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Maxilla Osteonecrosis: a differential diagnosis in patients with metastatic cancer on bisphosphonates

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Abstract

Bisphosphonate-induced osteonecrosis of the mandible and/or maxilla is an increasingly recognized, though still rare complication of bisphosphonate therapy. In the present case, the patient presented with a seven-month history of maxillary sinusitis and pain, and was originally diagnosed with a bony metastasis from her primary breast cancer. However, surgical excision and biopsy led to a diagnosis of bisphosphonate-induced osteonecrosis of the maxilla. As bisphosphonates are often prescribed for patients with metastatic disease, it is important to recognize that bisphosphonate-induced osteonecrosis may present similarly to bony metastases.

Keywords

Osteonecrosis; bisphosphonates; maxilla; metastasis

Introduction

Bisphosphonate-induced osteonecrosis (BON) is a rare side effect of bisphosphonate therapy in patients taking these medications for the prevention of skeletal complications in various diseases, including breast cancer.¹ BON most frequently affects the mandible and typically presents months to years after initiation of intravenous or oral bisphosphonates as painful and exposed necrotic bone in the oral cavity.²

We present a case of BON of the maxilla in a woman receiving IV zoledronic acid (Zometa) as an adjunct to treatment of advanced breast cancer with bony metastases. This case illustrates the potential for BON to present atypically with clinical findings similar to bony metastases. Awareness of the possibility of BON to present in this way will be useful to all in the field of otolaryngology.

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Presentation: None

Case Report

A 67-year old woman presented with a seven-month history of maxillary sinus pain, pressure, stuffiness, and post-nasal drip unresolved by antibiotic treatment. The pain was described as severe and intermittent, beginning in the nose and radiating to the head. Physical examination and endoscopy revealed a 1.5 cm fistula with visible necrotic bone and granulation tissue in the right maxillary sinus. Otherwise, no masses, purulence, or dental caries were present.

The patient's medical history was significant for osteoporosis and invasive ductal carcinoma of the left breast, with metastasis to the L1 vertebral body, 11th rib and 12th rib, currently being treated with monthly 4 mg IV injections of zoledronic acid (Zometa) and daily 2.5 mg letrozole (Femara). She also has a history of mild dementia due to multiple sclerosis.

Axial (Figure 1A) and coronal (Figure 1B) paranasal sinus CT images demonstrated right maxillary sinusitis with increased soft-tissue density which was nonspecific. Additionally, erosion of the posterolateral wall of the maxilla with oro-antral fistula was seen on imaging. Given her history, physical exam and imaging findings, there was concern this lesion could represent a bony metastasis from her breast cancer.

The patient was taken to the operating room for biopsy and debridement of her maxilla. Intraoperatively, necrotic bone in the posterior wall and lateral buttress of the maxilla were debrided along with polypoid, friable granulation tissue, which was sent for pathology and culture. There was no purulence. Sections from the biopsy demonstrate necrotic lamellar bone with pagetoid changes (Figure 2). The marrow is replaced by mixed oral flora organisms. Coupled with the clinical information, these histologic features support a diagnosis of bisphosphonate-induced osteonecrosis.

Discussion

Bisphosphonate-induced osteonecrosis (BON) is a rare, morbid condition first described in 2003.¹ Since then, a limited number of published studies have reported an estimated incidence of BON of roughly 1 % in patients receiving IV bisphosphonates.² Despite its low incidence, BON should remain in the differential in patients receiving bisphosphonates. Osteonecrosis of the maxilla remains a very rare entity, comprising only 25 % of cases of BON reported in the literature, and is an important diagnosis for the otolaryngologist to consider.³

Owing to their structural similarity to inorganic pyrophosphate (PPi), bisphosphonates bind strongly to hydroxyapatite crystals in bone, particularly in areas undergoing active resorption. Here, bisphosphonates prevent osteoclasts from adhering to the bony surface and producing protons necessary for bone resorption. Additionally, bisphosphonates induce apoptosis in osteoclasts.⁴ The mechanism of bisphosphonates is therefore different from other anti-resorptive agents like estrogen, selective estrogen receptor modulators (SERMs), calcitonin, and monoclonal antibodies against RANKL (denosumab). Bisphosphonates are currently indicated in the treatment of a wide range of disorders including multiple myeloma, breast and prostate cancer, osteoporosis, and Paget's Disease. In the past two

decades, several randomized controlled trials have shown that bisphosphonates are highly effective in preventing skeletal fractures and increasing bone mineral density in these patients.^{5,6}

The most common side effects of bisphosphonates are gastrointestinal irritation and musculoskeletal pain, which are typically self-limited.⁷ The first major adverse side effect of bisphosphonate therapy, BON, was described in a cohort of patients who presented with painful, necrotic, and exposed maxillary or mandibular bone after dental extractions.¹ Today, the major risk factors for development of BON include long-term IV administration of pamidronate (Aredia) or zoledronic acid (Zometa), concomitant use of glucocorticoids, and pre-existing dental caries and poor oral hygiene.⁸

Patients with BON classically present with pain, mucosal swelling and erythema around an area of exposed alveolar bone following various dental procedures⁵. It is hypothesized that the mandible may be more susceptible to micro-fractures with mastication and have a higher rate of bone turnover than the maxilla. This may explain the roughly 3:1 incidence of BON in the mandible vs. the maxilla as reported in the literature.⁶ Additionally, the proximity to the oral cavity allows for easy seeding of the necrotic bone with oral microbes. Given its low prevalence and clinical similarity to other conditions (e.g. osteoradionecrosis, bony metastases), a detailed history, medication list, imaging studies, and ultimately biopsy are essential for timely diagnosis of BON. In patients with a history of cancer, one's differential diagnosis should include metastatic disease to the maxilla which, although rare, remains a potential diagnosis.⁹

Panoramic radiography, non-contrast CT, and MRI are essential tools for the diagnosis and staging of BON and may help in the differentiation of BON from similar conditions like osteomyelitis, osteonecrosis, metastases, or osteosarcoma. CT may show sclerotic lesions, osteolysis, periosteal reaction, bony sequestrum, fractures, or fistulas involving the maxilla, mandible, or both.¹⁰ Imaging further serves to guide biopsy of the lesion for histologic confirmation and aids in surgical planning.

While the appropriate treatment strategy for BON remains controversial, previous studies support the use of analgesics, oral antibiotics, and antimicrobial mouth rinses in most patients.² As in the present case, surgical debridement is most appropriate for patients presenting with significant pain, infection, and oro-antral fistula. The decision to continue or withdraw bisphosphonate therapy after BON should be a careful one. Factors to consider include the severity of BON-related symptoms, potential for further bone necrosis and infection, and the possibility of fractures associated with discontinuing bisphosphonate therapy.²

The present case represents an unusual presentation of BON in a woman with a history of metastatic breast cancer. There was no history of inciting dental procedures and the patient's presenting symptoms were more consistent with a chronic maxillary sinusitis, showing healthy oral mucosa save for the oro-antral fistula. Given her history of malignancy, she was initially referred for evaluation for potential metastatic breast cancer. Malignancy could only be ruled out after definitive intraoperative biopsies. Diagnosis of BON in this patient was

further complicated by her dementia and dependent activities of daily living status secondary to multiple sclerosis. After confirming the diagnosis and gentle debridement, the patient chose opted obturator reconstruction of the fistula which is being performed closer to home.

Conclusion

This case highlights the essential role of the head and neck surgeon in the diagnosis and treatment of BON of the maxilla, and illustrates the need for awareness of this condition's variable presenting signs and symptoms. Particularly, there should be consideration of BON in the differential diagnosis of a patient undergoing bisphosphonate therapy, and surgeons should be aware of the potential for BON to masquerade as metastatic cancer. With increasing use of bisphosphonates for skeletal protection across many pathologic conditions, the incidence of BON in the field of otolaryngology will increase proportionally.

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Figure 1a

Figure 1b

Figure 1.

Representative Axial (Panel A) and Coronal (Panel B) CT scans without contrast showing osteonecrosis of the maxilla. There is bone destruction with soft tissue density in the maxillary sinus, which is nonspecific.

Figure 2. Representative hematoxylin and eosin stained sections of the maxillary bone at 20× magnification. There is necrotic lamellar bone with pagetoid changes. The marrow is replaced by mixed oral flora organisms.