

Bisphosphonate induced osteonecrosis of the jaw

George M Kushner & Brian Alpert

A new disease with possible orthopedic implications

There is an alarming new pathologic entity recently recognized in the jaws, which is reminiscent and comparable to osteoradionecrosis (ORN). It presents as painful exposed bone in the maxillary or mandibular alveolus with intra or extraoral drainage in patients on bisphosphonate therapy. Like ORN, it is refractory to conventional non-operative and operative surgical treatment.

RE Marx published the sentinel article in the *Journal of Oral and Maxillofacial Surgery* in 2003 where he tracked 36 cases of painful bone exposures in the maxilla or mandible which were relatively refractory to conventional treatment. In 2004, SL Ruggiero et al reported 63 similar cases. We have seen seven cases in the past year.

Bisphosphonate therapy

The single common denominator in this growing series appears to be the

use of bisphosphonate therapy. Bisphosphonates such as pamidronate (Aredia) and zoledronate (Zometa) are commonly used to manage the hypercalcemia associated with malignancies such as multiple myeloma or metastatic breast cancer. These medications essentially alter bone metabolism by inhibiting osteoclast activity, thus preventing bone resorption, which helps reduce calcium levels and preserves bone.

More recently, oral bisphosphonate therapy has been recommended to prevent osteoporosis, a major health care issue with significant clinical problems well known to the AO community. Vertebral compression and femoral head fractures among others, contribute significantly to patient morbidity and mortality. In North America, there are numerous TV commercials aimed at postmenopausal women, suggesting the avoidance of osteoporosis and its sequelae by the use of oral bisphos-

phonate preparations. That use is becoming extremely common.

The majority of osteonecrosis of the jaw (ONJ) cases have been associated with the IV forms of bisphosphonates, but many cases (including three of our seven) have been identified with the use of oral bisphosphonates. Many of the cases started after a simple dental procedure such as a tooth extraction. The patients present with painful, non-healing extraction sockets and exposed bone. Spontaneous exposure of painful bony sites has also been reported without any dental procedures, manipulations or trauma.

Management of the bisphosphonate induced osteonecrosis initially included debridement of necrotic bone, thought to possibly contain tumor. Neither the Marx nor the Ruggiero series identified malignancy in any of the debrided bone specimens. This has also been our experience here at the University of Louisville with our ONJ patients.

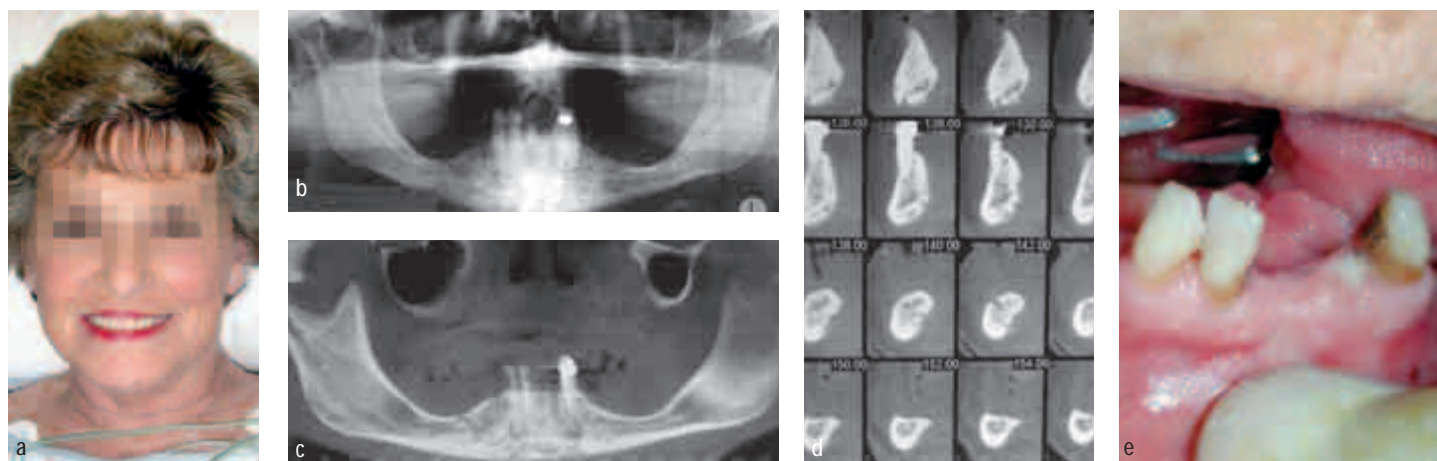


Fig 1a–e 67-year-old woman referred from another center with a 5-month history of mandibular pain, intra and extraoral drainage managed with a variety of IV antibiotics and several I&Ds. She had been taking Fosamax six months prior to initial symptoms for osteoporosis prevention. Panoramic x-ray and CT scan demonstrated extensive osteonecrosis of the lingual aspect of the mandible. Note the periodontally involved teeth.

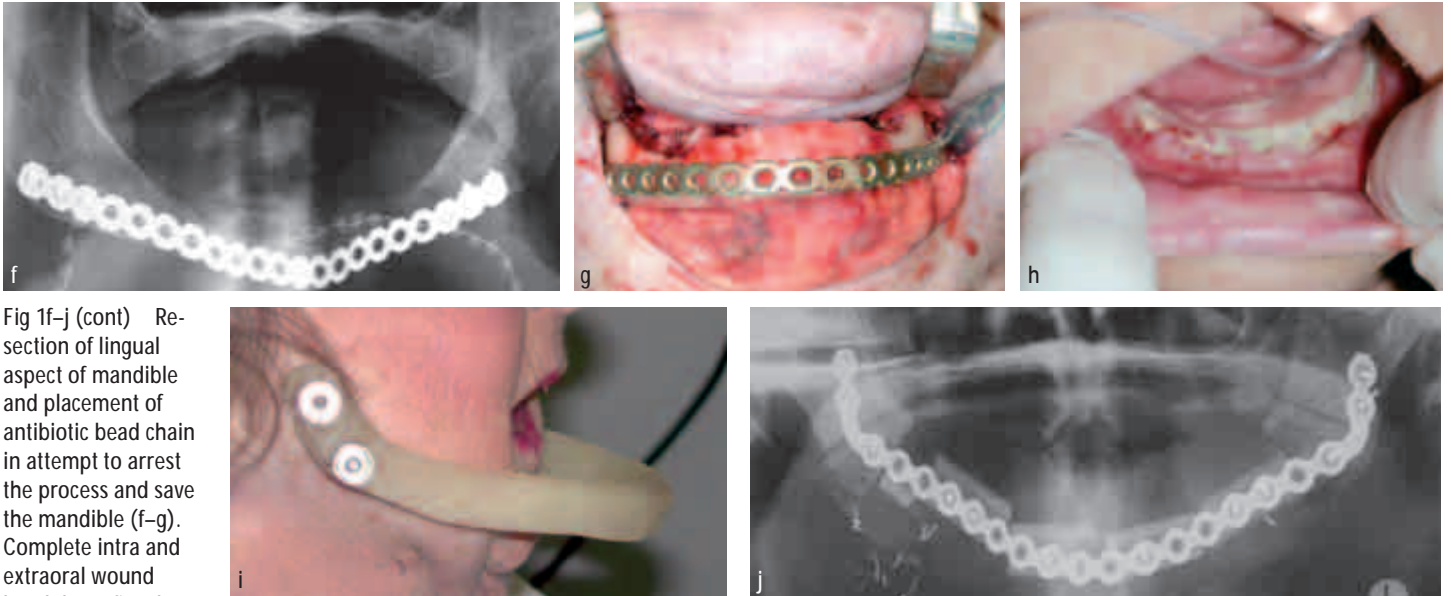


Fig 1f-j (cont) Resection of lingual aspect of mandible and placement of antibiotic bead chain in attempt to arrest the process and save the mandible (f-g). Complete intra and extraoral wound breakdown five days post op (h). Removal of remaining mandible from angle to angle. External fixation to hold position of angles. Note loss of skeletal chin support (i). Reconstruction three months later with free fibula flap (j).

Managing ONJ

The management of ONJ has yet to be finalized. Antibiotics, conservative debridements, irrigations and topical application of anti-infectives are seldom curative but may permit the patient to live with their disease. Hyperbaric oxygen does not seem to be effective. There are more advanced cases with patients who have responded poorly to conservative treatment that have required resection of the mandible or maxilla.

At this point, the best way to manage ONJ is to prevent it from occurring. There is a huge patient population taking bisphosphonate therapy and are at risk for ONJ, and many practitioners who are still unaware of this complication. The information is gradually getting out to treating physicians and dentists. Pharmaceutical companies have sent out letters to the oncologists and oral/maxillofacial surgeons, alerting them to this condition.

Patients currently taking bisphosphonates should be counseled to the risks of ONJ and be encouraged to seek dental care to optimize their oral health. Invasive dental procedures such as dental extractions and implant placement should be avoided if at all possible. Since bisphosphonate medications have half lives measured in years, stop-

ping the medication for weeks or months will have little if any effect. Patients who are planning bisphosphonate therapy should have a thorough oral exam and necessary work to eliminate all dental disease prior to the initiation of this therapy. The dental profession is accustomed to performing these pretreatment evaluations in high risk patients receiving head/neck radiation therapy, transplants, chemotherapy and heart valves, where dental complications in the post-treatment course can have significant morbidity and even mortality.

Future outlook

Currently, medical and dental practitioners, the pharmaceutical industry and government agencies are working to obtain additional information and provide answers as to the definitive management of this newly identified entity called ONJ. As practitioners, we must put ONJ on our radar screens when either treating pathology in the maxillofacial region or prescribing bisphosphonates so as to alert our patients to this possible complication of therapy. There is certainly more to come about bisphosphonate induced osteonecrosis of the jaws. We believe we are just seeing the tip of the iceberg.

Bisphosphonates

Pamidronate disodium **AREDIA**
 Zoledronic acid **ZOMETA**
 Alendronate **FOSAMAX**
 Risedronate **ACTONEL**
 Ibandronate **BONIVA**

George M Kushner, Associate Professor of Oral and Maxillofacial Surgery, University of Louisville School of Dentistry and Residency Program Director Louisville, KY, USA
george.kushner@louisville.edu

Brian Alpert, Chairman and Professor of Oral and Maxillofacial Surgery, University of Louisville School of Dentistry, Louisville, KY, USA
brian.alpert@louisville.edu

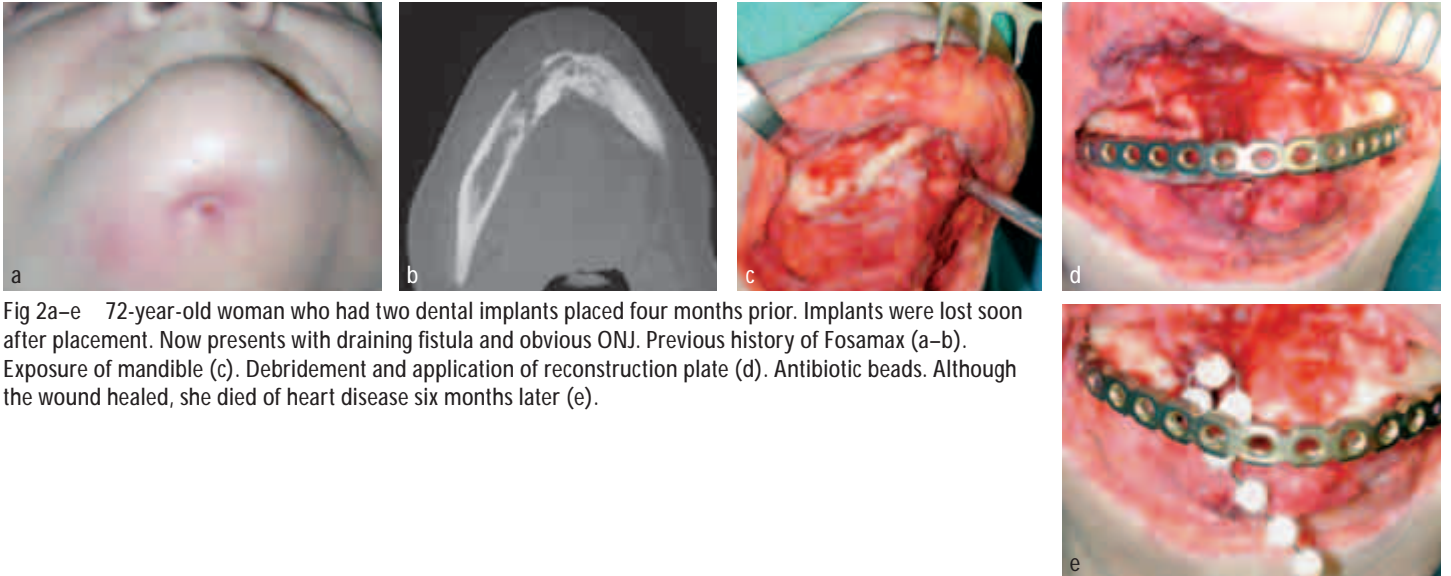


Fig 2a-e 72-year-old woman who had two dental implants placed four months prior. Implants were lost soon after placement. Now presents with draining fistula and obvious ONJ. Previous history of Fosamax (a-b). Exposure of mandible (c). Debridement and application of reconstruction plate (d). Antibiotic beads. Although the wound healed, she died of heart disease six months later (e).



Fig 3a-d 60-year-old woman with one year history of Fosamax use. She had dental implants placed three months prior and now presents with a fistula and pathologic fracture of the mandible. Area exposed and debrided (a-b). Reconstruction with locking plate and tibial bone graft. She healed uneventfully (c-d).

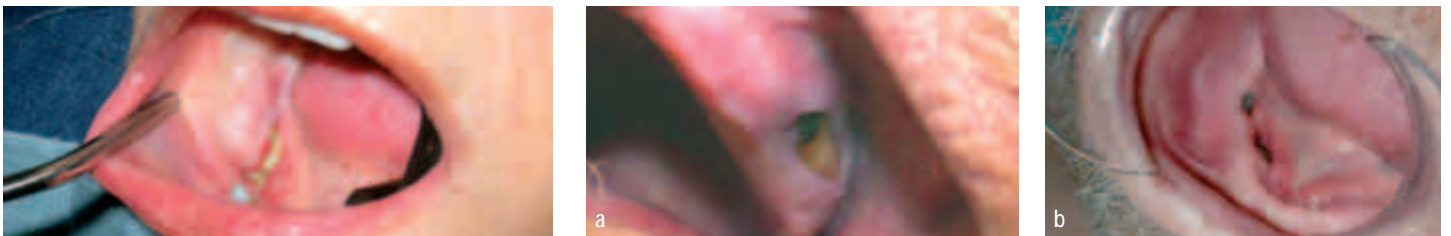


Fig 4 56-year-old woman with breast cancer taking IV bisphosphonate. Note exposed bone of right mandible

Fig 5a-b 71-year-old man with multiple myeloma managed with Aredia. Note exposed bone in both maxilla and mandible.

Bibliography

Marx RE (2003) Pamidronate (Aredia) and Zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofacial Surg*; 61:115-18.

Ruggiero SL, Mehrotra B, Rosenberg TJ (2004) Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofacial Surg*; 62:527-534.

Tarassoff P, Csermak K (2003) Avascular necrosis of the jaws: risk factors in metastatic cancer patients. *J Oral Maxillofacial Surg*; 61:1238-39.

Bagan JV, Murillo J, Jimenez Y et al (2005) Avascular jaw necrosis in association with cancer chemotherapy: series of 10 cases. *J Oral Pathol Med*; 34: 120-23.

Melo MD, Obeid G (2005) Osteonecrosis of the maxilla in a patient with a history of bisphosphonate therapy. *J Can Dent Assn*; 71(2) 111-13.

Carter GD, Goss AN (2003) Bisphosphonates and avascular necrosis of the jaws. *Aust Dent J*; 48(4) 268.

Lugassy G, Shaham R et al (2004) Severe osteomyelitis of the jaw in long term survivors of multiple myeloma: new clinical entity. *Am J Med*; 117(6) 440-41.