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CASE REPORT

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Medication-related osteonecrosis of the jaw: Case series and literature review

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Key Clinical Message

Medication-related osteonecrosis of the Jaw (MRONJ) is a rare complication of the jaws following the administration of antiresorptive or antiangiogenic drugs. This condition poses a major challenge to its management. Its prevention and management need a multidisciplinary collaboration. We described three patients with MRONJ including their presentation, investigations, management protocols, and outcomes. A brief appraisal of the literature on MRONJ was also done.

Abstract

Medication-related osteonecrosis of the jaw (MRONJ) is a rare complication of the jaws following the administration of antiresorptive or antiangiogenic drugs. This condition poses a major challenge to its management. We present an appraisal of the literature and three cases of MRONJ. An appraisal of 3 patients who presented to the oral and maxillofacial clinic with MRONJ was done. Relevant physical examination findings, radiological images, clinical photographs and follow-up was documented. One patient had multiple myeloma while the other two had metastatic cancer. All had received zoledronic acid before developing MRONJ. One patient was surgically treated and successfully recovered while two were managed conservatively. Patients taking antiresorptive medications are at risk of developing MRONJ. Prevention and management of the condition calls for a multidisciplinary collaboration. Patients taking antiresorptive medications need good education on the risks associated with the medications and how to recognize early signs and symptoms.

KEYWORDS

bisphosphonates, case report, jaw, osteonecrosis, zoledronic acid

1 | INTRODUCTION

1.1 | Definition

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse drug reaction, consisting of progressive bone necrosis in the maxillofacial region after exposure to either antiresorptive or antiangiogenic drugs. It presents as exposed bone that has lasted for more than 8 weeks in a patient on current or previous treatment with antiresorptive or antiangiogenic agents, without a history of radiation therapy to the jaws.[1]

1.2 | Associated drugs

Osteonecrosis of the jaw (ONJ) following the administration of medications, especially bisphosphonates (BPs) was first described in 2003 by Marx.[2] Since then, the condition has been studied and described by various authors.[3–5] The drugs associated with MRONJ are either antiresorptive drugs or antiangiogenic drugs. Antiresorptive drugs include BPs and Receptor Activator of Nuclear Kappa – beta Ligand (RANKL) inhibitors. BPs are classified as nitrogen-containing (Zoledronic acid, Pamidronate, Alendronate) or non-nitrogen-containing (etidronate, clodronate, tiludronate). RANKL inhibitors include denosumab and romosozumab. Antiangiogenic drugs include bevacizumab, imatinib, and sunitinib.[6]

1.3 | Risk factors

The primary parameter considered in the risk of developing MRONJ is the therapeutic indication of the drugs.[1,3] The risk of developing ONJ in patients taking these medications due to oncologic reasons, for example metastatic breast cancer is higher compared to those taking them due to osteoporosis.[3]

Risk factors for developing MRONJ are related to both the potency and duration of BPS therapy.[7] The risk among adult patients when taking intravenous (I.V) zoledronic acid is <5% (0%–18.0%) and 0%–6.0% when taking denosumab.[3] Ikesue et al studied 799 patients with bone metastasis undergoing treatment with Zoledronic Acid and Denosumab. Of the 799 patients, 58 (7.3%) developed MRONJ.[8] The risk among adult osteoporotic patients when taking zoledronic acid is 0.02%–0.05% when taking denosumab 0.04%–0.30%, and 0.03%–0.05% when taking romosozumab.[3]

Local factors such as dental caries, periodontitis, dentoalveolar procedures (teeth extractions, periodontal surgeries, implant surgeries), and poor oral hygiene increase the risk of developing MRONJ.[9,10] Tooth extraction after commencement of treatment with Zoledronic Acid or Denosumab was a significant risk factor in a study conducted in Japan.[8] Increased age (>65 years) is also a known risk factor.[1] MRONJ is commonly seen in the mandible compared to the maxilla though it can occur in both the maxilla and the mandible simultaneously.[3]

1.4 | Pathogenesis

Antiresorptive medications inhibit osteoclastic activity causing increased bone density as a result of decreased bone resorption.[5] The increased bone density interferes with bone microcirculation, and this causes avascular necrosis of bone which could be spontaneous or after minor oral surgical procedures in the mandible for example extractions. Antiangiogenic drugs target and inhibit vascular signaling molecules, such as vascular endothelial growth factor. This leads to decreased bone vascularity and avascular necrosis ensues.[5,11] Bacterial infection or inflammation in the jaws stimulates bone resorption via the production of local cytokines and contributes to bone necrosis.[11,12]

1.5 | Imaging

Radiographic tests are key to the diagnosis and staging of MRONJ.[13] Diffuse sclerosis, cortical erosion, and non-healing extraction sockets, for instance, can be early indications of MRONJ. Advanced phases of the condition, including thickening of the lamina dura, osteolysis, formation of bone sequestrum, and pathologic fractures, can resemble chronic osteomyelitis.[14] Imaging modalities such as orthopantomogram (OPG), Cone Beam Computed Tomography (CBCT), or Computed Tomography (CT) are necessary to identify affected areas for surgery planning.[14]

1.6 | Staging and management

The management protocol of MRONJ is case-dependent according to the disease stage and symptoms. It has four stages; stage 0 to stage 3.[1] Stage 0 patients lack signs of ONJ but have nonspecific symptoms. Analgesics and antibiotics are used for symptomatic management. Stage 1 patients have exposed necrotic bone but are asymptomatic without evidence of infection. They are managed using antibacterial mouth rinses and close clinical follow-ups. Stage 2 patients have exposed necrotic bone or fistulas associated with infection. Symptomatic treatment with antibiotics, oral antibacterial mouth rinse, pain control, and debridement of necrotic tissues is employed. Stage 3 patients have exposed necrotic bone extending beyond the alveolar region with infection. They are managed using an antibacterial mouth rinse, antibiotic therapy and pain control, surgical debridement, or resection of necrotic bone for longer-term palliation of infection and pain.

There is a paucity of cases reported in the literature. The purpose of this case series and literature review is to highlight 3 cases of MRONJ that presented in our clinic.

2 | CASE SERIES

2.1 | Case 1

2.1.1 | Case history

A 67-year-old African female patient presented to our clinic with pain and swelling in the lower posterior region

(Figure 1A). She had a recent extraction on the mandible (45) which persisted with a non-healing and tender socket. The patient had been diagnosed with multiple myeloma, 2 years before presentation at the maxillofacial clinic. She had been on the following medications: Rivaroxaban 20 mg OD for 6 months, Lenalidomide 10 mg OD for 1 month, IV Zoledronic acid 4 mg, every 2 months, and alendronate 10 mg OD for 6 months. On examination, the 44/45 area of the mandible was tender to palpation with a 2 × 1 cm suppurated bone exposure on the crest (Figure 1B).

2.1.2 | Methods and conclusion

Digital OPG showed a diffuse mixed radiolucent, radiopaque lesion in the 44/45 area (Figure 1C). Axial view of the CT scan revealed a mixed, radiolucent-radiopaque lesion, with buccal and lingual decortication on the 44/45 area of the body of the mandible with the formation of sequestrum (Figure 1D,E). The 3D reconstruction shows the extent of bone destruction just above the mental foramen (Figure 1F). A diagnosis of MRONJ stage 2 was established.

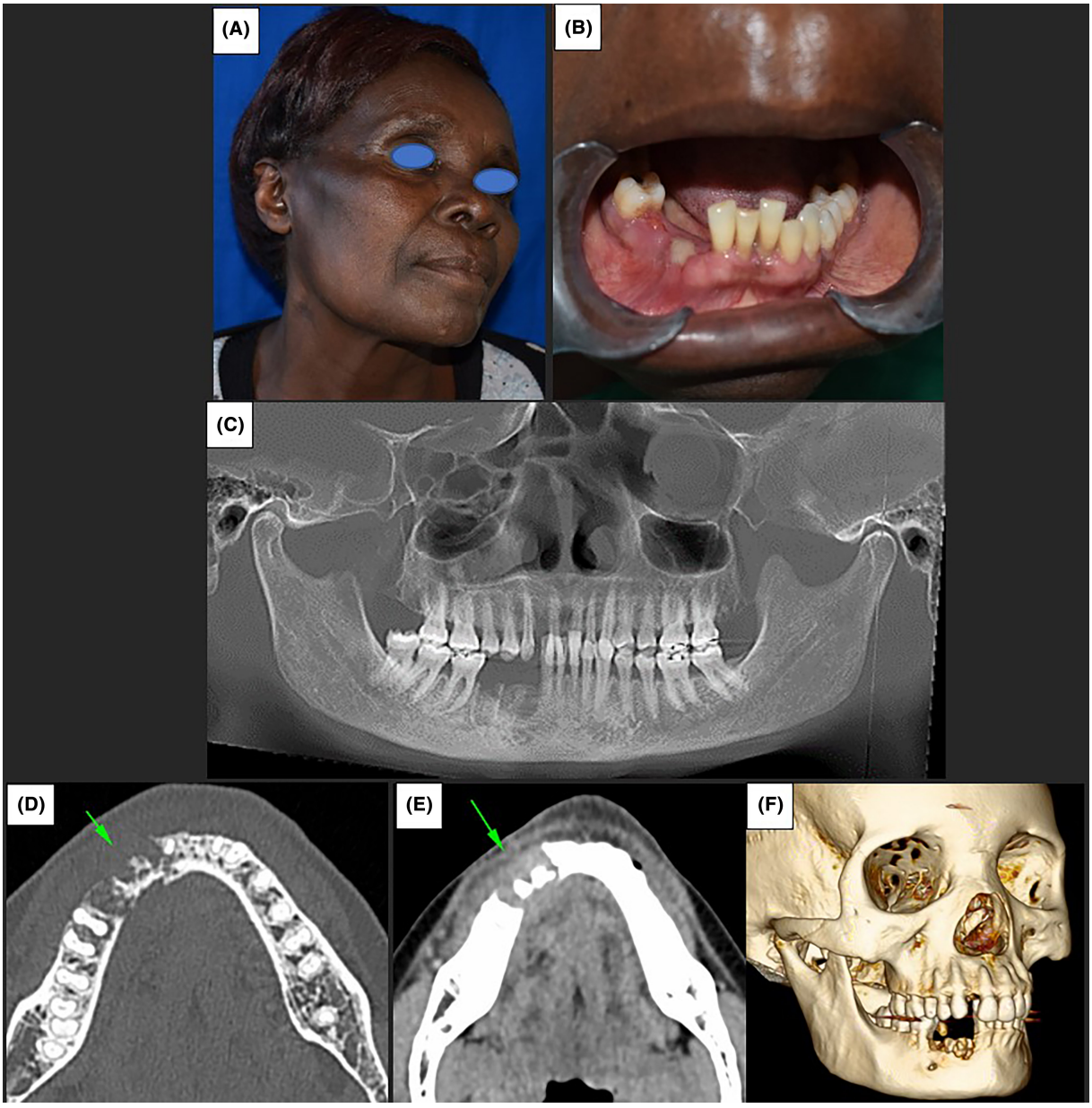

FIGURE 1 Clinical and radiological presentation. (A) Swelling on the right body of the mandible extending to the angle. (B) Exposed bone area on the 44/45 area with suppuration. (C) Digital OPG showing a mixed radiolucent-radiopaque lesion on the 44/45 area. (D) Axial view, bone window CT scan showing lingual and buccal decortication with sequestration. (E) Axial view, soft tissue window CT scan showing soft tissue extent. (F) CT 3D reconstruction showing an area of bone destruction on the 44/45 area.

The patient was scheduled for resection of necrotic bone and reconstruction of the resultant bone defect. Intraoperatively, the necrotic bone was exposed and noted to involve both the lingual and buccal cortices of the mandibular body on the right side (Figure 2A). Resection of necrotic bone (Figure 2C) was done till viable bone was reached. The resulting bone defect (Figure 2B) was reconstructed with Mastercraft (osteoconductive scaffold made of 15% hydroxyapatite and 85% beta-tricalcium triphosphate), (Figure 2D), and soft tissue closure was achieved using an advanced buccal mucoperiosteal flap (Figure 2E). Resected bone biopsy was done to rule out osteomyelitis or multiple myeloma. Histopathology showed bone with empty lacunae, no tumor or inflammation was visualized (Figure 3).

2.1.3 | Results

The patient recovered uneventfully and was on a close follow-up. After 2 years, a check OPG showed bone had formed adequately at the surgical site (Figure 4). The patient is still on a close follow-up and there are no signs of recurrence. She is very happy with the outcome of the surgical intervention and reports to lead a normal life and able to eat well.

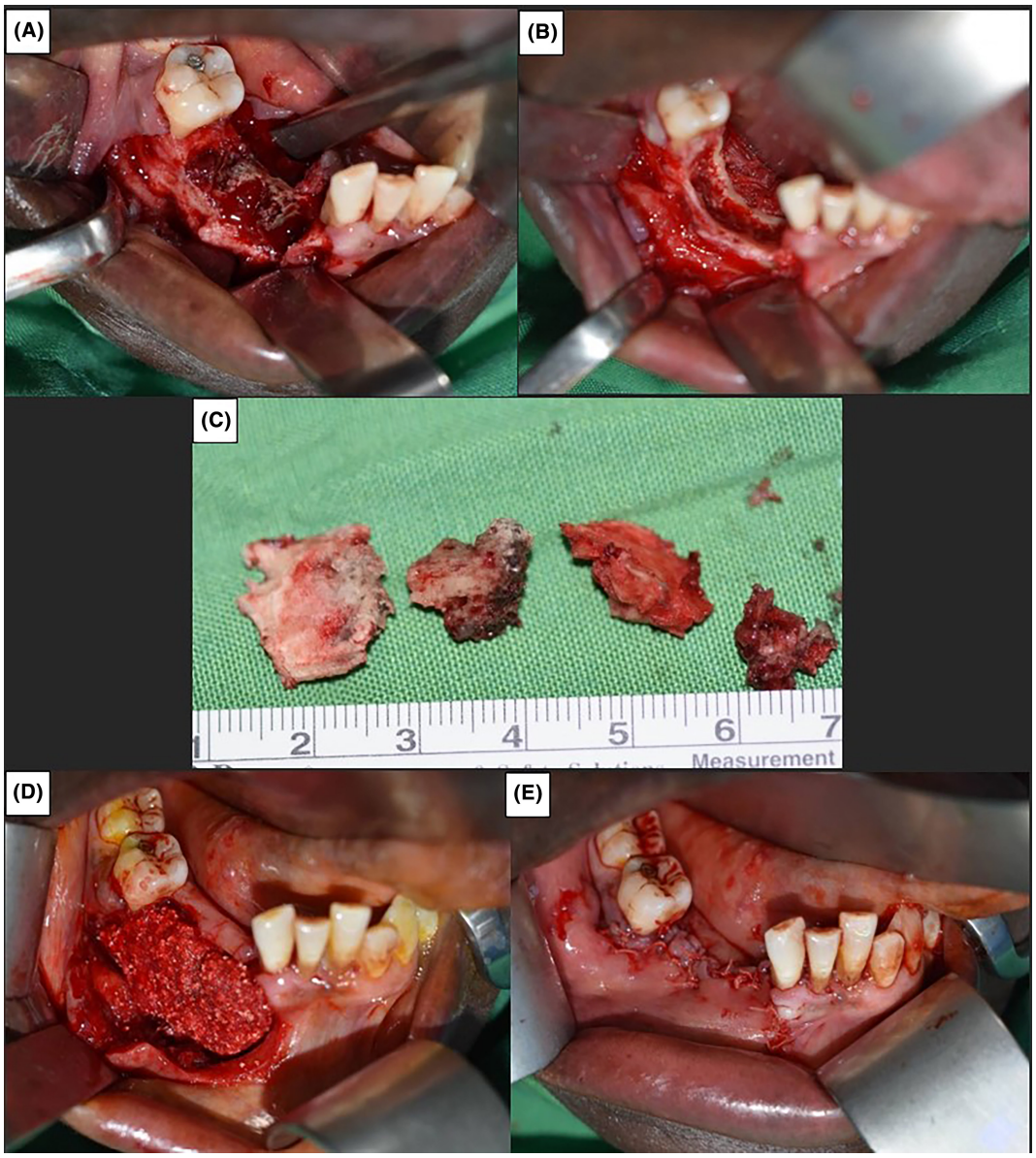

FIGURE 2 Intraoperatively. (A) Exposure of the necrotic bone. (B) Normal bleeding bone after resection of necrotic bone. (C) Resected necrotic bone. (D) Bone defect repaired with bone substitute (Mastercraft). (E) Soft tissue closure using an advanced buccal mucoperiosteal flap.

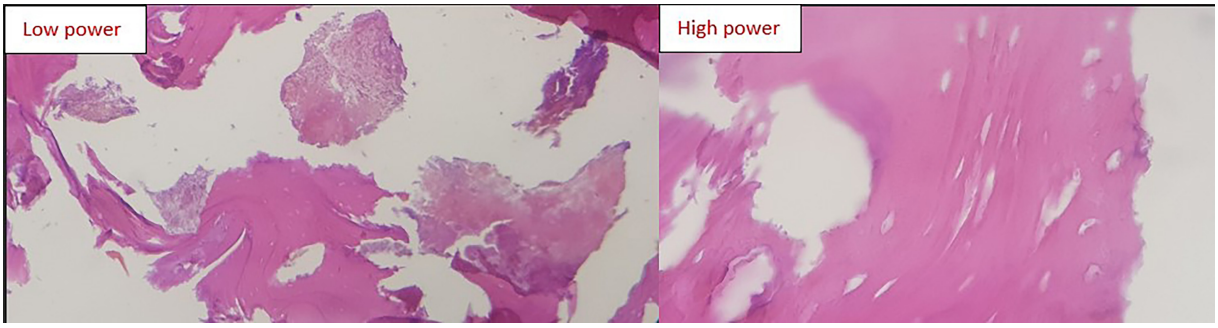

FIGURE 3 Histology showing bone with empty lacunae.

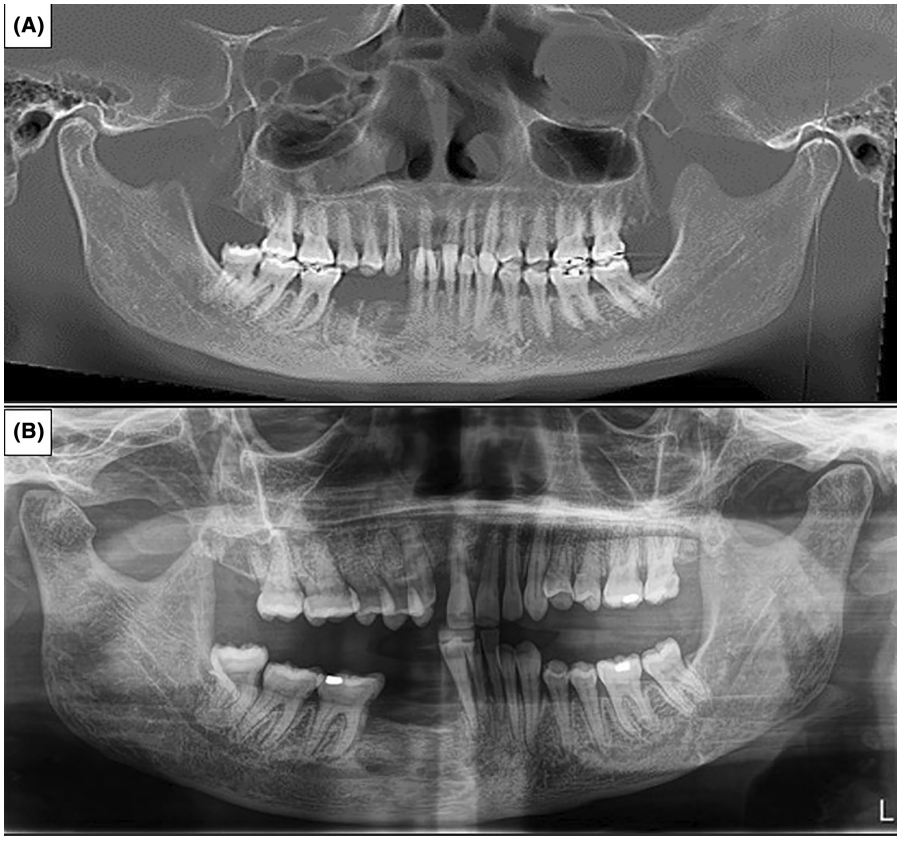

FIGURE 4 (A) Preoperative OPG (B) OPG taken 2 years postoperatively.

2.2 | Case 2

2.2.1 | Case history

A 64-year-old African female patient presented with pain in the lower right posterior region. She had a history of extraction of tooth 47, 6 months before presenting to the Maxillofacial clinic. She reported that the extraction site had not healed ever since. The patient had a history of breast cancer about 10 years ago which had been managed by breast preservation surgery (lumpectomy), chemotherapy, and radiotherapy. Three years after surgery, chemotherapy, and radiotherapy, she had a recurrence of breast cancer with lung metastasis. The patient was medicated on exemestane 25 mg OD for 6 months, everolimus 10 mg OD for 6 months, and monthly injections of zoledronic acid (4 mg) for 4 years. About 8 years after diagnosis of the recurrence, the patient had a tooth extraction at a peripheral facility and the extraction site did not heal. She presented to our clinic 6 months later after the extraction. On intraoral examination, there was bone exposure on the right side of the mandible extending from 46 distal to 48 mesial, exposing the buccal aspect of the alveolar ridge (Figure 5A).

2.2.2 | Methods and conclusion

Digital OPG revealed sclerotic changes on the alveolar margins of the mandible and a diffuse radiolucent

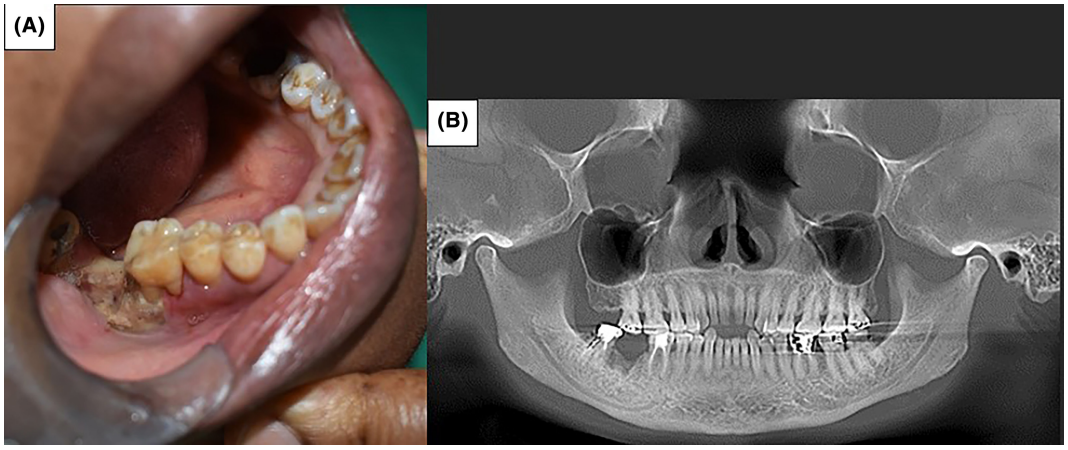

FIGURE 5 Clinical and radiological presentation. (A) Area of bone exposure extending from 46 distal to 48 mesial exposing the buccal aspect of alveolar bone. (B) Digital OPG showing diffuse radiolucent lesion on the 47 area.

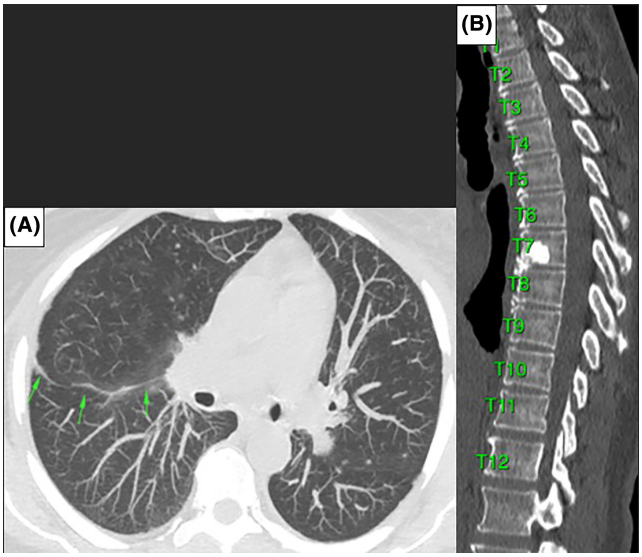

FIGURE 6 Chest and Vertebral body metastasis. (A) Nodular fissural pleural thickening. (B) T7 vertebral body well-defined sclerotic bone.

lesion on the 47 area (Figure 5B). High-Resolution Chest CT (HRCT) scan showed subtle nodular fissural pleural thickening (Figure 6A). A 12×12 mm well-defined sclerotic lesion was also seen within the T7 vertebral body (Figure 6B). Considering the morbidity of the patient, a conservative approach was selected in the management of the patient. This involved strict oral hygiene instructions and the use of a topical antimicrobial (0.2% chlorhexidine mouth rinse).

2.2.3 | Results

The patient was put on a close follow-up with reviews every 3 months, however, passed on after 8 months of follow-up.

2.3 | Case 3

2.3.1 | Case history

A 79-year-old Asian male patient presented with an area of bone exposure on the left side of the posterior mandible, intraorally. The patient had been treated for advanced prostate cancer 3 years previously entailing surgery and hormone therapy. The patient was medicated on Goserelin (Zoladex 3.6 mg monthly implant for 6 months), Finasteride (Proscar 5 mg tabs for 6 months), Enzalutamide (Xtandi 160 mg OD for 9 months), and monthly injections of 4 mg zoledronic acid for 3 years. Intraoral examination showed an area of necrotic bone with suppuration on the left side of the mandible, lingual to the 36 (Figure 7A).

2.3.2 | Methods and conclusion

CT scan revealed ill-defined mixed sclerosis/lucencies of the mandibular body bilaterally with irregular cortices. Osseous fragments were also noted on the lingual aspect centrally (Figure 7B). CT 3D reconstruction revealed mandibular buccal cortical destruction and extensive lingual cortical destruction (Figure 7C,D). Due to the patient's morbidity from prostate cancer, both the patient and his family declined surgical intervention. A conservative approach was considered. The patient was given oral hygiene instructions to brush his teeth twice daily, floss regularly, and rinse his mouth daily with warm saline.

2.3.3 | Results

The patient was glad that he did not undergo surgery. He was put on a close follow-up but unfortunately succumbed to metastatic prostate cancer after 1 year.

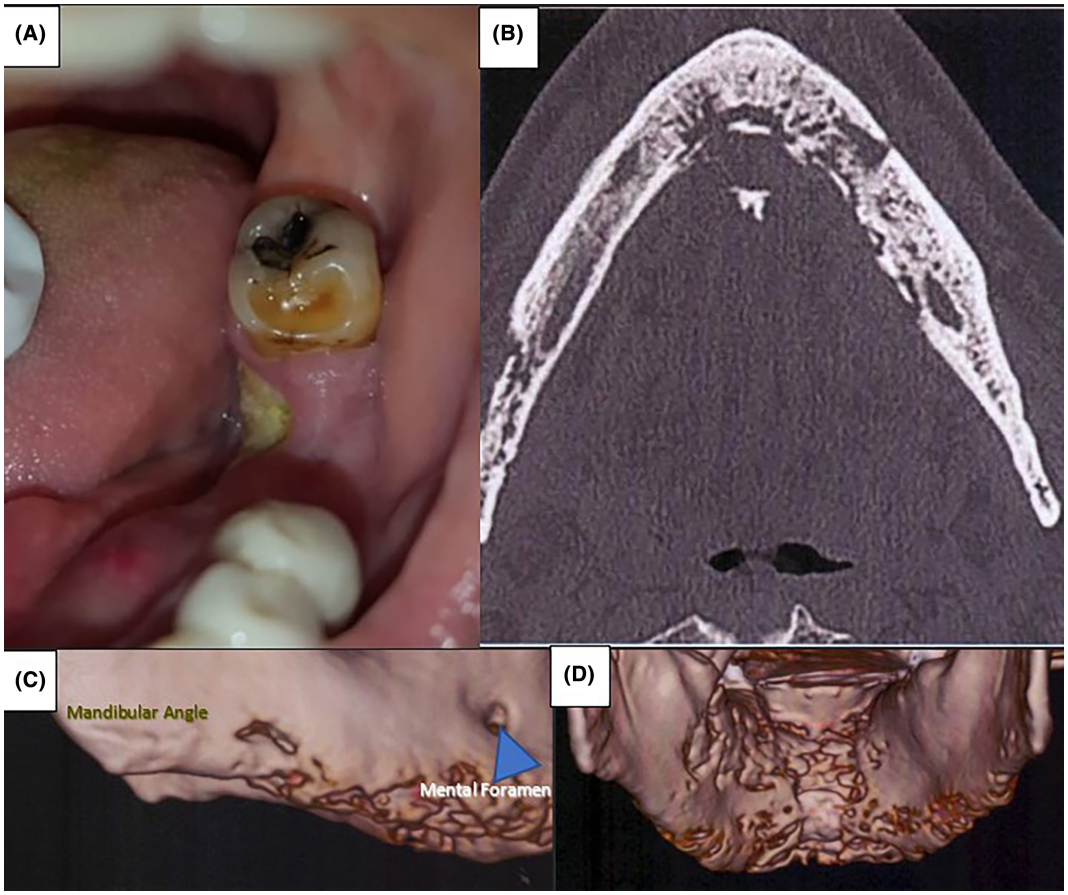

FIGURE 7 Clinical and radiological features. (A) An area of exposed bone with suppuration on the left side of the mandible, lingual to the 36. (B) Axial CT scan view of the mandible showing ill-defined mandibular mixed sclerotic pattern consistent with osteonecrosis. (C, D) Mandibular buccal cortical destruction and extensive lingual cortical destruction.

3 | DISCUSSION

MRONJ is reported to commonly occur in elderly female patients.[1,10] All the patients in this case series were >65 years old. The predilection to female patients could be seen to reflect the underlying condition for which antiresorptive or antiangiogenic agents are being administered, for example, osteoporosis or breast cancer. Jeong et al., reported that among 320 patients receiving bisphosphonates (BPs) therapy, eleven developed MRONJ and all were females aged above 65 years old.[15] There is limited data reporting the occurrence of MRONJ in the pediatric population.[1]

All our patients had received intravenous zoledronic acid. Zoledronic acid is a nitrogen-containing BP used in the management and prevention of skeletal-related events in patients with metastatic cancer to the bones.[6] In our case series, one of our patients had breast cancer, the other had prostate cancer and another one was being treated for multiple myeloma. All had metastasis to the bones. Limones et al., reported an incidence of 0.4%–1.6% after 1 year of exposure, 0.8%–2.1% after 2 years, and 1.0%–2.3% after 3 years of exposure to Zoledronic acid in cancer patients.[4]

Approximately 75% of MRONJ cases affect the mandible.[1] The mandible has a thinner mucosa compared to the maxilla which predisposes it to damage.[16] In addition, the mandible has a singular main blood supply hence prone to avascular necrosis.[6] The most common precipitating factor for necrosis is tooth extraction.[10,17] Two of our patients developed MRONJ after an extraction while one developed it spontaneously.

The management of MRONJ is generally difficult and a treatment strategy is not yet well established.[3] Therefore, prevention strategies play an important role in the reduction of the risk of necrosis of bone.[1,13] MRONJ in two of the three cases was preceded by tooth extraction in peripheral facilities. Adequate dental evaluation before starting antiresorptive and antiangiogenic medications is mandatory. Invasive procedures such as extractions should be completed before treatment starts. Patients should also be educated about the risk of developing MRONJ and made cognizant of the signs and symptoms.[5]

Prevention and management call for multidisciplinary collaboration among dentists, oral surgeons, physicians, nurses, and oncologists. There is a need to develop local guidelines for clinicians on how to approach patients scheduled for antiresorptive medications or those who are currently taking them and need dental treatment. This will help prevent the development of MRONJ as in the case of two of our patients or reduce the morbidity of the disease. Bramati et al reported a 100% relative risk reduction of developing MRONJ in patients who received dental preventive measures and education before receiving antiresorptive therapy compared to patients who did not receive dental prevention.[18]

Clinicians managing patients taking antiresorptive medications play an important role in prevention of MRONJ.[3] Before a patient commences antiresorptive therapy, they need to undergo a thorough oral examination where all carious teeth need to be managed through dental fillings, root canals or extractions. The patient also needs to undergo full mouth scaling and polishing as well as receive topical fluoride therapy to prevent caries formation. The patient then needs to be counseled on their risk of developing MRONJ and instructed on the need to adhere to strict oral hygiene and regular dental checkups.[5,17]

The management of MRONJ ranges from conservative to surgical therapy based on the stage of the disease.[1] All the patients presented with stage 2 disease. Two of the patients were managed conservatively while one received surgical management. Conservative management involves the use of antimicrobials, pentoxifylline and vitamin E therapy, teriparatide, and hyperbaric oxygen therapy.[1,3,5,6] The patients were given strict oral hygiene instructions and 0.2% chlorhexidine gluconate (Corsodyl) mouthwash was prescribed.

Surgical management involves debridement and marginal or segmental resection of necrotic bone, Soft tissue closure, microvascular composite tissue grafting, and reconstruction procedures.[1,6] Marcianò et al reported to have carried out 128 surgical procedures for the management of MRONJ. These were either radical sequestrectomy till bleeding of adjacent bone was achieved or extensive bone surgery involving resection of necrotic bone.[19] One patient underwent surgical management that involved resection of necrotic bone and reconstruction of the bone defect using bone substitute and an advanced buccal mucoperiosteal flap to cover the defect. All patients were put on a close follow-up routine.

Prevention is better than management of MRONJ. During treatment with antiresorptive medications close follow-ups and meticulous oral hygiene routine should be followed by the patients. Patients taking antiresorptive medications need good education on the risks associated with the medications and how to recognize early signs and symptoms. Since most of these patients are first seen by oncologists, the latter should insist on oral health evaluation before the start of treatment.

AUTHOR CONTRIBUTIONS

Denis Kimathi: Conceptualization; formal analysis; writing – original draft. **Fawzia Butt:** Conceptualization; supervision; writing – review and editing. **Symon Guthua:** Methodology; supervision; writing – review and editing. **Wairimu Waweru:** Data curation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICAL APPROVAL

Not required for the case series.

CONSENT

Written informed consent was obtained from the patients to publish this report following the journal's patient consent policy.

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