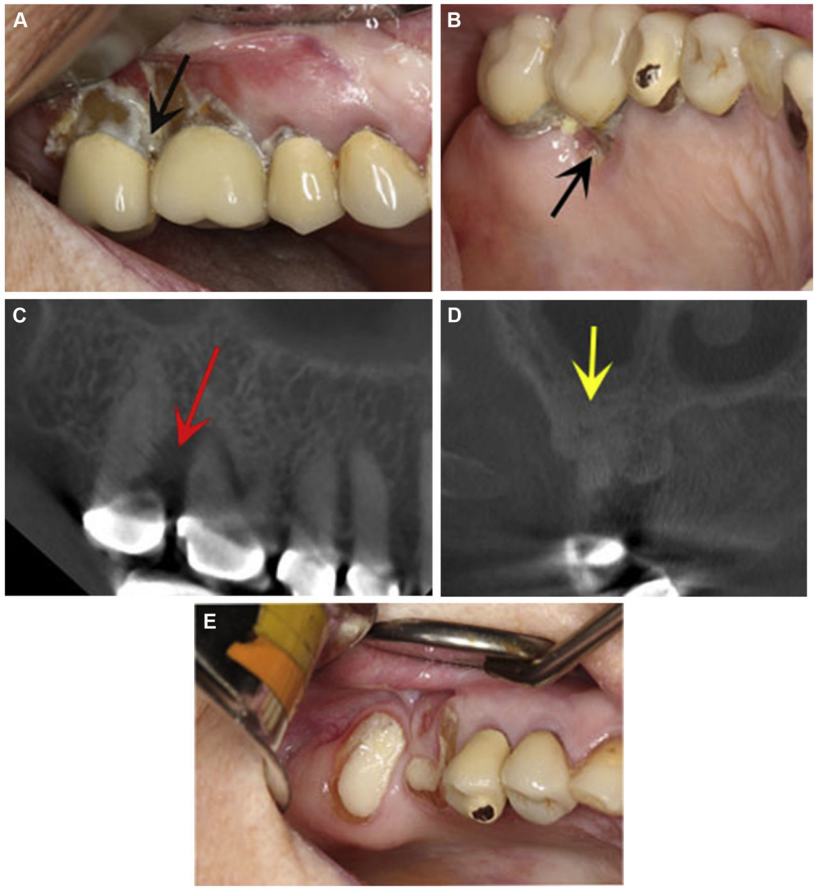

FIGURE 1.

A, Exposed buccal bone between the upper right second molar and upper right first molar. *B*, Exposed palatal bone of the upper first third molar with surrounding plaque and erythema (*black arrows*). *C*, Cone-beam computed tomogram displays serious bone loss (*red arrow*). *D*, Cone-beam computed tomogram shows sclerotic bone (*yellow arrow*) in the right posterior maxilla. *E*, Substantial improvement is seen, without exposed bone, after endodontic therapy performed on the upper right second molar and upper right first molar and the teeth are sectioned at the gingival level.

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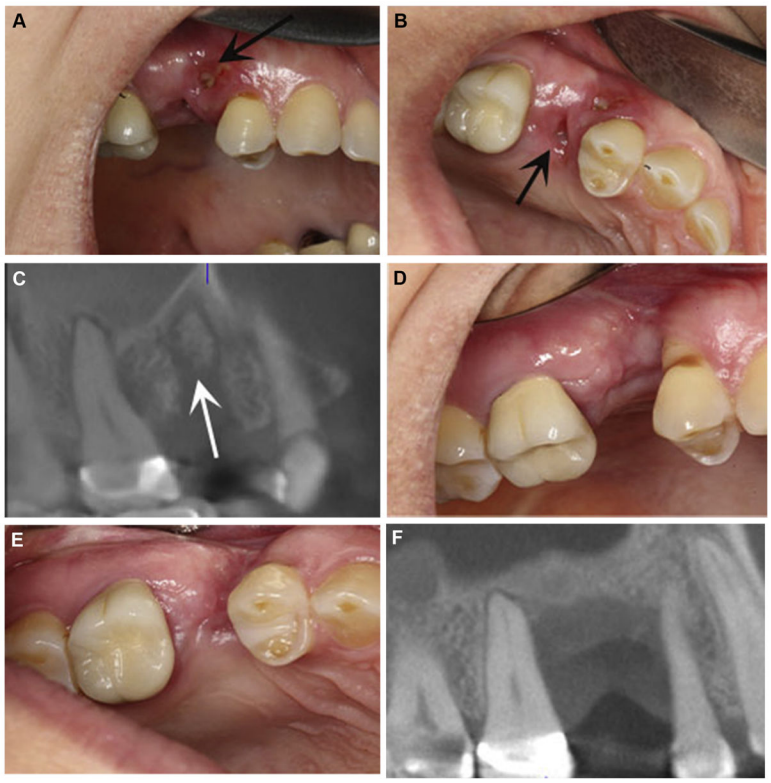

FIGURE 2.

A, *B*, Exposed bone is visible on the buccal and alveolar crest of the upper right second premolar extraction site (*black arrows*). *C*, Cone-beam computed tomogram depicts bony sequestra (*white arrow*) and residual bone graft material. *D*, *E*, After sequestra exfoliation, the area has healed. *F*, Healed area but with a large bony defect.

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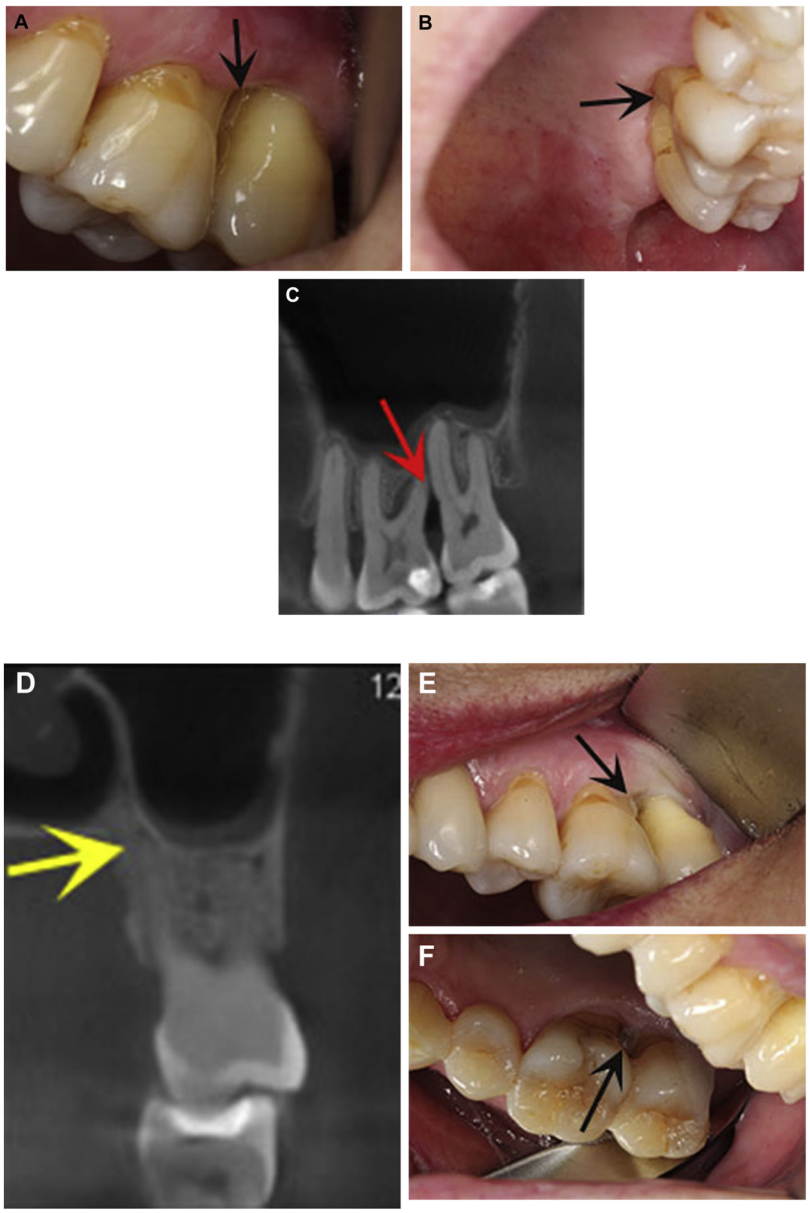

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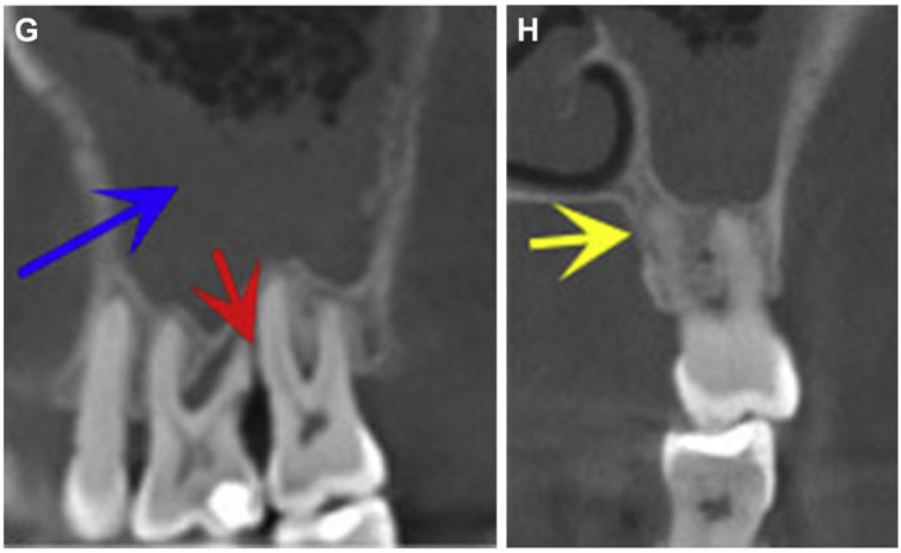

FIGURE 3.

Bone that can be probed through the gingiva is seen from the *A*, buccal and *B*, palatal views (*black arrows*). *C*, Cone-beam computed tomogram shows a large bony defect between the upper left first molar and upper left second molar (*red arrow*). *D*, Cone-beam computed tomogram shows sclerotic trabecular bone (*yellow arrow*). *E*, *F*, After 2 years, the exposed bone has progressed clinically (*black arrows*). *G*, *H*, Radiographically, there is maxillary sinusitis (*blue arrow*) and an increased bony defect (*red arrow*) with trabecular sclerosis (*yellow arrow*).

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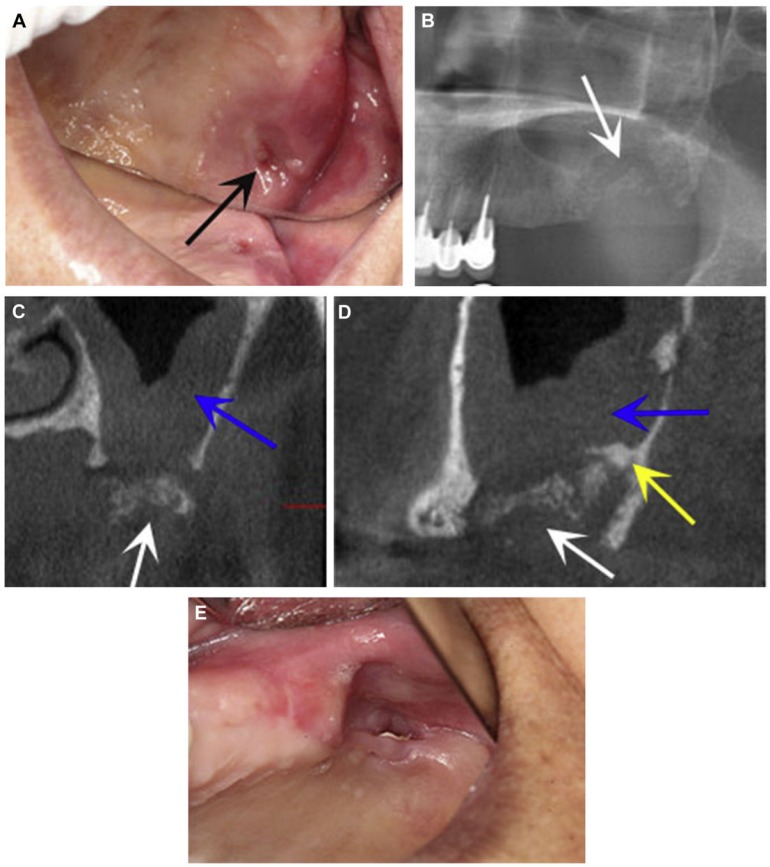

FIGURE 4.

A, A small erythematous lesion where bone can be probed through the mucosa is seen on the left maxillary alveolar ridge (*black arrow*). *B*, Panoramic radiograph visualizes some possible bony sequestra (*white arrow*). *C*, *D*, Cone-beam computed tomograms clearly display the bony sequestra (*white arrows*). A large osteolytic lesion, trabecular sclerosis, and substantial thickening of the sinus membrane (*blue arrows*) also are visualized. *E*, After exfoliation of the bony sequestrum, the area appears healed, but a large bony defect remains.

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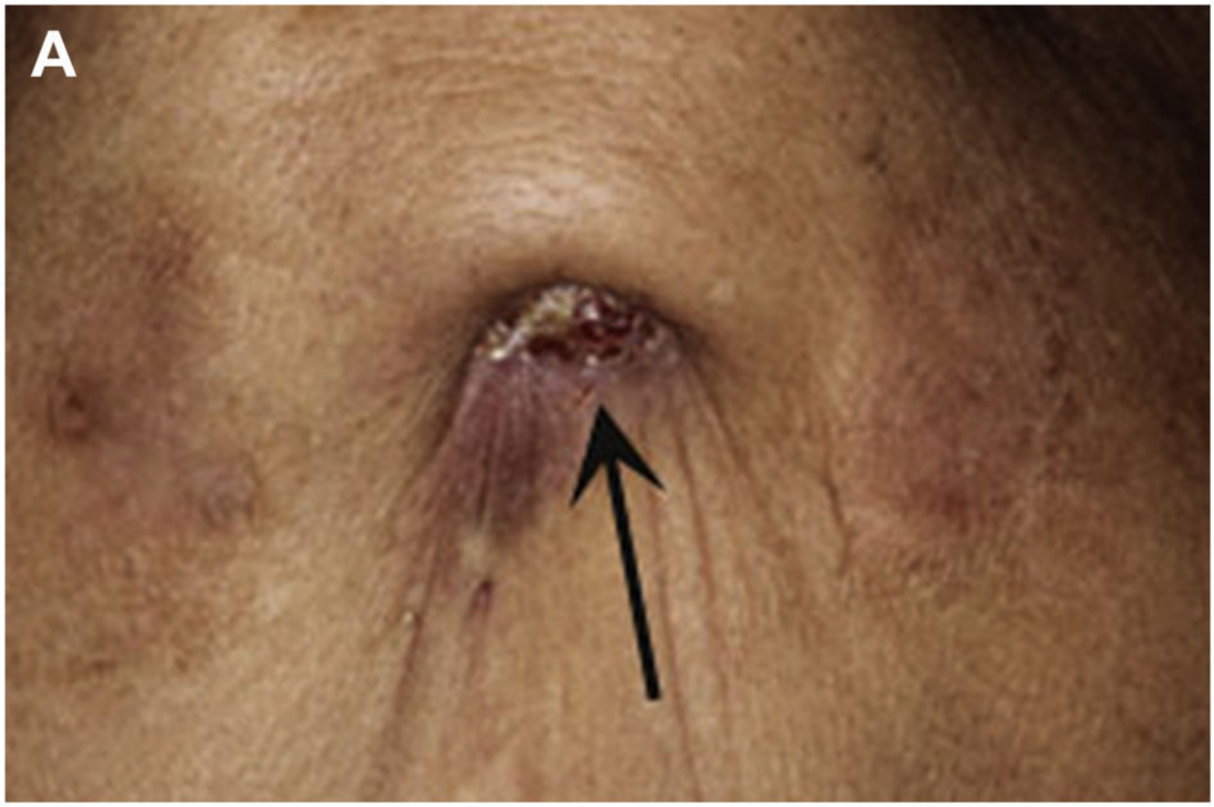

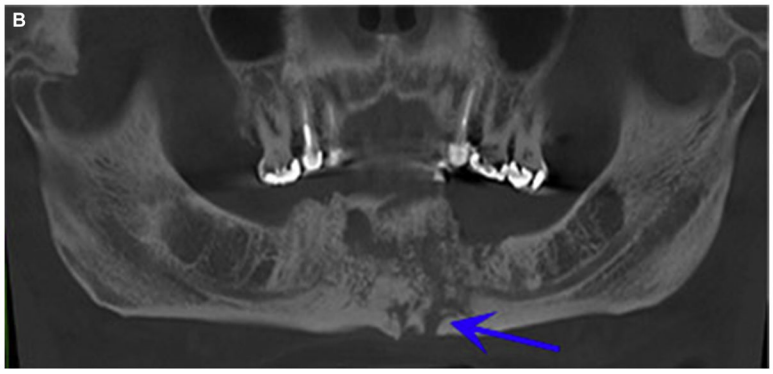

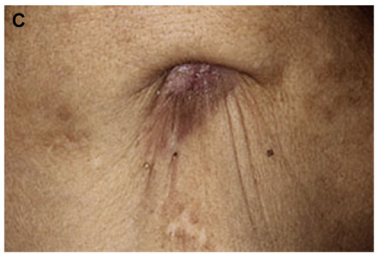

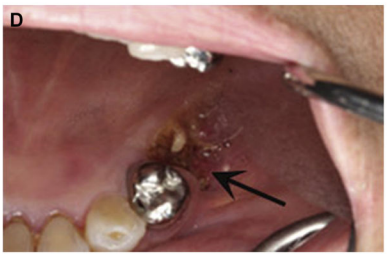

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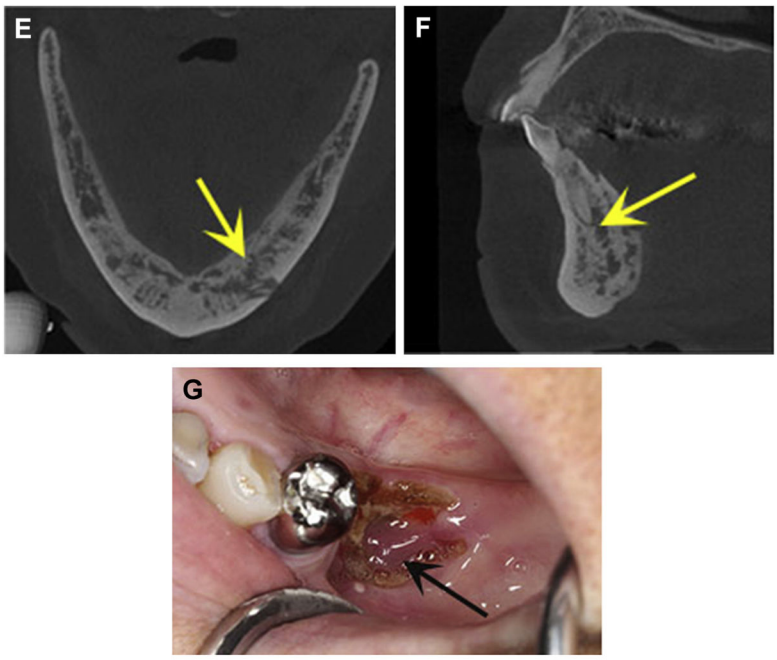

FIGURE 5.

A, An extraoral fistula (*black arrow*) is seen in the left submental area that represents sclerotic bone and a possible pathologic fracture. *B*, Cone-beam computed tomogram depicts the possible fracture (*blue arrow*). *C*, Extraction socket of the lower left second molar exhibits exposed bone (*black arrow*). *D*, *E*, Cone-beam computed tomograms also depict severe trabecular sclerosis (*yellow arrow*). *F*, After conservative therapy, the fistula has closed but has scarred. *G*, Exposed bone is still evident, but without signs of infection (*black arrow*).

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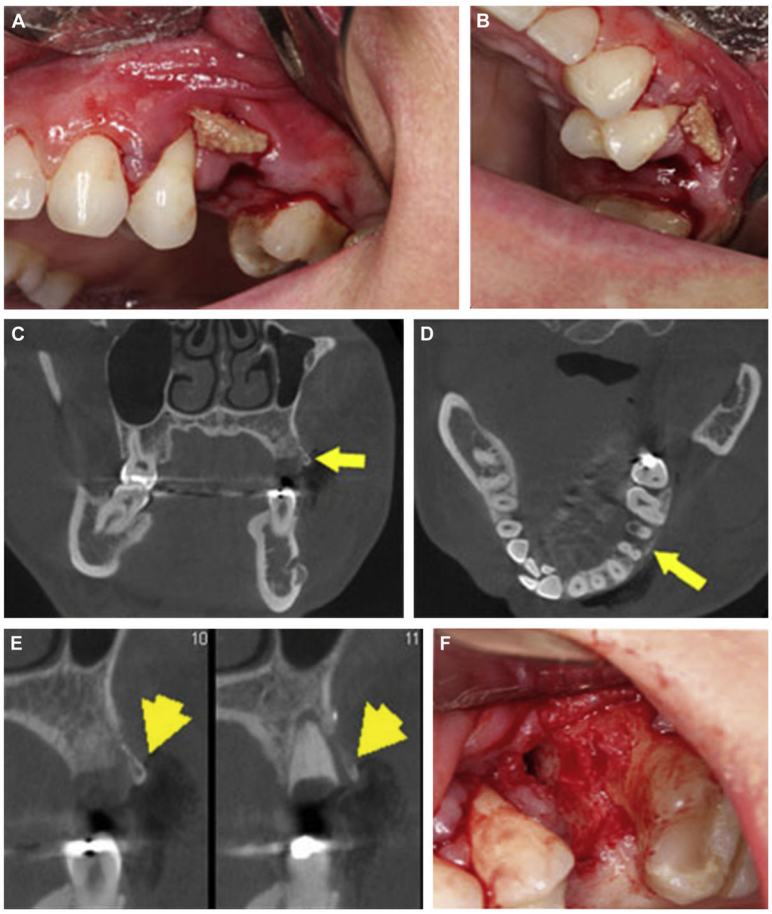

FIGURE 6.

A, *B*, Exposed bone is seen on the left buccal alveolar ridge. Cone-beam tomograms visualize bone sequestra from *C*, coronal, *D*, axial, and *E*, sagittal views (*yellow arrows*). *F*, Exfoliation of the sequestra and extraction of the root.

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Table 1

DEMOGRAPHICS OF SIX CASES OF ONJ WITHOUT RELEVANT ANTIRESORPTIVE OR ANTIANGIOGENIC EXPOSURE

Case	Age (yr)	Gender	Disease	Medications Likely Associated With ONJ	Inciting Event	Location	Stage	Imaging Findings	Outcome
1	83	F	Rheumatoid arthritis	Methotrexate	Periodontal disease	Right posterior maxilla	III	Localized bone loss between upper right second molar and upper right first molar, thickening of sinus mucoperiosteal lining	Complete resolution
2	42	F	Rheumatoid arthritis	Prednisone, etanercept	Extraction	Right maxilla site of upper right second premolar	II	Irregular trabeculation of alveolar ridge and extraction socket	Complete resolution
3	52	F	Lymphoma	Prednisone, rituximab	Periodontal disease, bone recontouring	Left posterior maxilla	III	Craterlike defect with localized severe bone loss and mildly sclerotic trabecular bone	Increased severity
4	70	F	Arthritis	Hip steroid injections	Unknown	Left posterior maxillary alveolar ridge	III	Large osteolytic defect, sequestrum and trabecular sclerosis	Moderate improvement
5	66	F	Rheumatoid arthritis	Etanercept, adalimumab, history of alendronate	Extraction	Anterior, posterior mandible	III	Extensive sclerosis with irregular lytic lesions and partial sequestrum	Minimal improvement
6	41	F	Fibromyalgia	None	Periapical and periodontal disease	Left buccal maxilla	II	Sequestrum	Minimal improvement

Abbreviations: F, female; M, male; ONJ, osteonecrosis of the jaw.

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