Osteonecrosis of the jaw in a patient with rheumatoid arthritis treated with an oral aminobisphosphonate: a clinical case report

Lorena Longato¹
Loredana Cavalli²
Gemma Marcucci²
Alessia Metozzi²
Francesca Giusti²
Maria Luisa Brandi²
Prisco Piscitelli^{2,3}

¹ Local Health Authority ASL Biella, Biella, Italy

² Department of Internal Medicine, University of Florence, Florence, Italy

³ Euro Mediterranean Biomedical Scientific Institute (ISBEM), Brindisi, Italy

Address for correspondence:

Lorena Longato

Local Health Authority Biella

Via Marconi 23

13900 Biella, Italy

Phone: +39 015 3503115

E-mail: l.longato@tiscali.it

Summary

Osteonecrosis of the jaw (ONJ) has been recently described after intravenous administration of amino-bisphosphonates and – less frequently – in association with the use of oral bisphosphonates. Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) may affect mandible bone (65%), maxilla bone (26%) and rarely (9%) both sites simultaneously. Although causality may never be proven, emerging experimental data have established a strong association between monthly intravenous bisphosphonate administration and ONJ. Current level of evidence does not fully support a cause and effect relationship between the use of oral BPs and ONJ. In this paper, we report a clinical case of BRONJ in a 73 years old woman affected by rheumatoid arthritis (RA) and periodontitis, after three years of treatment with alendronate 70 mg one a week, plus daily calcium and vitamin D. The patient developed a tooth abscess at the lower jaw, accompanied by increased inflammatory markers, that never returned to normal range despite antibiotic therapy, inducing deterioration of joint synovium. The worsening of joint status after the onset of ONJ was reflected by the progressive increase in the number of swollen (SJ) and tender (TJ) joints, by the deterioration of the score DAS 28 (which passed from 5.46 to 7.07), pain (with VAS increasing from 60 to 90), and by a progressively impaired quality of life, as reported using the HAQ score (from 1.25 to 2.5). The patient was switched to antifracture therapy with strontium ranelate and the osteonecrosis was successfully treated with antibiotics, surgical curettage and local ultrasounds.

KEY WORDS: Osteonecrosis of the jaw (ONJ); Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ); Rheumatoid Arthritis (RA).

Introduction

Osteonecrosis of the jaw (ONJ) has been described in association with the use of white phosphorus, radiotherapy, chemotherapy and more recently intravenous amino-bisphosphonates (Bisphosphonate-Related Osteonecrosis of the Jaw, BRONJ) (1). An association between the exposure to intravenous bisphosphonates (BPs) and ONJ may be hypothesized based on the observation of a positive correlation between bisphosphonates potency or duration of therapy and risk for developing BRONJ (1, 2) as well as a negative correlation between bisphosphonates potency and duration of BPs exposure prior to developing ONJ (1, 2). The occurrence of ONJ after the use of oral BPs has been less frequently observed (3). However, the current level of evidence does not fully support a cause and effect relationship between BPs exposure and ONJ, although emerging experimental and epidemiologic studies have established a firm foundation for a strong association between monthly intravenous bisphosphonate administration and ONJ (3). BRONJ has been more frequently described for the mandible bone (65% of the cases), less frequently to the maxilla bone (26%) and rarely (9%) in both sites simultaneously (3).

The onset of BRONJ is sneaky, characterized by chronic inflammation of the gums with scarce signs of healing after a tooth extraction or implant surgery; paresthesias, odontalgia or lingual dysesthesia, loss of teeth which cannot be explained by chronic periodontal diseases, peri-apical or periodontal fistula not associated with caries may occur in the stage 0 (4). Later stages (1 to 3) are characterized by the displaying and necrosis of a bone yellowish-white area, often suppurating, sometimes fistulizing in the oral cavity or externally to the skin and bleeding. The gingival mucosa is red, swollen and ulcerated. Radiographic images show typical peri-radicular bone thinning, compatible with chronic periodontal infection, with impaired breathing, trismus, and dysphagia. Histological examination shows typical confluent areas of necrotic and of living tissue, alternated with remarkable infiltration of inflammatory cells, in contrast to radiotherapy-associated ONJ, where necrosis is compact and uniform. Moreover, BRONJ shows a preserved capillary microcirculation, which can be increased due to reactive inflammation, with numerous osteoclasts not always activated. Several bacterial strains are usually isolated in case of BRONJ, mainly belonging to the resident flora of the oral cavity, or bacteria commonly isolated in periodontal diseases and dental abscesses. In particular, actinomyces is the most frequently isolated strain, so that the clinical picture is more similar to osteomyelitis rather than to osteonecrosis induced by radiotherapy (5).

Case report

In this work we report a clinical case of BRONJ in a 73 years old woman affected by rheumatoid arthritis (RA). Since 1977, the baseline disease (RA) was complicated with ankylositis of the wrists, elbows, and feet. The patient had previously undergone total left knee arthroplasty (in year 2004), left ankle prosthesis, left astragalus-calcaneus-navicular arthrodesis (2005) and implant of a plaque of stabilization at the atlanto-occipital joint (2000). Since 1977, she was assuming background therapy for rheumatoid arthritis (gold salts, methotrexate, leflunomide), as well as steroids, that the patient has never been able to stop. In 2003, following the detection of multiple vertebral fractures, the patient started to take a specific therapy for osteoporosis, starting alendronate 70 mg weekly dosage, daily oral calcium and vitamin D3. In August 2006, the patient reported a tooth abscess at the lower jaw, accompanied by increased inflammatory markers, that never returned to normal range despite antibiotic therapy, inducing deterioration of joint synovium. The worsening of joint status after the onset of ONJ was reflected by a progressive increase in the number of swollen (SJ) and tender (TJ) joints, deterioration of the score DAS 28 (which passed from 5.46 to 7.07), pain (with VAS increasing from 60 to 90), and a progressively impaired quality of life, as reported using the HAQ score (from 1,25 to 2,5).

In April 2007, after excluding any other focus of inflammation, an orthopantomography was performed, showing the presence of a pocket on the lower jaw bone between the two front incisors and two canines (Figure 1). The patient underwent tooth extraction, under antibiotic treatment; a cleaning of necrotic area was carried out. Histological examination showed bone necrosis with accumulation of PAS-positive actinomycetes. Dental scan (computed tomography, CT) showed rarefaction of trabecular bone with a large osteo-necrotic lesion in the median symphysis region of the inferior maxillary bone (Figure 2). On the basis of the clinical, histological, and instrumental examinations, osteonecrosis of the jaw induced by the treatment with alendronate was diagnosed. The patient, initially, assumed antibiotic therapy with amoxicillin, and the treatment with alendronate was replaced with strontium ranelate because this latter antifracture drug is able to activate osteoblasts. The patient underwent regular dental visits to clean and remove the necrotic material. No reactive response of the surrounding bone was observed. Later, a treatment with fluconazole associated to amoxicillin resulted in progressive but slow limitation of the osteonecrosis. Supported by a minimal progressive improvement, the dentist decided to use an ultrasound technique,

Figure 1 - Orthopantomography showing the presence of a pocket on the lower jaw bone between the two front incisors and two canines (April 2007).

Figure 2 - Dental scan (CT) performed in November 2007 showing rarefaction of trabecular bone with a large osteo-necrotic lesion in the median symphysis region of the inferior maxillary bone, immediately up to the central and lateral incisor, bounded by 33 and 43 almost completely avulsed. An abscess with bubbles was also noted to extend into the mouth and tongue mucosae.

long reported (6) as able to allow a better removal of necrotic material without increasing bone trauma typically induced by normal surgical curettage with an immediate reduction in pain and paresthesia symptoms. At the same time, ultrasounds led to a complete normalization of inflammatory markers, that were persistently high.

Discussion

Bone necrosis can potentially affect each skeletal district. The most common form is osteonecrosis of femoral head, an avascular or aseptic necrosis generally due to a trauma or coagulopathy and likely correlated to a deficient blood supply at local level. At the opposite of BRONJ, it is never associated with bacterial contamination. Several studies have shown that BPs do not alter the healing process that occurs after a fracture, and their experimental use in some kinds of peri-odontitis or tooth loosening does not cause osteonecrosis or delayed healing. The main risk factors for ONJ seem to be the use of high-dose intravenous BPs in association with trauma of the oral cavity for a long time. The 60-85% of cases of BRONJ occur after dental work, usually dental extraction or implant. The median time of onset after surgery is about 7 months (3-12 months), but in 22-38% no history of trauma or surgery is reported. Usually, after a dental surgery, there is a rapid wound healing without infections. The most typical feature of the BRONJ is a slow and difficult healing of the alveo-

lar cavity with an infection caused by oral resident germs. Both acute and chronic peri-odontal diseases, predisposing to the penetration of germs, have been reported in 84% of cases of BRONJ, while a tooth decay has been observed in 29%, and a dental abscess in 13% of affected people. Immunodepression associated with cancer, diabetes, multiple myeloma, immunosuppressive therapy or steroid treatment during chemotherapy represents a remarkable risk factor for BRONJ. The association of ONJ with bisphosphonate therapy is likely to be demonstrated for aminobisphosphonates and – among these – most frequently (94% of cases) for parenteral zoledronic acid and pamidronate (7). However, zoledronate is commonly used in the treatment of neoplasms at dosage much higher than those used for osteoporosis. There are also studies that describe association between oral risedronate, ibandronate and alendronate with ONJ (7). The duration of bisphosphonate treatment, the potency of the drug, the number of intravenous treatments and the total infusion hours may also influence the risk of BRONJ (8).

The first case of BRONJ was described in 2003 (9). People affected by cancer seem to be at higher risk with a prevalence of 1,5%, while in Australia an average frequency of 1,15% was reported, reaching 7,8% in cancer patients undergoing dental work. In different series, subjects with myeloma have a prevalence nearly double (55.9%) than those with breast cancer (33.4%) or prostate cancer (4.6%), although in all three cases an identical treatment protocol is provided for the control of metastatic bone lesions with zoledronate or pamidronate.

In this clinical case report, ONJ is detectable as an adverse event of a 3-year therapy with a weekly oral aminobisphosphonate. The crucial factor in the onset and development of osteonecrosis remains a superinfection with actinomycotic bacterial strains in the frame of a previous periodontal disease. In the described case, osteonecrosis was already present before tooth extraction which has only highlighted the osteonecrotic area. The worsening of arthritis symptoms were a consequence of the ONJ already active. As confirmed by our case report, a 3-year therapy with aminobisphosphonates is able to make bone less responsive to mechanical stimuli (10). The removal of the necrotic area of the jaw was followed by a complete normalization of the inflammatory markers. The piezoelectric bone surgery, employing ultrasonic waves to cut mineralized tissues without producing overheating (11, 12), results in a reduction of bleeding, time for healing, hematoma and postoperative pain. Piezo-surgery

might be the technique of choice for the cleaning of the necrotic area as well as for the extraction in all risk conditions predisposing to the onset of BRONJ (11,12). Samples from patients treated with piezo-surgery revealed the absence of osteoclastic activity and the presence of fibro-vascular granulation tissue in the central surface of the cutting, with good adherence of fibrin to the bone surface (11, 12).

Disclosures: MLB has received grants for research, consulting and speech from Servier, MSD, Eli Lilly, AMGEN; PP has received consulting fees from Eli Lilly, Servier and AMGEN; LL, LC, GM, AM, FG: no disclosures.

References

1. American association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaw_2009 update. Task Force on Bisphosphonate-Related Osteonecrosis of the Jaws.
2. Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. *Bone* 2008;42:841-847.
3. Russell RGG, Watts NB, Ebetino FH, Rogers MJ. Mechanisms of action of bisphosphonates: similarities and differences and their potential influence on clinical efficacy. *Osteoporos Int* 2008;19:733-759.
4. Reid IR, Cornish J. Epidemiology and pathogenesis of osteonecrosis of the jaw. *Nat Rev Rheumatol* 2011;29;8(2):90-96.
5. Lee CY, Pien FD, Suzuki JB. Identification and treatment of bisphosphonate-associated actinomycotic osteonecrosis of the jaws. *Implant Dental* 2011;20(5):331-336.
6. Horton JE, Tarpley TM, Jacoway JR. Clinical application of ultrasonic instrumentation in the surgical removal of bone. *Oral Surg Oral Med Oral Pathol* 1981;51:236-242.
7. Marini F, Tonelli P, Cavalli L, Cavalli T, Masi L, Falchetti A, Brandi ML. Pharmacogenetics of bisphosphonate-associated osteonecrosis of the jaw. *Front Biosci (Elite Ed)*. 2011 Jan 1;3:364-70.
8. Stumpe MR, Chandra RK, Yunus F, Samant S. Incidence and risk factors of bisphosphonate-associated osteonecrosis of the jaws. *Head Neck* 2008.
9. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003;61(9):1115-7.
10. Siddiqi A, Payne AGT, Zafar S. Bisphosphonate-induced osteonecrosis of the jaw: a medical enigma? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009.
11. Vercellotti T. Technological characteristics and clinical indications of piezoelectric bone surgery. *Minerva Stomatol* 2004;53(5):207-14.
12. Robiony M, Polini F, Costa F, Vercellotti T, Politi M. Piezoelectric bone cutting in multipiece maxillary osteotomies. Technical Note. *Journal of Oral and Maxillofacial Surgery*. 2004;62(6).