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CASE REPORT

Jaw bone necrosis without previous dental extractions associated with the use of bisphosphonates (pamidronate and zoledronate): a four-case report

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Jaw bone necrosis is a clinical condition associated with defects in vascularization of the maxilla or the mandibular bone, usually present following head and neck radiotherapy and/or oral surgical interventions. Bisphosphonates are synthetic analogues of pyrophosphate used in the treatment of patients with hypercalcemia as a result of malignancy, bone metastasis and for the treatment of other disorders such as metabolic bone diseases, Paget's disease and osteoporosis. Over last 10 years, cases of jaw bone necrosis have been associated with the use of bisphosphonate therapy. In particular, Ruggiero et al. (*J Oral Maxillofac Surg* 2004; 62: 527–534) in 2004 described a large group of patients (63) with jaw bone necrosis probably related to the use of these drugs. It should be noted that all the patients in the group described either underwent head and neck radiotherapy or had a dental extraction while taking bisphosphonates. In the present study, we reported four cases of jawbone necrosis in patients taking pamidronate (Aredia) and zoledronate (Zometa) without having undergone any kind of radiotherapy or dental surgery. All the patients were females between the ages of 56 and 71 years; three were treated with bisphosphonates for bone metastasis and one for multiple myeloma. All the patients received surgical treatment with bone curettage, with partial and/or temporary improvement of the lesions. Although a treatment for bisphosphonate-induced bone lesions has not yet been established, we suggest careful evaluation of the patients' oral health before prescribing bisphosphonate treatment.
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Keywords: bisphosphonates; bone metastasis; bone necrosis; multiple myeloma; pamidronate; zoledronate

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Introduction

The osteonecrosis is characterized by the death of bone that results as a natural consequence of a wide variety of systemic and local factors compromising the blood flow of the bone; among these factors, we can consider haemoglobinopathies, anticardiolipin antibodies and defects of the thrombotic and fibrinolytic systems, fat emboli, alcoholism, systemic lupus erythematosus and corticosteroid administration (1–3).

Bone necrosis of the jaws can appear as an exposure of avascular bone in the mandible, in the maxilla or both (1). The exposed necrotic bone appears infected and the area is generally painful; patients complain of difficulty in eating and speaking, pain, bleeding and, when the necrosis is extensive and near the mandibular branch of the trigeminal nerve, paresthesia of lower lip (4). The main cause of bone necrosis is a defect in vascularization (1, 2). In the oral cavity, bone necrosis of immunocompromised patients is probably related to the presence of problematic teeth, which may increase the risk of infection: bone necrosis is usually related to tooth extraction. In some cases these lesions could be associated with corticosteroid therapy or radiotherapy.

The correlation between the use of bisphosphonate therapy in malignancy and the presence of jaw bone osteonecrosis has been recently reported maybe due to the action of the drug on bone vascularization and on the osteoclastic activity.

The four cases reported in this study were referred to the Sezione di Odontostomatologia (Oral Medicine Department) at the University of Parma, Italy, by four different Oncology Departments in Parma, Piacenza and Reggio Emilia, in January 2004.

Case report

Medical history

The age of the four female patients described ranged from 56 to 71 (Table 1); two of these patients had been

Table 1 Characteristics of patients: medical history, symptomatology and therapy

	C.M.	*B.L.*	*R.C.*	*S.E.*
Sex	F	F	F	F
Age	56	64	59	71
First diagnosis	Breast cancer	Pleura mesothelioma	Breast cancer	Multiple myeloma
Time of first diagnosis	1993	1997	2000	2002
Diagnosis of metastasis	1997 (March)	2002 (February)	2001	–
Metastasis type	Bone metastasis	Mesothelioma and bone metastasis	Liver and bone metastasis	–
Chemotherapy	Ciclofosfamid + metotrexate + 5-fluorouracil (5-FU; June 1993–February 1994; February 2000–July 2000; February 2003–August 2003); Epiadriamicina + docetaxel (March 2000–) Vinorelbine + 5-FU (October 2003–December 2003)	Gemcitabine + vinorelbine (March 2002–January 2004)	Ciclofosfamid + metotrexate + 5-FU (March 2000–April 2002); Epiadriamicina + docetaxel (April 2002–March 2004) Vinorelbine + 5-FU (April 2004–)	–
Therapy	Pamidronate	Pamidronate	Zoledronate	Zoledronate
Dosage	90 mg/28 die	90 mg/28 die	4 mg/28 die	4 mg/28 die
Start therapy	2002 (November)	2001 (February)	2003 (January)	2002
Replacement therapy	2003 (September)	2002 (April)	–	–
New therapy	Zoledronate	Zoledronate	–	–
Dosage	4 mg/28 die	4 mg/28 die	–	–
Symptomatology	Pain, bleeding, paresthesia lower lip, ear pain	Pain	Pain	Pain, paresthesia lower lip
Beginning of symptomatology	2003 (August)	2002 (December)	2003 (June)	2003 (April)
Localization of bone necrosis	Left mandible	Right mandible	Left maxilla	Left mandible
Dental extraction	–	–	–	Tooth 3.5
Time of dental extraction	–	–	–	2002 (March)

diagnosed with breast cancer, one with multiple myeloma and one with pleura mesothelioma.

None of these patients reported fever. Different haematological values were observed in the patient with multiple myeloma, such as alteration of blood tests with pancytopenia (mean corpuscular volume: 76.1 fl; haemoglobin: 10.2 g/dl; mean corpuscular haemoglobin: 24.6 pg, haematocrit: 31.7%; white blood cells: $2.1 \times 10^3/mm^3$; platelets: $58 \times 10^3/mm^3$) and Bence-Jones proteinuria.

In three of these patients bone metastasis was diagnosed within a period between 4 and $4\frac{1}{2}$ years from the original cancer diagnosis; in the fourth patient bisphosphonate therapy was used to treat and control multiple myeloma. None of these patients reported endocrine disorders, particularly parathyroid diseases, frequently associated with bone disease. Because of the nature of their neoplasia, all these patients were treated with various kind of chemotherapy drugs before starting treatment with bisphosphonates (Table 1).

Bisphosphonate therapy was initially given to the patients affected by breast cancer and pleura mesothelioma following the detection of bone metastasis; while in the patient suffering from multiple myeloma, where no sign of bone disease were apparent from bone scan, the treatment was prescribed as preventive measure.

Two patients started therapy with pamidronate, which was subsequently replaced with zoledronate; the other two patients immediately following diagnosis began therapy with zoledronate. The dosage of pamidronate was 90 mg every 4 weeks (intravenously over a 2- to 4-h period) and the dosage of zoledronate was 4 mg every 4 weeks (infusion over a period of 15 min; Table 1).

None of these patients underwent radiotherapy or corticosteroid treatment. It is necessary to note that all these patients were, at the time of the first oral evaluation, edentulous and wearing total dentures without signs of trauma on their oral mucosa. Only one patient reported tooth extraction in the same site of subsequent bone necrosis, but this extraction had been performed more than 1 year before the necrosis was observed. None of these patients had developed any other extraoral areas of bone necrosis.

Clinical examination

At the first oral examination all patients showed an ulcerative lesion with bone exposure (2–4 cm) (Figs 1–4). They complained of pain, bleeding and paresthesia of the lower lip, which began between 1 and 10 months from the start of bisphosphonate therapy (Table 1).

None of these patients referred traumatic risk factors or habits possibly correlated with the aetiology of oral ulceration.

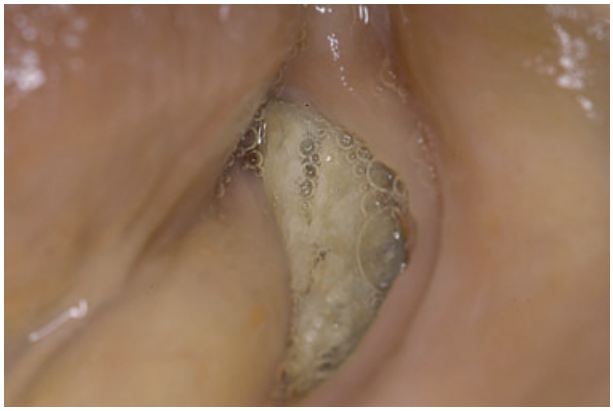

Figure 1 Bone necrosis of the left mandible on a female patient (C.M.) with bone metastasis under treatment with pamidronate and zoledronate.

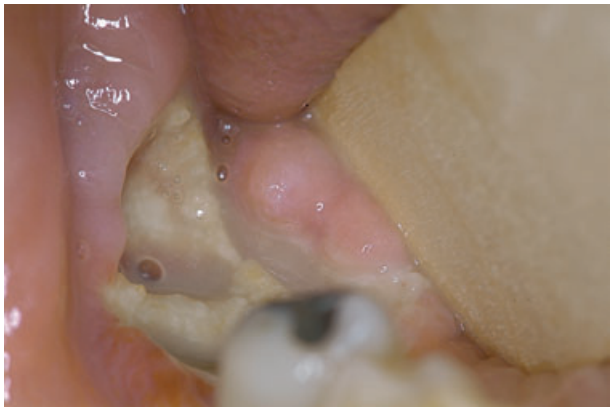

Figure 2 Bone necrosis of the right mandible on a female patient (B.L.) with mesothelioma and bone metastasis under treatment with pamidronate and zoledronate.

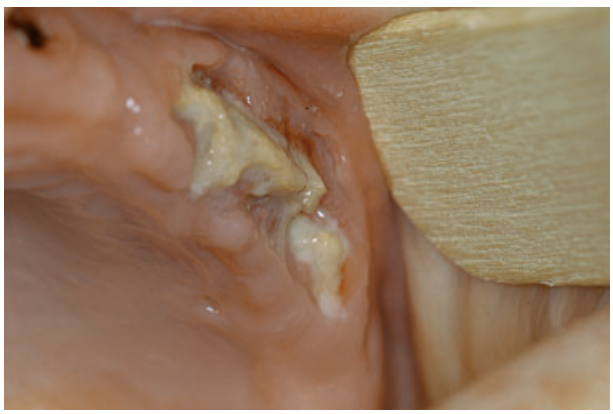

Figure 3 Bone necrosis of the left maxilla on a female patient (R.C.) with liver and bone metastasis under treatment with zoledronate.

Histological and microbiological examination

The histopathological examination revealed a necrotic osteitis associated with the presence of a mixed lymphocyte and granulocyte infiltrate. There was no histopathological evidence of metastatic bone disease within the examined lesions; in particular, in the biopsy taken from the patient affected by multiple myeloma there was no evidence of plasma cells related to the original neoplastic disease.

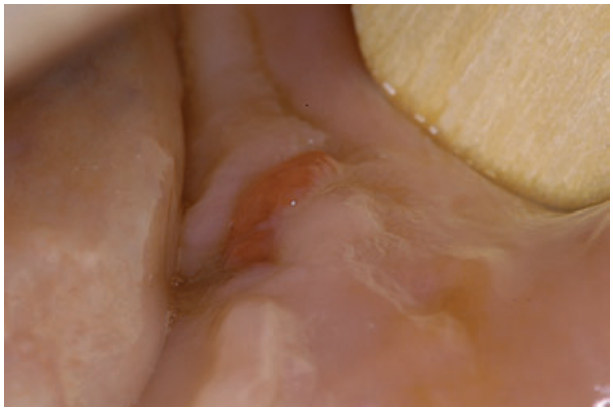

Figure 4 Bone necrosis of the left mandible on a female patient (S.E.) with multiple myeloma under treatment with zoledronate; in the figure, the bone is covered with granulation tissue.

The presence of *Candida albicans* was microbiologically observed in two of the patients affected by the oral osteonecrosis, while in a third one the presence of *Actinomyces* was detected within the bone lesion examined both using microbiological and histopathological assays (Figs 5 and 6).

Treatment

All the evaluated patients underwent surgical treatment followed by curettage of the residual cavity to remove necrotic bone, under local anaesthesia. Medical treatment with antibiotics (ceftazidim 1 g/die i.m. and metronidazole 500 mg/die per os) and antimycotics (fluconazole 100 mg/die per os) was started and continued for 15 days. Mouthwashes with chlorexidine and hydrogen peroxide were also prescribed.

Six months after the surgical treatment, a relapse of disease with new regions of exposed necrotic bone was observed in three of the previously treated patients (only for one patient a reoccurrence was seen 1 month after surgical treatment). One patient did not return for the follow up. Interestingly, the reoccurrence was always seen in mandible bone and never in the maxillary one.

All these patients interrupted bisphosphonate therapy at the time of first oral evaluation with their oncologists' approval. None had resumed bisphosphonates after the surgical treatment.

Discussion

In this report, we described one possible side-effects of bisphosphonate (particularly of pamidronate and zoledronate) which are widely used for their efficacy in the treatment of patients affected by hypercalcaemia of malignancy or bone cancer metastasis.

Bisphosphonates are stable analogues of pyrophosphate characterized by a P-C-P structure and two side chains attached to the carbon atom: the first chain

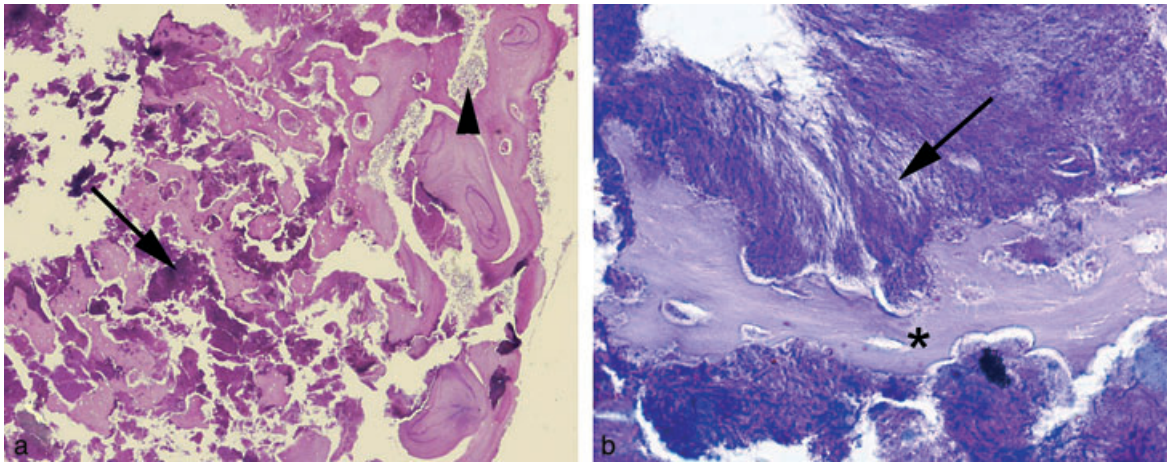

Figure 5 (a) Low power appearance of a sequestrated necrotic bone showing clusters of micro-organisms (arrow) diffusely filling the medullary space as well as a granulocytic infiltrate (arrowhead; haematoxylin and eosin, original magnification ×4). (b) Detail of a fragment of necrotic cancellous bone (asterisk) is surrounded by colonies of *Actinomyces* appearing as filamentous micro-organisms [arrow; periodic acid-Schiff (PAS), original magnification ×20].

controls the ability to bind to crystals in bone, the second chain determines the efficiency of the bisphosphonates (5, 6). Pamidronate and zoledronate are nitrogen-containing bisphosphonates which act by inhibiting the enzymes of the mevalonate pathway (7). Bisphosphonates are absorbed, stored and excreted unchanged from the body; the plasma half-life is short (between 20 min and 2–3 h), while the bone half-life is very long, ranging from several months to years. About 50% of the absorbed drug is located in the bone and the drugs have a high affinity for bone areas where bone resorption and formation is taking place (8). The action of bisphosphonates is related to their effect upon osteoclasts and to the resorption of bone, limiting the tumour growth. The bisphosphonates also cause the apoptosis of tumour cells by the action on mevalonate pathway (5, 9). Moreover, the nitrogen bisphosphonates (pamidronate and zoledronate) have shown the ability to inhibit the adhesion of tumour cells to and over bone matrix *in vitro*. In addition, bisphosphonates also inhibit various metalloproteinases (MMPs) (such as MMP-2, -9, -12) involved in cancer growth and metastasis *in vitro* (10, 11). A decrease of osteoclastic activity reduces bone resorption, and bisphosphonates are therefore used for the treatment of multiple myeloma and controlling hypercalcemia in some malignancies and bone metastasis osteolysis (12–20).

Recently, it has been demonstrated that bisphosphonates inhibit endothelial cell functions and that pamidronate in particular inhibits the bone blood flow, associated with bone resorption and bone loss (21–23).

These bisphosphonates are more efficient than other non-nitrogen-containing bisphosphonates used today and do not generally cause bone necrosis. The non-nitrogen-containing bisphosphonates such as etidronate, residronate and tiludronate, generally used to treat osteoporosis, are potent osteoclast inhibitors and although not as efficacious for malignant osteolytic disease, do not cause jaw bone necrosis (24).

Recently, several authors reported bone necrosis of jaws associated with the use of nitrogen-containing bisphosphonates (25–29). Generally, patients develop these oral lesions after radiotherapy and/or dental extractions. Interestingly, the four patients observed in our Unit, did not present any risk factor for osteitis such as past or contemporary radiotherapy, treatment with corticosteroids or dental surgery.

It is particularly difficult to correlate bisphosphonates use and the presence of oral bone lesions due to the lengthy metabolism of these drugs in the bone tissue. For this reason, their possible necrotic effect on the jaws is usually difficult to treat. All patients evaluated in this report had interrupted the bisphosphonate treatment before undergoing surgical intervention.

Although it is generally reported that dental extractions and/or radiotherapy may increase the risk of bone necrosis, careful evaluation of the oral health of patients is vital before undergoing treatment with bisphosphonates. Patients should be examined in terms of good oral hygiene and plaque control, and appropriate restorative, endodontic, periodontal and surgical treatments should be performed in order to eliminate any possible cause of infections which may reach the bone.

However, even if different authors have recently described jaw bone lesions associated with bisphosphonates therapy but the correct management of these lesions is still uncertain. In patients who developed jaw bone lesions after bisphosphonates use we suggest that surgical treatment of the lesions be performed, associated with systemic antibiotic and antimycotic therapy that should be continued for at least 10 days. Moreover, a strict follow up must be also carried out because of the high risk of bone disease recurrence.

Finally, all the recurrences observed in the patients evaluated in this report were always detected in the mandible bone. This observation could be explained by the different characteristics of this bone tissue, which is

more compact and less vascularized in comparison with the maxillary one.

Because of the increasing number of reports on jaw bone lesions in patients treated with nitrogen-containing bisphosphonates, we recommend research into a more suitable treatment of these lesions, as a standardized management of this disorder has not yet been approved.

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