INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 25, no. 1, 311-316 (2012)

LETTER TO THE EDITOR

POSSIBLE ROLE OF ORAL IBANDRONATE ADMINISTRATION IN OSTEONECROSIS OF THE JAW: A CASE REPORT

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Received July 4, 2011 – Accepted January 19, 2012

We describe a case of Osteonecrosis of the Jaw (ONJ) that developed in a 65-year-old Caucasian woman with osteopenia and other risk factors who was receiving low doses of oral bisphosphonate therapy (ibandronate, 150 mg monthly). Computed tomography (CT), panoramic radiographs (OPT), 99mTc-Sn-MDP scintigraphy, and magnetic resonance imaging (MRI) were performed to study the diseased area; cytological examination also revealed the presence of suppurative material around the area of exposed bone. A diagnosis of bisphosphonate-related osteonecrosis of the jaw complicated by osteomyelitis was made. The patient was prescribed a drug protocol consisting of metronidazole 250 mg 2 times daily, chlorhexidine mouthwashes 3 times daily and chewing exercises for two months. Ibandronate was stopped and replaced with strontium ranelate. The symptoms improved and the patient is still under close follow-up. Assessment of the benefits versus risks is particularly necessary in patients with several risk factors to ascertain their eligibility for treatment with antiresorptive drugs and when this is not possible to choose alternative medications.

We present a case of Osteonecrosis of the Jaw (ONJ) that developed in a patient with osteopenia and other risk factors who was receiving oral bisphosphonate therapy (ibandronate). Few cases have reported this rare side effect due to the use of oral ibandronate.

Since 2003 case reports and case series of ONJ in connection with bisphosphonate use have appeared in literature (1), mainly in oncological patients receiving high doses of intravenous therapy (zoledronic acid or pamidronate) (2). On the other hand, the prevalence of ONJ associated with osteoporosis, which is treated with less powerful low doses of oral bisphosphonates (alendronate, risedronate and ibandronate), has been estimated to range between 0.0004% and 0.04% in the general population (3). The limited data on reported cases of ONJ have not allowed identification of the underlying pathophysiological mechanism and the role of risk factors.

We know that bisphosphonates bind divalent ions such as Ca^{2+} and hence are rapidly cleared from the blood circulation, adsorbed into bone tissue and are "ingested" by osteoclasts through endocytosis (4). Bisphosphonates cause an inhibition of osteoclast recruitment, shorten the life span of osteoclasts due to apoptosis and destruction of the osteoclastic cytoskeleton, inducing a decrease in osteoclastic activity (4). This results in a reduction of bone turnover.

Key words: osteonecrosis of the jaw, ibandronate, osteopenia

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0394-6320 (2012)

The reason for the predilection of bisphosphonate-related necrosis for the jaw is unknown: probably bisphosphonates bind to the jaw because it is an active remodeling site characterized by a high turnover rate, resulting in local concentrations that exceed those in other skeleton sites (5). Moreover, bisphosphonates are not metabolized, therefore high concentrations remain in the bone for extended periods of time and long-term use (more than three years) reduces bone turnover and compromises healing of even physiological microinjuries within bone that occur as a result of day-to-day stress (6).

According to this hypothesis, ONJ could result from the inability of hypodynamic and hypovascular bone to meet an increased demand for repair and remodeling owing to physiological stress (mastication), iatrogenic trauma (tooth extraction or denture injury), or tooth infection that involves the underlying bone (*Actinomyces israelii* are often reported in biopsy specimens of ONJ) (7).

In patients with comorbidities, like those in our patient, such events may occur more frequently, even if the ibandronate is administered at low doses and taken orally.

Case presentation

A 65-year-old Caucasian woman visited her dentist in August 2009 complaining of oral pain and swelling in the posterior left side of the jaw. At the time of the consultation, the medical history revealed that ten years previously she had been diagnosed with rheumatoid arthritis which was treated with corticosteroids (methylprednisolone 4 mg daily) and immunosuppressive therapy (azathioprine 50 mg three times a week). She also had a history of chronic renal failure probably associated to improper use of nonsteroid anti-inflammatory drugs. In order to avoid loss of bone induced by chronic treatment with corticosteroids, the patient, who also presented a condition of osteopenia (T-score:

Table I. *Biochemical features.*

	November 2009	March 2010
Creatinine (0.60-1 mg/dl)	1.63	2.33
Creatinine clearance (95-160 ml/min)	25	25
Calcemia (8.5-10.1 mg/dl)	7.7	8.6
Calciuria 24 ore (42-353 mg/24h)	16	35
Phosphoremia (2.5-4.9 mg/dl)	4.3	5
Phosphaturia 24 h (400-1300 mg/24h)	473	570
Vitamin D3-25-OH-D3 (10-68 ng/ml)	7.27	18
Parathormon-i PTH (17.3-72.9 pg/ml)	322	177.2
ESR (erythrocyte sedimentation rate) (1-20 mm/h)	49	35
CRP (C-reactive protein) (0.0-0.5 mg/dl)	2.5	2.93

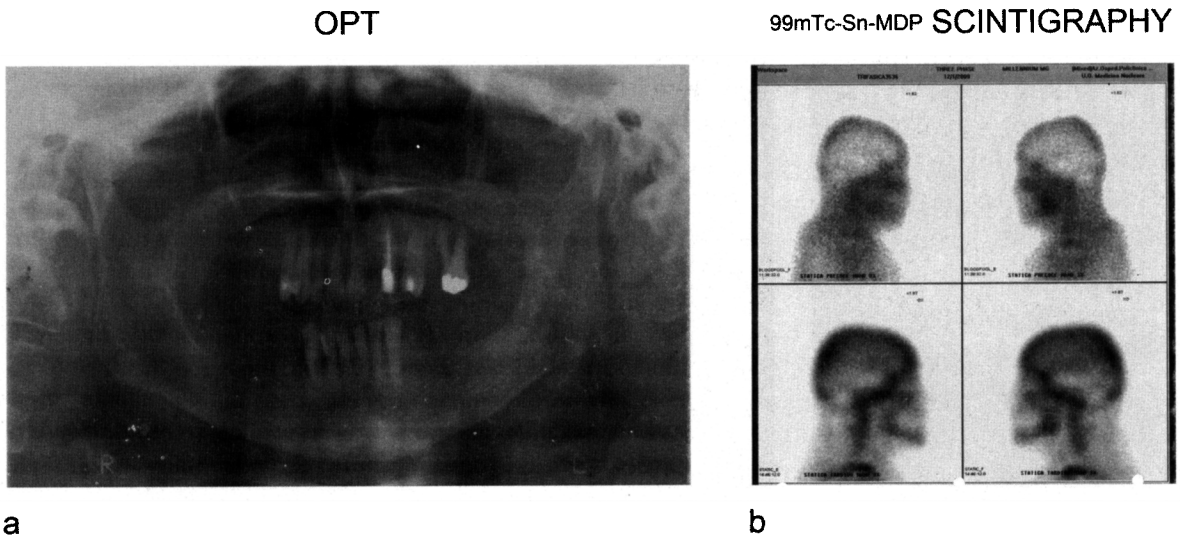

Fig. 1. *a) Panoramic radiographs (OPT) show severe edentulism. b) ^{99m}Tc-Sn-methyldiphosphonate scintigraphy demonstrates increased uptake in the left jaw, one of the typical markers of inflammation.*

- 1.44), had been receiving ibandronate for two years (Bonviva 150 mg, oral doses monthly). She had no history of radiation therapy to the head or neck and did not report teeth extraction on the posterior left side of the jaw.

Clinical inspection showed poor oral hygiene, edentulous regions due to parodontopathy and a fenestration which exposed a necrotic bone fragment close to the left mandibular alveolar ridge. An ONJ was suspected. Bone biopsy was avoided because according to current literature it can cause damage and progression of ONJ (8).

Computed tomography (CT) Dentascan was performed; this showed a reduction of the bone mineral density, especially of the alveolar bone that appeared atrophic. It also showed confluent osteolytic areas near the angle of the mandible and a non-healing site between the alveolar ridge and the upper border of the mandible canal, confirming the clinical suspicion of ONJ. Although bisphosphonate therapy was not suspended, antibiotic therapy was started, obtaining pain control until October 2009. Because of the subsequent reappearance of oral pain, jaw swelling on the left side and limited food chewing, the patient was hospitalized. Clinical oral examination showed reactive lockjaw associated to local inflammation; this condition was supported by an increased erythtrocyte sedimentation rate (ESR). The calcium and phosphonate balance showed hypocalcemia, hypocalciuria, hypovitamin D and secondary hyperparathyroidism (Table I).

Several instrumental examinations were performed. Panoramic radiographs (OPT) showed an empty socket with an associated periosteal reaction and loss of corticomedullary differentiation (Fig. 1)

Jaw scan revealed periosteal interruption (8 mm) and thickening of the masseter muscle. ^{99m}Tc-Sn-Methyldiphosphonate Scintigraphy demonstrated an increased uptake in the left jaw (Fig. 1), subsequently confirmed as suppurative material by cytological examination. T2 weighted Magnetic Resonance (MR) images showed a high signal intensity related to osteonecrosis (Fig. 2); instead T1 weighted MR and short tau inversion recover (STIR) images showed lymphadenopathy and soft tissue enhancement surrounding the left mandible (Fig. 2). A no dentascan jaw CT was performed and compared with the previous one. It showed sclerosis of the left mandible with areas of cortical erosion both internally and externally, in particular close to the angle of the mandible; it also revealed a dyshomogeneous lesion in close contact with the

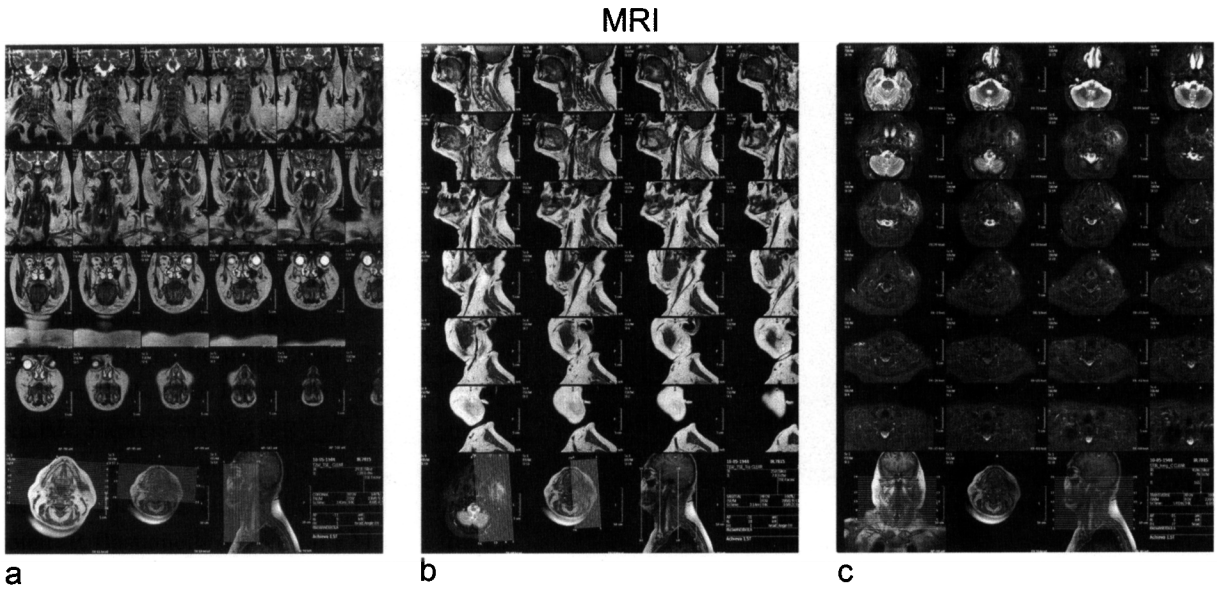

Fig. 2. *Magnetic Resonance (MR) images show a high signal intensity related to osteonecrosis.* ***a)*** *T2 weighted MR images show a high signal in the left side of the jaw (**b, c**) T1 weighted MR and short tau inversion recover (STIR) images show soft tissue enhancement surrounding the left mandible that is related to the presence of oedema.*

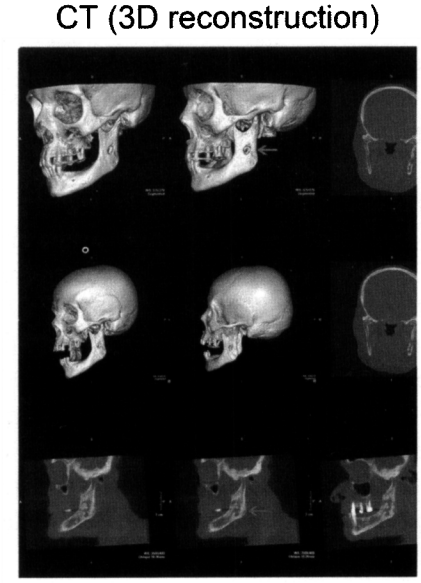

Fig. 3. *A no dentascan jaw CT (3D-reconstruction) shows sclerosis of the left mandible with areas of cortical erosion both internally and externally*

masseter muscle (Fig. 3).

According to the clinical presentation and radiographic pictures, a diagnosis of bisphosphonate-associated osteonecrosis complicated by osteomyelitis was made. The patient was prescribed a protocol consisting of metronidazole 250 mg 2 times daily, chlorhexidine mouthwashes 3 times daily and chewing exercises. Ibandronate was stopped and replaced with another antiresorptive drug (strontium *ranelate).* Symptoms improved and the patient is still under close follow-up.

DISCUSSION

ONJ is a rare side effect described during bisphosphonate use: most publications in the literature refer to the oncological settings (1, 2). However, the growing numbers of spontaneous reports of ONJ in patients taking oral bisphosphonates for the prevention and the treatment of osteoporosis, suggest that this adverse event may be multifactorial and that the type, dosage, duration of treatment and route of administration of bisphosphonates are not sufficient to determine this rare condition (9). To date, however, no potential risk factors have been identified and they remain speculative.

In the case described it was not possible to determine with any certainty whether the ONJ was determined exclusively by the use of ibandronate or was also favored by the coexistence of various risk

factors: elderly age (65 years), rheumatoid arthritis, poor oral hygiene and edentulous regions, as well as the use of glucocorticoids and immunosuppressive agents.

Recent studies have demonstrated a frequent association between periodontal disease and chronic inflammatory diseases, such as rheumatoid arthritis. Probably these diseases share a common pathway that involves the release of cytokines, such as interleukin 1-beta (IL-1β), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), that activate collagenolytic enzymes leading to tissue destruction (10). So the presence of a dysregulation of the host inflammatory response could raise the risk of developing ONJ.

Chronic renal failure could also have an effect on the bioavailability of bisphosphonates, that is very low in normal conditions (less than 1 percent of the dose of a bisphosphonate taken orally), causing high concentrations of the drug in bone for more extended periods (11, 12).

Common dental comorbidities such as poor oral hygiene, periodontitis, and the presence of edentulous regions make it necessary to perform a dental examination to identify and correct predisposing conditions before and during treatment to prevent and delay the progression of ONJ (13, 14).

Glucocorticoids and immunosuppressive agents could interfere with wound healing and epithelialization through two mechanisms: on one hand they could damage oral mucosa exposing bone to oral infections (15); on the other hand, they have angiogenetic properties that reduce the capacity to meet an increased demand for repair and remodeling leading to avascular necrosis.

All patients are potentially at risk of developing ONJ, but rheumatological patients seem to be more predisposed to this event because of the combination of an impaired immune system and chronic use of medications. Nevertheless, accurate data on the risk of this particular population have not yet been published.

Assessment of the benefits versus risks is particularly necessary in these patients to ascertain their eligibility for treatment with antiresorptive drugs and, when this is not possible, to choose alternative medications.

Preventive measures of ONJ, including routine follow-up dental visits, close monitoring of oral hygiene and resolving dental problems prior to treatment with the bisphosphonates, have to be strongly recommended by the rheumatologists before prescribing this class of drugs. ONJ follow-up should proceed also after the discontinuation of the therapy because the possibility of recurrent and spontaneous ONJ still remains in predisposed patients (16).

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