

Skin involvement of medication-related osteonecrosis of jaws in an immunocompromised, bisphosphonate-treated patient



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Key words: bisphosphonate; medication-related osteonecrosis of jaws; osteoporosis; skin involvement.

INTRODUCTION

Medication-related osteonecrosis of jaws (MRONJ), a term first proposed in 2014 by the American Association of Oral and Maxillofacial Surgeons, is a rare but debilitating disease that can seriously affect a patient's quality of life.¹ Although it is most commonly identified by dentists due to the bony and intraoral manifestations of MRONJ, it can also be present on the skin. However, it is a relatively less recognized disease among dermatologists and can be a diagnostic challenge. To our knowledge, only 4 cases of cutaneous involvement of MRONJ have been previously reported by dermatologists.^{2,3} Herein, we report a case of MRONJ in a patient with breast cancer and a history of treatment with bisphosphonate injection.

CASE REPORT

A 67-year-old Korean woman presented with an ulcerative lesion with surrounding erythema on the right cheek for the previous 3 months (Fig 1, A). The lesion was accompanied by tenderness without warmth. She denied having any history of trauma. She was undergoing chemotherapy, including cytotoxics (docetaxel and doxorubicin), hormone antagonists (letrozole and exemestane), and mammalian target of rapamycin inhibitor (everolimus) for metastatic breast cancer. Until about 4 months ago, she had been given intravascular

Abbreviation used:

MRONJ: medication-related osteonecrosis of jaws

injections of zoledronic acid every month for 3.5 years for osteoporosis.

Initially, under the impression of infectious skin disease, microorganism culture was performed, and empirical antibiotics were prescribed. After 1 week, the culture result was negative, but a yellow-greenish discharge was observed (Fig 1, B and C). Swab culture of the discharge was performed, and punch biopsy with tissue culture was performed to rule out metastatic skin cancer and deep tissue infection. The biopsy specimen demonstrated infiltration of inflammatory cells consisting of neutrophils, some plasma cells, and eosinophils in the deep dermis (Fig 2, A and B). It did not reveal any evidence of malignancy. Grocott's methenamine silver and periodic acid–Schiff staining were both negative. Additional bacterial culture and polymerase chain reaction for *Mycobacterium tuberculosis* and nontuberculosis mycobacteria were all negative. After exclusion of infectious causes, oral steroids and intralesional steroid injection were tried under suspicion of pyoderma gangrenosum, but they were not effective (Fig 1, C).

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Funding sources: Supported by the National Research Foundation of Korea funded by the Korean government (grant no. 2019R1C1C1002243).

IRB approval status: This study received a consent exemption determination (no. 10-2011-102) from the institutional review board of the Seoul Metropolitan Government-Seoul National University Boramae Medical Center.

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JAAD Case Reports 2022;20:10-3.
2352-5126

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<https://doi.org/10.1016/j.jcdr.2021.12.007>



Fig 1. Clinical manifestations. **A**, Ulcerative lesion with surrounding erythema on the right cheek. **B**, The lesion accompanied by yellow-greenish discharge after 1 week. **C**, Progression of the lesion without response to oral and intralesional steroid treatment.

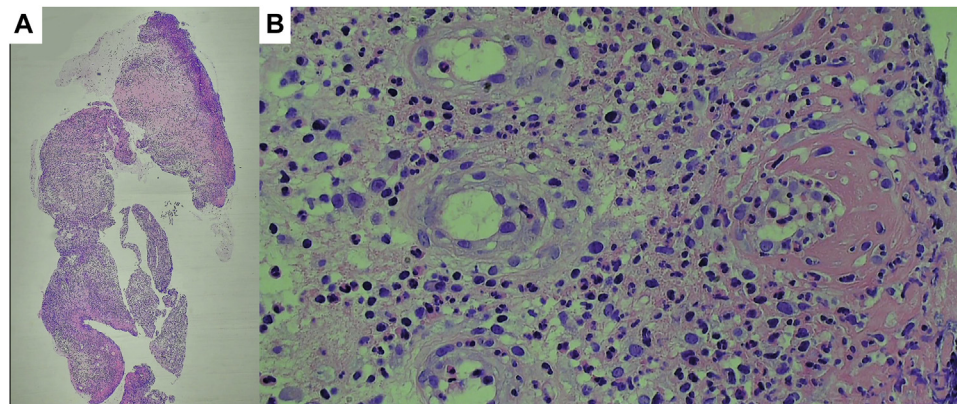


Fig 2. Histopathology. **A**, Ulcer and infiltration of inflammatory cells into deep dermis. **B**, Mixed inflammatory cell infiltration consisting of neutrophils, lymphocytes, plasma cells, and eosinophils. (**A** and **B**, Hematoxylin-eosin stain; original magnifications: **A**, $\times 40$; **B**, $\times 400$.)

Repeated history taking and medical record review revealed that she had undergone sequestrectomy of the right posterior maxilla a year ago due to the sequestrum. The sequestrum occurred 2 months after extraction of the right maxillary teeth, which were located at the extraction site with oroantral fistula. She was then diagnosed with stage III MRONJ by an oral surgeon (Fig 3, A to C). At that time, additional radical sequestrectomy and fistula closure were strongly recommended by the oral surgeon, but she refused additional surgery. Because the location of the skin lesion was adjacent to that of the untreated oroantral fistula, the skin lesion was finally diagnosed as a skin manifestation of MRONJ. She was referred to the oral surgeon, and her diagnosis was confirmed.

DISCUSSION

Avascular necrosis of the jaw caused by bisphosphonate treatment was first described in 2003. As antiresorptive and antiangiogenic treatment became popular, the number of osteonecrosis cases increased, and the term “medication-related osteonecrosis of jaws” was proposed in 2014.¹

Usage of antiresorptive or antiangiogenic drugs, concomitant chemotherapy, immunosuppression, smoking, dental procedures such as tooth extraction, and poor oral hygiene are known risk factors or triggering factors of MRONJ.^{4,5} The incidence of MRONJ in patients with denosumab- or zoledronic acid-treated cancer is reported to be approximately 0.4% to 2.1% after 1 year and 1.0% to 3.2% after 3 years of exposure to these drugs.⁶ In addition to antiresorptive therapies, increasing numbers of new agents in cancer therapy, including tyrosine kinase inhibitors, monoclonal antibodies, mammalian target of rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators, and immunosuppressants, have been implicated in the development of MRONJ. In the present case, it is likely that chemotherapeutic agents may have contributed to MRONJ in conjunction with bisphosphonate.⁷

The pathogenesis of MRONJ is still unclear. Nonetheless, excess inhibition of osteoclast-mediated bone remodeling, resulting in ischemia and sclerosis of bone, has been suggested as a possible pathogenetic mechanism.⁴

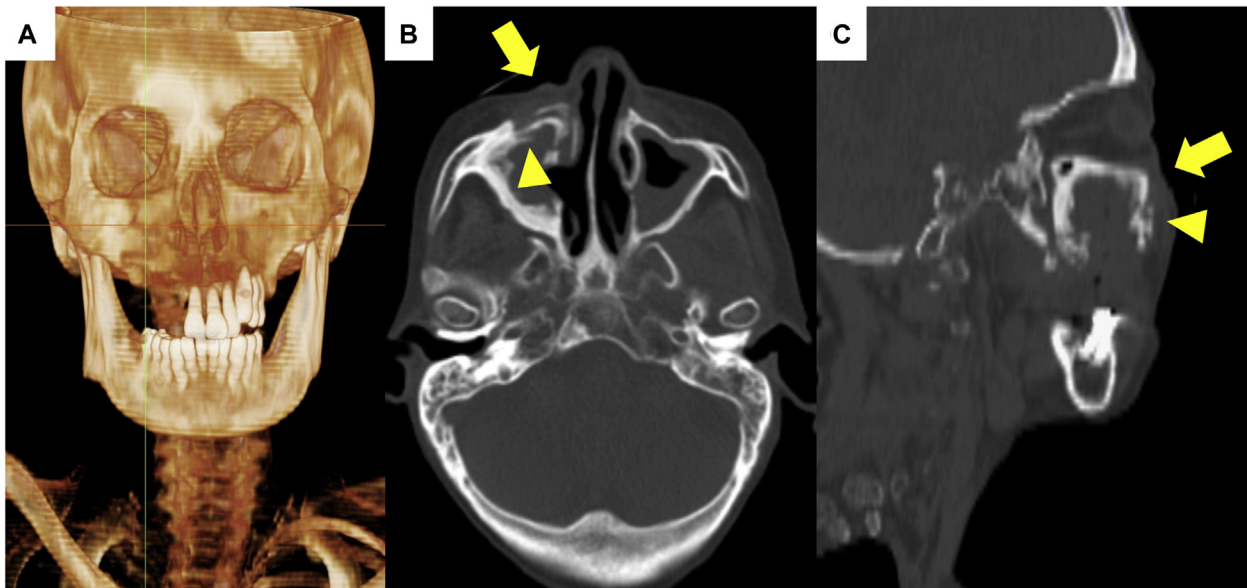


Fig 3. Radiologic examination. **A**, Orientation of computed tomographic image. The red and green lines correspond to the axial plane in **(B)** and the sagittal plane in **(C)**, respectively. **B**, Axial image. Skin lesion (arrow), osteonecrotic lesion (arrowhead). **C**, Sagittal image. Skin lesion (arrow), osteonecrotic lesion (arrowhead).

The American Association of Oral and Maxillofacial Surgeons has suggested the diagnostic criteria for MRONJ on the basis of pharmacologic history, clinical manifestation, and radiologic features.⁷ MRONJ can be diagnosed when the patient has been or is being treated with antiangiogenic or antiresorptive drugs, and when the bone in the maxillofacial area is exposed or has not healed after more than 8 weeks without a history of radiation therapy in the head and neck or metastasis in the jaw.⁸

The staging system of MRONJ by the American Association of Oral and Maxillofacial Surgeons is as follows: stage 1, necrotic exposed bone without infection and symptoms; stage 2, necrotic exposed bone with infection and pain; and stage 3, stage 2 plus other complications such as pathologic fracture, extraoral, oroantral, or oronasal communication, or necrosis beyond the alveolar bone area.¹ In the present case, we think that severe untreated MRONJ resulted in skin involvement because progressive osteonecrosis can cause a cutaneous fistula as well as oroantral communication. Because MRONJ can be accompanied by skin manifestations, dermatologists should be familiar with MRONJ and suspect the disease in a patient with compatible features and predisposing factors. According to previous reports, MRONJ is more likely to affect the mandible (73%) than the maxilla (22.5%); however, it can appear in both jaws (4.5%). Dermatologists should be aware that skin manifestations of MRONJ may appear in the cheeks as well as the submental area.

The treatment of MRONJ is still controversial. Conservative treatments, such as maintaining good oral hygiene, regular dental visits, antibiotics, and surgery, should be considered.^{5,8} In addition, low-level laser therapy and photodynamic therapy are reported to be beneficial by reducing pain and edema and by controlling associated infection, respectively.⁹ A recent systematic review suggests that there is no gold standard of treatment, and surgical treatment should be minimally performed with caution, especially in patients with cancer.¹⁰ Therefore, treatment of patients with MRONJ may require a multidisciplinary approach.

We report skin manifestations of MRONJ in a patient with breast cancer who was treated by intravenous bisphosphonate and who had a history of sequestrectomy after tooth extraction. This case is representative, given the patient's risk factors for MRONJ. Because the number of MRONJ cases is increasing and MRONJ can be accompanied by skin manifestations, dermatologists need to be vigilant for this disease.

Conflicts of interest

None disclosed.

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