

Multiple osteonecrosis of the jaw, oral bisphosphonate therapy and refractory rheumatoid arthritis (Pathological fracture associated with ONJ and BP use for osteoporosis)

Sirs,

Osteonecrosis of the jaws (ONJ) is a recently described adverse side effect of bisphosphonate therapy (1). Patients with multiple myeloma and metastatic carcinoma to the skeleton who are receiving intravenous, nitrogen-containing bisphosphonates are at greatest risk for osteonecrosis of the jaws. There may be contributing comorbid factors such as jaw infection, ill-fitting dentures, dental decay, poor dental hygiene and periodontal disease, dentoalveolar surgery, corticosteroids and immunosuppressive agents and, recently proposed, diabetes (2-4). But we have not found any case with the association of ONJ, oral bisphosphonate and refractory rheumatoid arthritis (RA) as the patient we describe below.

A 64-year-old white female patient presented in February 2004 with irregularity of the mandible. She was admitted to evaluate a possible osteomyelitis versus osteonecrosis complication of dental extraction. She had a long history of aggressive and refractory RA.

RA had set in at the age of 49. She was treated initially with non-steroidal anti-inflammatory drugs, low doses of corticoids and parenteral gold salts. Due to a negative response to the treatment, she received successively a combination of oral gold salts, methotrexate, chloroquine and cyclosporine. In October 1996, she began treatment with 150 mg/day of oral cyclophosphamide, low doses of corticoids and a supplement of calcium and vitamin D. Cyclophosphamide was withdrawn due to hematuration 6 months later but her arthritis had improved. Later, she was treated with leflunomide and chloroquine with control of the inflammatory activity of RA until today. She was in a "burned RA" situation. She began with 70 mg of weekly alendronate in February 2002 for osteoporosis.

She was evaluated by a maxillofacial surgeon in March 2004. A cranial CT showed lesions with detached bone in the mandible, therefore surgical cleaning was carried out. In June of 2006 she again had pain in the mandible, and an x-ray image of mandible osteonecrosis was obtained. A new CT was made that showed several osteonecrosis lesions. In October of 2006 she suffered acute pain and infection. A fracture of the right part of the jaw was detected. Surgical cleaning of the mandible was done, the jaw was blocked with the superior dental prosthesis and systemic antibiotics were administered. Histological studies showed "bone tissue necrosis" without infection. At this

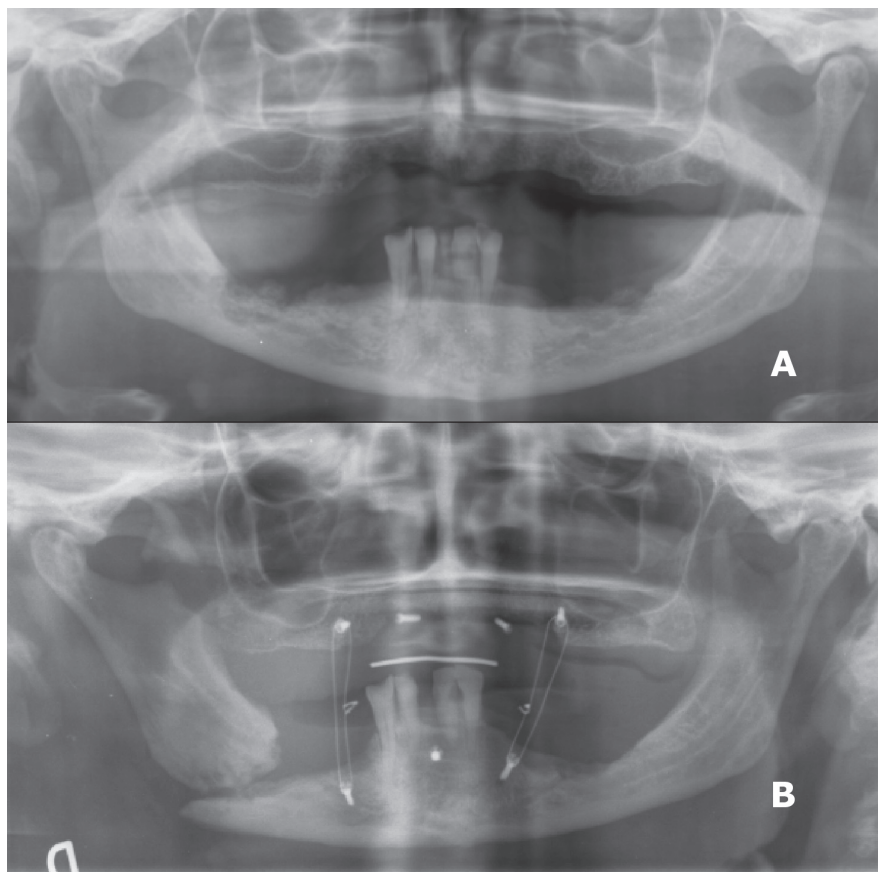


Fig. 1. Ortopantomography evolution of multiple ONJ in a RA patient treated with oral bisphosphonates for osteoporosis: **A.** May 17, 2006 Rx – Osteonecrotic lesions at both branches of mandible. **B.** October 11, 2006. – Fracture of right branch of mandible and its coronoid process.

moment, the diagnosis of ONJ associated to bisphosphonates was made, and the alendronate and the corticoids treatment were withdrawn. The patient was sent for treatment in a hyperbaric chamber. At present she is free of infection. Figure 1 shows the sequential evolution of lesions.

Osteonecrosis of the jaw is characterized clinically by an area of exposed bone in the mandible, maxilla, or palate that typically heals poorly or does not heal over a period of 6 to 8 weeks. The diagnosis is primarily a clinical one, but imaging studies such as computed tomography can be helpful. It is a well-known but rare situation related to radiotherapy and chemotherapy for malignancy (5).

This condition in connection with bisphosphonate use was first reported in 2003; it was rarely seen before then. Most of the reported cases (95%) have been associated with zoledronic acid or pamidronate given intravenously to control metastatic bone disease (1, 2). The reported incidence of osteonecrosis of the jaw in these cases has ranged from 1.3% (6, 7) to 7% (1). Myeloma and breast cancer are by far the most common cancers associated with intravenous bisphosphonate use and ONJ.

The cause-effect relationship between bisphosphonates therapy and ONJ remains

open for discussion. Some authors related ONJ more with malignancy and its therapy than with bisphosphonates use, and do not recommended their interruption (5). Moreover, a favourable response of diffuse sclerosing osteomyelitis of the mandible to alendronate was recently published (8), and experimental alendronate use in amputated rat molar seems useful and not complicated with ONJ (9). But the growing number of reports regarding this complication suggests a bisphosphonates biological influence on the microtraumatic lesions self-restorative ability of the jaw bone. This site may be affected because the jawbones are in constant use and are characterized by active remodelling. For this reason, bisphosphonates might accumulate preferentially in the jaw, resulting in concentrations that exceed those found elsewhere in the skeleton. The possible antiangiogenic effects of nitrogen-containing bisphosphonates and the effects of these agents on T-cell function have also been hypothesized.

Osteonecrosis of the jaw has developed far less often among patients who have received oral bisphosphonates at the lower doses used for osteoporosis. Among several million patients who have received oral treatment for osteoporosis, fewer than 50 cases of osteonecrosis of the jaw have been

reported to date (1). Some authors believe that 1 in 100,000 patient-years is a reasonable estimate of the incidence for this complication (3, 10)

Rheumatoid arthritis patients can be associated with poor mouth health and loose teeth, particularly patients with Sjögren's syndrome, and they are also often treated with corticosteroids and immunosuppressive agents. This may increase the risk of developing ONJ during treatment with aminobisphosphonates.

To the best of our knowledge, this is the first published case of multiple ONJ, refractory RA and oral use of BP. The degree of risk for osteonecrosis in these patients taking oral bisphosphonates for osteoporosis is uncertain and warrants careful monitoring.

J. GRAÑA, MD, PhD, Rheumatologist

I. VAZQUEZ MAHIA, MD, Maxillofacial Surgeon

M.-O. SÁNCHEZ MEIZOSO, MD, Documentalist

T. VÁZQUEZ, MD, Training Rheumatologist

Juan Canalejo University Hospital Complex, Coruña, Spain.

Address correspondence to: Dr. Jenaro Graña, Juan Canalejo University Hospital Complex, Xubias de Arriba 84, 15006 A Coruña, Spain.

E-mail: jgrana@ser.es

Competing interests: none declared.

References

1. WOO SB, HELLSTEIN JW, KALMAR JR: Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. *Ann Intern Med* 2006; 144: 753-61. Review. Erratum in: *Ann Intern Med* 2006; 145: 235. Comment in: *Ann Intern Med* 2006; 145: 791-2; author reply 792. *Ann Intern Med* 2006; 145: 791; author reply 792.
2. MELO MD, OBEID G: Osteonecrosis of the jaws in patients with a history of receiving bisphosphonate therapy. Strategies for prevention and early recognition. *JADA* 2005; 136: 1675-81.
3. BILEZIKIAN JP: Osteonecrosis of the jaw – Do bisphosphonates pose a risk? *N Engl J Med* 2006; 355: 2278-81.
4. KHAMAISI M, REGEV E, YAROM N *et al.*: Possible Association Between Diabetes and Bisphosphonate-

Related Jaw Osteonecrosis. *J Clin Endocrinol Metab* 2006 Dec 19; [Epub ahead of print].

5. LENZ JH, STEINER-KRAMMER B, SCHMIDT W, FIETKAU R, MUELLER PC, GUNDLACH KK: Does avascular necrosis of the jaws in cancer patients only occur following treatment with bisphosphonates? *J Craniomaxillofac Surg* 2005; 33: 395-403. [Epub 2005 Oct 25].
6. HOFF AO, TOTTH B, ALTUNDAG K *et al.*: Osteonecrosis of the jaw in patients receiving intravenous bisphosphonate therapy. *J Bone Miner Res* 2005; 20 (Suppl. 1): 1218 (abstract).
7. POLIZZOTTO MN, COUSINS V, SCHWARER AP: Bisphosphonate-associated osteonecrosis of the auditory canal. *Br J Haematol* 2006; 132: 114.
8. HINO S, MURASE R, TERAKADO N, SHINTANI S, HAMAKAWA H: Response of diffuse sclerosing osteomyelitis of the mandible to alendronate: follow-up study by Tc-99m scintigraphy. *Intl J Oral Maxillofac Surg* 2005; 34: 576-8.
9. CENGİZ SB, BATIRBAYGİL Y, ONUR MA *et al.*: Histological comparison of alendronate, calcium hydroxide and formocresol in amputated rat molar. *Dental Traumatol* 2005; 21: 281-8.
10. BOLLAND MJ, GREY A, REID IR: Osteonecrosis of the jaw and bisphosphonates. *BMJ* 2006; 333: 1122-3.