

Bisphosphonate-Related Osteonecrosis of the Skull Base

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Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is reported in up to 18.6% of patients treated with intravenous bisphosphonates and can result in significant morbidity. Most cases are managed by oral surgeons with only a handful of reports appearing in the otolaryngology literature. We present a unique case of extensive BRONJ involving the maxilla, sinuses, and skull base, complicated by sinusitis and an intracranial abscess. This is the first description of BRONJ involving the skull base. The pathogenesis and management of this process are reviewed.

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CASE REPORT

A 61-year-old African-American female presenting with headache and purulent nasal drainage was admitted to the Infectious Disease service with the diagnosis of sinusitis complicated by left frontal lobe abscess diagnosed on computed tomography (CT) scan. An area of discontinuity of the left lamina papyracea with soft tissue edema of the left periorbital area was noted (Fig. 1). The patient had a history of multiple myeloma, which had been treated with Zoledronate, and she was being followed for bisphosphonate-related osteonecrosis of the jaw (BRONJ), involving the left maxilla (Fig. 2). Other significant past medical history included: pathologic vertebral fracture, chronic pain syndrome, 25 pack-year of smoking, and an undiagnosed left renal mass. The patient was placed on intravenous antibiotics and antifungals. Neurosurgery, Oral and Maxillofacial Surgery, Ophthalmology, and Otolaryngology services were consulted.

On examination, the patient had left proptosis and moderate periorbital edema with intact vision and extraocular mobility (cranial nerves II through VI).

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Rhinoscopy demonstrated purulent material with black necrotic debris in the left nasal cavity. Oral cavity examination showed a 2 cm exposed area of tender necrotic bone of the left posterior maxilla. There was no lymphadenopathy. Her blood work was unremarkable, and blood cultures were negative. A magnetic resonance imaging (MRI) scan of the brain demonstrated a 1.75 cm × 1.5 cm ring enhancing intracranial lesion adjacent to the left ethmoid roof with evidence of dural enhancement and inflammation of the ethmoid and medial orbit (Fig. 3). Endoscopic cultures of the middle meatus and biopsy of the middle turbinate and ethmoid bulla were performed at the bedside under local anesthesia. Cultures revealed light growth of *Staphylococcus aureus* and moderate growth of *Eikenella corrodens*. The fungal culture was negative. Pathology demonstrated inflammation with osteonecrosis. There was no evidence of fungus or malignancy. After one week of intravenous antibiotics, the patient did not improve, and the MRI of the brain was repeated and remained unchanged.

She was taken to the operating room. An intracranial abscess was drained by neurosurgery via bifrontal craniotomy. A left endoscopic maxillary antrostomy, total ethmoidectomy, and frontal sinusotomy were performed concurrently. Significant necrosis and erosion of the bones of the maxillary and ethmoid sinuses was encountered. The skull base (ethmoid roof) and lamina papyracea were also extensively involved. Devitalized and frankly necrotic tissues were debrided from the skull base, and the affected lamina papyracea was removed via a medial orbital wall decompression approach (Fig. 4). The left maxilla was also biopsied transorally. There were no complications. Pathology of the skull base, lamina papyracea, sinus contents, and maxilla all showed acute and chronic inflammation with osteonecrosis consistent with bisphosphonate-related osteonecrosis. The final diagnosis was intracranial abscess secondary to sinusitis and extensive bisphosphonate-related osteonecrosis involving the maxilla, sinuses, and skull base. The patient recovered well and was discharged home on postoperative day 8 on 4 weeks of antibiotics via peripherally inserted central catheter (PICC) line. She was subsequently diagnosed with renal cell carcinoma and underwent nephrectomy. She was doing well at 13 months follow-up.

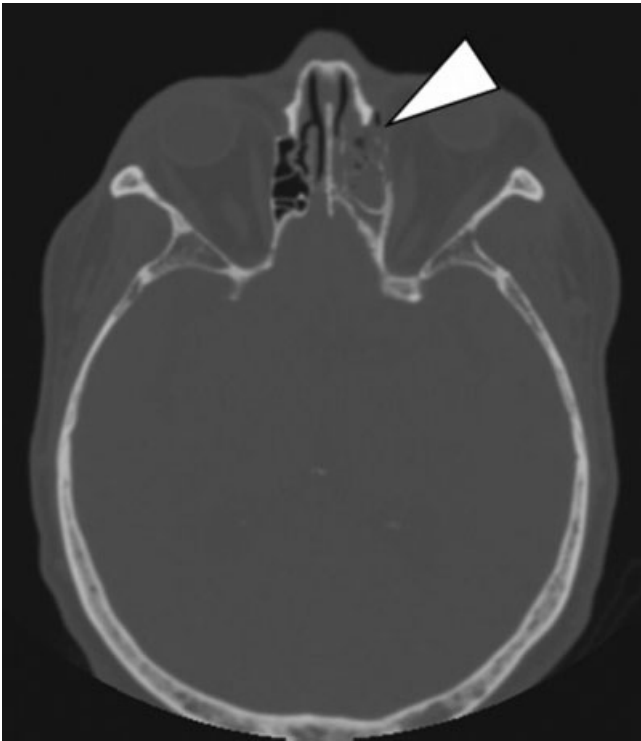


Fig. 1. Noncontrast axial computed tomography scan demonstrating significant opacification of the left ethmoid. An area of dehiscence of the left lamina papyracea (arrowhead) and associated periorbital inflammation are seen.



Fig. 2. Non-contrast axial computed tomography scan showing "punched out" lesion of left maxilla (arrowhead), consistent with bisphosphonate-related osteonecrosis of the jaw.



Fig. 3. T1-weighted coronal magnetic resonance imaging scan with gadolinium showing a ring enhancing intracranial lesion (*). Dural enhancement (white arrowhead) associated with the left ethmoid roof is also seen. The black arrowhead demonstrates dehiscence of the left lamina papyracea with associated intraorbital inflammation.

DISCUSSION

Bisphosphonates are analogues of inorganic pyrophosphates that have a high affinity for hydroxyapatite bone mineral surfaces, particularly regions with high

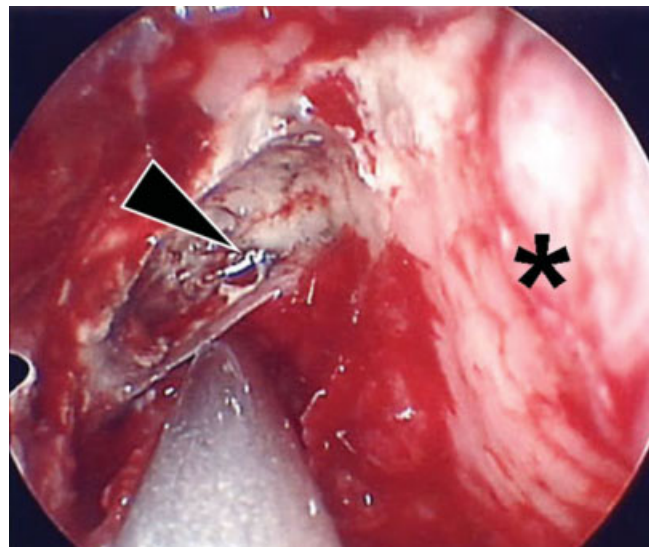


Fig. 4. Endoscopic view of the left ethmoid cavity during surgery. The pointer is on the skull base (ethmoid roof), which shows extensive osteonecrosis (black arrowhead). Inflamed periorbital (*) is seen along the lateral nasal wall after resection of the lamina papyracea during debridement of necrotic tissues. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

bone turnover.¹ They prevent bone resorption by inhibiting the osteoclast activity at the molecular, cellular, and tissue level and have been used to treat various disorders of bone since the 1970s.² Oral bisphosphonates have become the standard of care to treat osteopenia and osteoporosis and are also used for Paget's disease and *Osteogenesis imperfecta*. Intravenous bisphosphonates pamidronate (Aredia) and zoledronate (Zometa) (Novartis Pharmaceuticals Corporation, East Hanover, NJ) are newer generation drugs that contain a nitrogen side-chain, preventing them from being metabolized and making them much more potent. They are used for the treatment of multiple myeloma and metastatic bone lesions and prevent skeletal complications, pathologic fractures, spinal cord compression, and hypercalcemia of malignancy. More than three million patients have received zoledronate for cancer therapy worldwide.³

In 2003, osteonecrosis of the maxilla and mandible was reported as a complication of intravenous bisphosphonate treatment by an oral-maxillofacial surgeon.¹ Following this, osteonecrosis of the jaw was reported in patients taking oral forms of bisphosphonates for osteoporosis.^{2,4} Since then, there have been an increasing number of patients reported to have BRONJ; however, the incidence estimates vary considerably from less than 1% to 18.6%.⁵ The drug potency, route of administration and duration of therapy are determining factors with the highest incidences reported for zoledronate (Zometa) and a relatively low incidence for the oral forms. The intravenous route of administration and longer duration of therapy are associated with higher risk. Other risk factors for BRONJ include: advanced age, female gender and Caucasian, presence of lingual or palatal tori, being edentulous, poor oral hygiene, periodontal and dental infections or abscesses (seven times higher risk), dentoalveolar surgery, cancer, diabetes mellitus, anemia, coagulopathy, and concurrent use of chemotherapy, corticosteroids, tobacco or alcohol.^{1-4,6}

Two mechanisms are thought to play a role in the pathogenesis of BRONJ. First, the osteoclast inhibiting effect of bisphosphonates leads to cessation of bone remodeling and turnover, which causes the osteon to become acellular with subsequent involution of blood vessels that leaves the bone avascular and necrotic.¹⁻³ The second is related to inhibition of neoangiogenesis by the intravenous bisphosphonates that leads to loss of blood vessels and avascular necrosis in the jaw.¹⁻³ The jaw is at risk not only because the bisphosphonates concentrate and act in the jaw, but also because the jaw is minimally protected by a thin mucosal covering. Breakdown of the overlying mucosa because of any mechanism (infection, trauma or surgery) exposes the avascular, necrotic bone, which then fails to heal.

Of particular interest to otolaryngologists, the clinical and radiological presentation of BRONJ is strikingly similar to osteoradionecrosis (ORN) of the jaw. The American Association of Oral and Maxillofacial Surgeons (AAOMS) require three necessary criteria be met for the correct diagnosis of BRONJ: 1) current or previous treatment with bisphosphonates, 2) exposed or necrotic bone in the maxillofacial region that has persisted for more than

TABLE I.
Staging and Management of BRONJ.

BRONJ Staging	Management Strategies
At risk category: No apparent exposed/necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment indicated, patient education
Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse Clinical follow-up on a quarterly basis Patient education and review of indications for continued bisphosphonate therapy
Stage 2: Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Symptomatic treatment with broad-spectrum oral antibiotics, e.g., penicillin, cephalexin, clindamycin, or fluoroquinolone Oral antibacterial mouth rinse Pain control Only superficial debridement to relieve soft tissue irritation
Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extra oral fistula, or osteolysis extending to the inferior border	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain

BRONJ = bisphosphonate-related osteonecrosis of the jaw.
Adapted from AAOMS Position Paper. *J Oral Maxillofac Surg.* 2007;65:369-376.

8 weeks, and 3) no previous history of radiation to the jaw. BRONJ may remain asymptomatic for many months, becoming symptomatic only when the site is secondarily infected or traumatized.⁶ The most frequent symptoms include pain, swelling, loosening of teeth, drainage, and fistula formation. Unlike ORN where the maxilla is involved in only 5% of cases, maxillary involvement is much higher, up to 43% in BRONJ.⁷ Maxillary BRONJ can result in involvement of the paranasal sinuses and can cause sinusitis as well as significant complications such as periorbital cellulitis and oroantral fistulas.^{2,7} Recognition of high-risk patients, such as the one presented, and prevention by keeping good oral hygiene and avoiding tooth extractions and dental trauma are important.

Once BRONJ develops, the treatment depends largely on the symptoms, site, and degree of involvement and varies from conservative management to radical resections with reconstruction with vascularized free tissue.⁸ The AAOMS has developed a staging system and recommended treatment strategies,⁶ summarized in Table I. The patient presented had extensive BRONJ involving the ethmoid and skull base, complicated by sinusitis and an intracranial abscess, which required a combined endoscopic and neurosurgical approach for management. To our knowledge, this is first case of bisphosphonate-related osteonecrosis involving the skull base.

CONCLUSION

Bisphosphonate-related osteonecrosis usually affects the jaw (BRONJ) but may involve other bones of the face. With the widespread use of bisphosphonates and the significant morbidity associated with this condition,

it is likely that otolaryngologists will be increasingly involved in the care of these patients. Otolaryngologists need to understand the diagnosis and treatment of this poorly understood disease entity, which can have significant morbidity.

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