ORIGINAL

Jaw osteonecrosis in patients receiving bisphosphonate therapy: results from a single institution

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Abstract

A growing number of reported cases of jaw osteonecrosis in patients receiving bisphosphonate have been published in the last several years. The clinical features of this condition include pain, paresthesia, bone exposure and fistula. Risk factors have been recognized and classified as local and/or systemic. **Objective:** The aim of this study was to demonstrate the clinical data of the patients with osteonecrosis assisted at a single institution. **Patients and Methods:** A total of 42 patients presenting 49 areas of jaw osteonecrosis were evaluated. Medical records were analyzed in order to collect information on underlying disease, bisphosphonate information, clinical features related to bisphosphonate-induced osteonecrosis of the jaw, as well as precipitating events related to its occurrence. **Results:** Most patients were female (71%) and the mean age was 64.7 years old. Breast cancer was the most frequent underlying disease (40.5%) followed by multiple myeloma, prostate cancer, lung and osteoporosis. In addition, the average use of bisphosphonate was 36.8 months and most patients had received zoledronic acid. The posterior region of the mandible was the main affected site. Among the possible triggering factors, exodontia was associated with 73.8% of the cases. The treatment modalities consisted of surgical, local irrigation with clorexidin and antibiotics and a majority of cases presented complete or partial remission. **Conclusion:** Most cases of jaw osteonecrosis were related to tooth extraction and surgical interventions showed a good control of the osteonecrosis cases.

Keywords: bisphosphonate, bisphosphonate-associated osteonecrosis of the jaw, mandible, osteonecrosis.

INTRODUCTION

Bisphosphonates (BPs) are compounds characterized by two carbon-phosphate bonds, with activity on decreasing bone resorption, varying greatly from different classes of BPs[1]. Bisphosphonates are classified as non-nitrogen BPs (etidronate and clodronate) and nitrogen BPs (risedronate, aledronate, pamidronate, and zoledronate)[2]. These drugs are widely used in the treatment of bone metabolism diseases (Paget's disease and osteoporosis), hypercalcemia related to malignancy and multiple myeloma[3-6].

Adverse effects related to intravenous BPs generally include acute systemic inflammatory reaction, ocular inflammation, renal failure, nephrotic syndrome and osteonecrosis of the jaws[7]. Bisphosphonate-related osteonecrosis of the jaws (BOJ) is defined as exposed and necrotic bone which occurs in the maxillofacial region and has persisted for more than 8 weeks. Patients with BOJ have a history of previous/current treatment with BPs and are not submitted to radiotherapy in the head and neck area[8]. Although bone remodeling suppression related to BPs is well established and is the main hypothesis for its pathogenesis, the entire mechanism of BOJ pathogenesis remains unclear[9].

Local factors such as dental extraction, periodontal diseases and abscesses are involved with the development of this pathology. However, some osteonecrosis cases developed without previous local irritation[8]. The aim of this study was to evaluate the clinical features and patients' treatment response for bisphosphonate-induced osteonecrosis of the jaws followed-up in a single institution.

PATIENTS AND METHODS

This was a retrospective observational cohort study which evaluated clinical features of BOJ. All patients were evaluated at the Stomatology Department of Hospital A.C. Camargo (São Paulo, Brazil) from December 2005 to June 2010. The study was performed in accordance with the Helsinki Declaration and Resolution 196/96 of the Brazilian National Health Council, with local ethical committee approval (nº 1027/08).

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Inclusion criteria

Patients who were submitted to at least one single dose of intravenous bisphosphonate therapy and had been clinically diagnosed with BOJ were included in this study.

Exclusion criteria

Excluded from the study were patients who had been submitted to radiotherapy in region of head and neck.

Data collected

The following patients' information was obtained from careful examination of medical charts: gender and age; underlying disease; type of BP, period and dose administrated, and; underlying disease. Also obtained were the clinical characteristics of BOJ such as: number and size of osteonecrosis areas; occurrence of suppuration, local bleeding, malodour and symptoms related to pain or paresthesia; possible triggering events for BOJ occurrence, and; response to BOJ treatment.

Data collected were summarized due to a clinical interpretation through a descriptive presentation from its results.

RESULTS

Patients' characteristics

The sample consisted of 42 patients with a mean age of 64.7 years, ranging from 35 to 76 years and 71% of patients were women. Most patients were using BP due to bone metastases of breast cancer and zoledronate was the main BP. In addition, information about base disease, BP type and patients' status are presented in Table 1.

The 42 patients presented 49 areas of BOJ (36 patients had 1 area, 5 patients had 2 areas and 1 patient had 3 areas). The mandible was more affected than the maxilla, with 22 areas in the posterior region (44.9%) and 5 in the anterior region (10.2%). While in the maxilla, there were 16 and 6 in the posterior and anterior region, respectively (Table 2).

We verified the association between osteonecrosis with local irritant factors, in which their occurrences were related to previous exodontia for 32 patients and implant removing for 3. A single patient presented BOJ occurrence related to prosthesis trauma. However, BOJ occurrence was spontaneous for 5 patients (Table 3).

Osteonecrosis characteristics

Clinically, bone exposition was observed in 32 patients (Figure 1A-C). In relation to complaints, the majority of patients (21/42) related pain, 10 complained of malodor and 2 patients had paresthesia, but 8 patients were asymptomatic. Pus drainage was observed in 24 patients.

Before osteonecrosis manipulation, the systemic condition of each patient was assessed and discussed with the oncologist. Only 1 patient was treated with weekly

Table 1. Clinical data from 42 patients with jaw osteonecrosis in therapy with bisphosphonates.

	N	%
Gender		
Female	30	71.4
Male	12	28.6
Base disease		
Breast cancer	17	40.5
Multiple myeloma	9	21.4
Prostate cancer	7	16.7
Lung cancer	5	11.9
Osteoporosis	4	9.5
Type of BP		
Zoledronate	23	54.8
Pamidronate and zoledronate	8	19.0
Pamidronate	6	14.3
Aledronate	3	7.1
Aledronate and zoledronate	2	4.8
Status		
Alive	25	62.0
Death	14	33.0
Lost to follow-up	3	7.0

Table 2. Distribution of jaws regions affected with BOJ occurrence.

Location	Patients (%)	Areas
Posterior mandible	19 (45.2%)	19
Posterior maxilla	9 (21.4%)	9
Anterior mandible	4 (9.5%)	4
Anterior maxilla	4 (9.5%)	4
Left and right posterior maxilla	2 (4.8%)	4
Posterior maxilla and posterior mandible	2 (4.8%)	4
Anterior maxilla and anterior mandible	1 (2.4%)	2
Anterior maxilla and posterior mandible	1 (2.4%)	3
Total	42 (100%)	49

Table 3. Signs and symptoms related to BOJ occurrence.

	Patients	Areas
Bone exposure	32	37
Suppuration	24	28
Pain	21	25
Odor	10	12
Fistula	10	12
Asymptomatic	8	9
Paresthesia	2	2
Bleeding	2	2

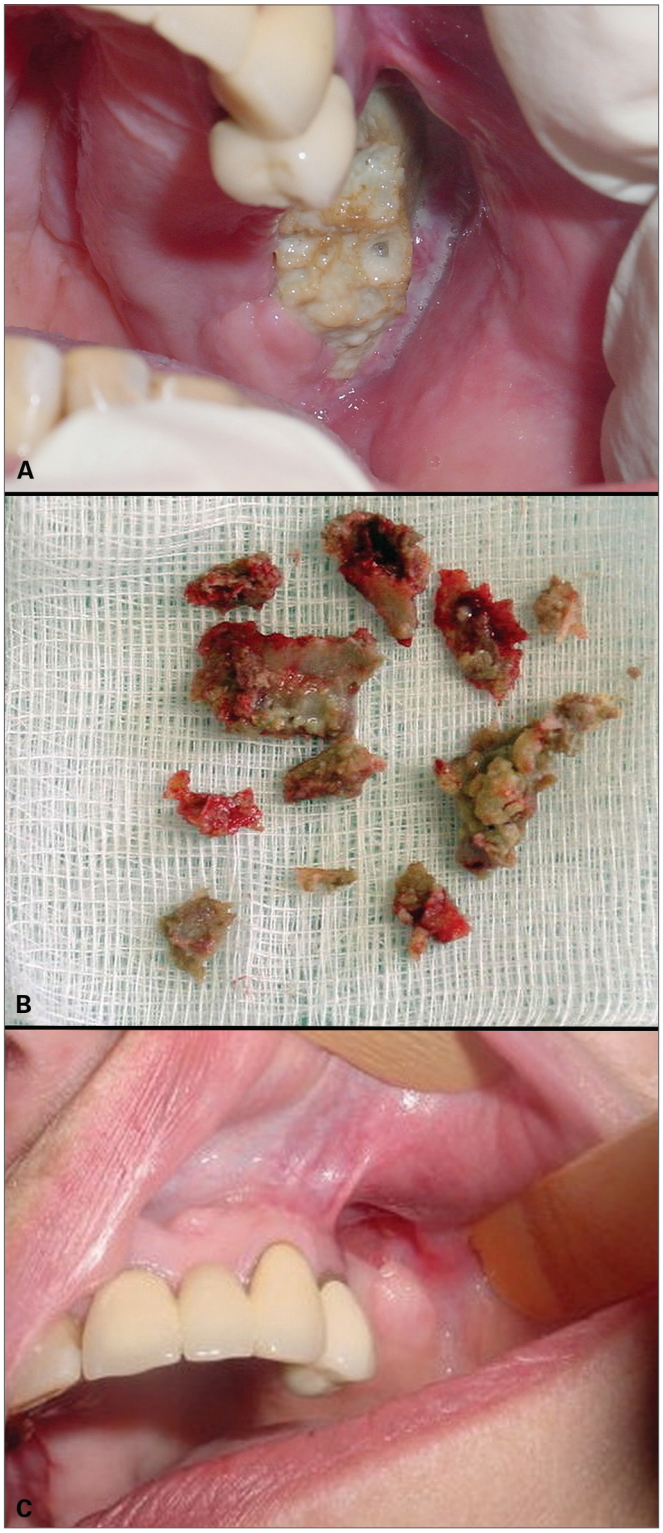

Figure 1. A-C: Large area of osteonecrosis in a patient using zoledronic acid; B: Necrotic bone removed from the maxilla; C: Complete response after 30 days of surgical intervention.

irrigation without any surgery. Debridement was performed in 27 patients and bone resection for 21 patients. All interventions were performed under antibiotic prophylaxis. Patients were oriented to perform rigorous local hygiene between and after the interventions.

The majority of osteonecrosis areas had complete remission (19 areas, 38.7%) or partial response (20 areas, 47.6%). There was not any treatment response for 1 area (2.4%) and 2 areas (4.8%) presented exposed bone increased (Table 4). In relation with status, 13 patients died due to base disease, 1 patient died due to other cause, 3 patients were lost to follow up and 25 patients remained alive (Table 1).

Table 4. Clinical data related to BOJ occurrence: signs and symptoms, inciting factor, treatment approaches and follow-up after treatment.

	Areas	Patients
Signs and symptoms		
Bone exposure	32	37
Suppuration	24	28
Pain	21	25
Odor	10	12
Fistula	10	12
Asymptomatic	8	9
Other	3	4
Paresthesia	2	2
Bleeding	2	2
Inciting factor		
Tooth extraction	32	37
Spontaneous occurrence	5	6
Implant removal	3	4
Trauma by prosthesis	2	2
Treatment		
Debridement	27	23
Irrigation with clorexidin	1	1
Bone resection	21	18
Follow up		
Complete response	19	22
Partial response	20	23
Worse	2	2
No response	1	1

DISCUSSION

Cancer treatment can cause numerous side effects in the oral cavity and recently Marx[10] described the osteonecrosis of the jawbones in patients receiving bisphosphonate therapy. Since 2003, a growing number of reports, letters and case reports about this pathology have been published[11-15]. However, the specific mechanism for its development was not completely elucidated and it remains a challenge for oncology researchers[9,13]. A

number of theories have been proposed and possibly interlinked, such as the suppression of bone turnover soft tissue toxicity[9,16-17]. Therefore, this affected tissue by diverse mechanisms of drug interactions may be more affected by colonizations of *Actinomyces spp*[16,18-19] and other comorbidities[16].

In general, osteonecrosis of the jaw is an uncommon event that has been reported in cancer patients receiving complex treatment regimens, including radiation, chemotherapy and other cancer treatments. There have been several reports of BOJ occurrence in cancer patients who treatment regimens include an intravenous (IV) bisphosphonate[17,20-21]. A retrospective cohort study performed with claim data from an administrative health insurance database revealed that, among a cancer cohort of 46,542 patients, there were 87,677 patients non-exposed to BP, whereas there were 12,638 person-exposed to oral BP, 4,451 person-exposed to IV-bisphosphonate and 649 person-exposed both IV-bisphosphonate and oral BP. One hundred and two potential BOJ cases were assessed, in which only 52 met BOJ definition for this study. Concerning cancer diagnosis, BOJ incidence was higher for patients with multiple myeloma and user of IV bisphosphonate[22]. Additionally, BOJ has been reported in patients who are receiving oral bisphosphonates for noncancerous indications[5,21,23]. A recent systematic review points to an estimate of BOJ incidence ranging from 0.0028% to 4.0. A cohort study from large insurance-based care claims conducted by the same authors of the systematic review assessed a cohort of 4,934 BP users for osteoporosis diagnosis, whereas 84 patients were classified as potential BOJ cases. However, only one dentist-confirmed BOJ was found when surveyed[24].

Recent meta-analysis review reveled rates of BOJ in observational studies ranging from 0% to 51% for patients with multiple myeloma treated with BP[25]. Zervas et al.[20] evaluated 303 patients with multiple myeloma; only the patients that were using bisphosphonates presented jaw osteonecrosis (28/254, 11%) and found an increased risk for osteonecrosis in those receiving thalidomide and bisphosphonate. Similarly, in the present study, the patients presented different pathologies and different drugs were used in their treatment. However, BFs were the single drug used in common by the patients.

Painful exposed bone in the mandible and/or maxilla has been the main complaint of the patients with jaw osteonecrosis[21,22,26]. In our series, most patients (21/42) also reported pain. On the other hand, 8 out of 42 patients were asymptomatic. The pain is likely related with secondary infections of bone or surrounding soft tissue and surgical procedures plus antibiotics appear to relieve their symptoms. Montebugnoli et al.[27] also found that antibiotic protocols can stop the progression of osteonecrosis and that patients can live with some exposed bone without pain.

Many authors[8,11,23,28] have emphasized the association between jaw osteonecrosis and tooth extraction, periodontal diseases or other dental problems in patients receiving bisphosphonate. The majority of our cases, 37 out of 49 areas, were also related to previous dental participation; 32 related to extractions, 3 implant removal and 2 traumas by prosthesis. Nevertheless, 5 areas occurred apparently without a local cause and they were considered spontaneous. A panel of experts[26] representing oral and maxillofacial surgery, oral medicine, endocrinology, and medical oncology was convened to review the literature and clinical evidence to identify risk factors for jaw osteonecrosis. They emphasized the importance of maintaining excellent oral hygiene to reduce the risk of dental and periodontal infections. Removable dentures should be examined for their potential to induce soft-tissue injury, especially tissue overlying bone, and adjusted if required. Routine dental cleanings should be performed carefully, with emphasis on avoiding soft-tissue injuries. We agreed with this statement, considering that most of our patients presented poor oral hygiene (data not shown) in the moment of osteonecrosis diagnosis.

The natural history of jaw osteonecrosis generally begins with a superficial mucosal ulcer, then progresses to detectable bone exposure, necrosis and sequestration. Months later, it is common to find other and distant necrotic lesions in both jaws[18]. Bagan et al.[18] had 20 patients with 47 areas of osteonecrosis (mean 2.3 per patient), the average size of the exposed areas was 1.96 cm. Differently, our data showed that 42 patients had 49 osteonecrosis areas (mean 1.16 area per patient).

In some cases, osteonecrosis can likely begin without a predisposing local factor and occur first in the inner bone. The exact mechanism of action that leads to the induction of osteonecrosis by bisphosphonates is unknown. Interestingly, most osteonecrosis associated to bisphosphonate cases have occurred in jaw bones. Why is this pathology almost exclusive of these bones? Certainly, the local risk factors as extractions and others are important.

There is as yet no consensus in the literature despite the treatment of jaw osteonecrosis. The position paper of American Academy of Oral Medicine[29] shows that although several reports of this complication have been published, there have been no documented uniform treatment strategies that would yield consistent resolution and healing of osteonecrosis. Treatment modalities included local surgical debridement, bone curettage, local irrigation, antibiotics and hyperbaric oxygen therapy[18,22]. We tried to standardize the surgical procedures. Normally, the first intervention was done interrupting the bisphosphonate therapy and a major procedure was required (bone resection) but segmental resections were not performed. Antibiotics (amoxicillin + metronidazole or clindamycin) were prescribed in all surgical intervention for approximately 10 days. The patients maintained intensive

local care in the operated areas, as this procedure can be useful to prevent secondary infection during the healing.

This fact is similar to that which occurs in *osteoradionecrosis* (bone necrosis in irradiated patients). The ionizing radiation promotes irreversible cellular and vascular damage resulting in a hypoxic, hypocellular and hypovascular tissue which loses its repair ability and the mandible is more affected than maxilla[30]. The maxilla bone presents a greater blood supply than mandible, thus, this could be determinant for healing.

The benefit of bisphosphonate for the treatment of hypocalcemia of malignancy and the prevention of skeletal complications from bone metastases has been well established[31-32]. For BP interruption, the patient's oncologist should be consulted. Besides, the real efficacy to stop the bisphosphonate before osteonecrosis treatment is controversial because these drugs are incorporated into the mineral matrix for several years[29]. Based on the fact that it is important to maintain a determinate level of bisphosphonate monthly to control hypocalcemia and bone pain, we could obtain some benefits for stopping. However, prospective randomized controlled studies should be further tested to confirm the impact of this procedure.

In summary, we have presented the clinical characteristics and treatment from 42 patients presenting 49 areas of jaw osteonecrosis. Pain was the most frequent symptom; however, 2 patients had paresthesia in the mandible. Most jaw osteonecrosis was related to dental extraction. Surgical interventions consisted of debridement and bone resection. The majority of osteonecrosis areas (45.2%) had complete remission or partial response (47.6%), Exposed bone increased 4.8% and 1 area was not treated. In relation with status, 13 patients died due to base disease, 1 patient died due to other reasons and 25 remain alive. Surgical interventions resolved the majority of the cases, but local hygiene care was important for preventing infections.

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