

ORIGINAL ARTICLE

## Clinical aspects and management of bisphosphonates-associated osteonecrosis of the jaws

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### Abstract

**Objective.** An increasing incidence of osteonecrosis of the jaws (ONJ) in patients treated with intravenous bisphosphonates has been reported in the literature. The aim of this study was to evaluate the clinical aspects, diagnostic investigations, and management of ONJ associated with bisphosphonates in a series of 12 patients. **Method.** Our patients included 1 asymptomatic and 11 symptomatic subjects. For the symptomatic patients, the osteonecrosis was diagnosed through histological investigations of exposed bone that showed avascular and necrotic tissue with inflammatory infiltrate. The patients were complaining of swelling, fever, and bone exposure involving the jaws. The asymptomatic patient presented as an occasional finding during a routine dental examination and the necrosis was confirmed on the basis of imaging investigations. Radiographic, scintigraphic, and microbiological examinations were carried out for all patients. Treatment included antibiotics, minor surgical interventions, and hyperbaric oxygen therapy. **Results.** The radiological investigations revealed osteolytic areas and the scintigraphy demonstrated increased bone metabolism. The microbiological analysis showed pathogenic micro-organisms in the majority of patients. Therapy was useful in obtaining short-term symptomatic relief. **Conclusions.** Histological, radiological, nuclear medicine, and microbiological investigations are important diagnostic tools for patients with bisphosphonates-associated osteonecrosis of the jaws. However, a long-term follow-up is necessary if we are to better understand the treatment outcome.

**Key Words:** *Avascular necrosis, bone metastasis, swelling*

### Introduction

The indication for use of endovenous bisphosphonates (zoledronic acid and pamidronate) in the treatment of metastatic bone lesions and osteoporosis has grown rapidly and these are now regularly administered across medical fields such as oncology, rheumatology, and haematology. The American Society of Clinical Oncology has proposed some guidelines for the use of bisphosphonates. These drugs, in conjunction with antineoplastic chemotherapeutic agents, are considered to be the standard therapy for treatment of hypercalcemia associated with malignancy and for metastatic osteolytic lesions secondary to breast cancer and multiple myeloma [1,2]. Zoledronic acid, in particular, has demonstrated the broadest

clinical activity in patients with a wide variety of tumor types [3]. The efficiency of pamidronate in reducing bone pain, hypercalcemia, and skeletal complications in patients with advanced breast cancer and multiple myeloma has also been reported [4].

Following the documentation of a growing number of cases of bone necrosis of the jaws associated with the use of bisphosphonates, the United States Food and Drug Administration has recently drawn attention to osteonecrosis as a possible complication of their intravenous use.

The aim of this study was to describe the features of osteonecrosis of the jaws and its management in 12 oncologic patients who underwent therapy with zoledronic acid.

## Material and methods

From January through September 2005 eleven patients were referred to the Dental Institute, University of Trieste, to investigate a specific facial swelling occurring in association with bone exposure, pain, and occasional fever. All patients had previously been diagnosed with an extraoral tumor: eight of them had bone metastases (six secondary to breast cancer and two secondary to carcinoma of the lung) and three had multiple myeloma with generalized bone lesions. All patients had been treated with intravenous zoledronic acid (4 mg via a 15-min infusion every 3 weeks) for at least 9 months and were therefore at risk of having developed bisphosphonate-associated osteonecrosis of the jaws (ONJ). A biopsy of the exposed bone was performed for every patient to exclude metastatic bone involvement. The specimens were embedded in formalin 10% and sent to the Department of Pathological Anatomy, Histopathology, and Citodiagnosis of the University of Trieste. The specimens were processed and their sections were stained with hematoxylin-eosin in order to perform a routine histological evaluation. In all cases the histological report revealed the presence of necrotic bone and the diagnosis of bisphosphonates-associated ONJ was therefore confirmed.

The patient's symptoms, the localization of the necrosis, the presence of fistulae or suppuration, and the association with previous extractions or traumas as possible triggering factors for onset of the lesion were recorded.

Radiological investigations including digital orthopantomography (Kodak 8000C Digital Panoramic & Cephalometric System; Eastman Kodak, Rochester, New York), computed tomography scan (Toshiba Aquilion 16; Toshiba Italia, Milan, Italy) and 99mTc-MDP 3-phase bone scan (Infinia-Hawkeye; G.E. Healthcare) were also carried out. Three-dimensional reconstructions of the CT images were performed using the Osirix Medical Imaging Software, MacOs X 10.3. Patients were imaged by magnetic resonance using a 1.5T Super Conductive Magnet (Philips Gyroscan Intera, Best, The Netherlands).

For all patients, swabs and bone cultures were carried out to assess the presence of secondary infection. A sterile agar transport swab suitable for both aerobes and anaerobes micro-organisms (Copan, Italy) was taken from the exposed bone after debridement of superficial layers. A small amount of biopsied bone was placed in sterile containers for bone cultures. The specimens were forwarded for aerobic, anaerobic, and fungal cultures.

Another patient attending our clinic for a routine dental examination had a history of multiple myeloma and was being treated with zoledronic acid. At the time of examination she reported that 8 months

earlier she had had a non-surgical dental extraction without apparent complications. Despite not complaining of oral symptoms or discomfort, she was considered at risk of developing either bisphosphonate-associated osteonecrosis or bone metastasis. The above-mentioned radiological investigations were therefore carried out. The orthopantomography showed a radiolucent lesion corresponding to an empty socket and in the same region the scintigraphy demonstrated an area of increased uptake of the radionuclide. These radiological features were consistent with a diagnosis of osteonecrosis and the patient was included in our series of cases.

None of our patients had a prior history of radiation therapy to the jaw region or neoplastic disease that directly involved the jaws.

All symptomatic patients were treated with broad spectrum antibiotics (amoxicillin and clavulanic acid 1 g twice a day in association with metronidazole 250 mg four times per day) for at least 7 days, repeated as necessary. Patients allergic to penicillin were given clarithromycin 250 mg twice per day. A cycle of 30 sessions of hyperbaric oxygen therapy (HBOT) was carried out for all the symptomatic patients. Minor debridement of the exposed bone necrosis was performed during the acute stage and, when total remission of the symptoms was obtained, the patients were followed and treated conservatively with local wound care and antibiotics irrigations (Rifampicin 250 mg/3 ml). In six patients with evident bone sequestrum, the exposed bone was covered with a mucosal flap.

## Results

The mean age of the patients was 71.42 years (range 57–84 years). Seven out of eight with bone metastases were females and among the four subjects with multiple myeloma the gender was equally distributed.

Table I summarizes the main clinical features of the osteonecrosis in our series of patients.

### *Clinical manifestations*

All symptomatic patients with mandibular involvement were complaining of facial swelling in correspondence with the area of bone exposure. The swelling was accompanied by a constant dull pain exacerbated by palpation. The exposed bone was yellowish in color and the surrounding soft tissues were often inflamed owing to secondary mucosal infection. On probing, the bone was asymptomatic and bleeding was not evident. In three cases the lesion was localized in the maxilla, while eight patients showed mandibular involvement. In one subject, osteolytic lesions were present simultaneously in both maxilla and mandible. In all the symptomatic patients a mobile bone sequestrum was

Table I. Clinical features of osteonecrosis in our series of patients

Patients	Age	Gender	Reason for taking Zometa	Site of necrosis	Fistula	Pain	Bone sequestrum	Fever	Possible associated factor
1	84	F	Bone metastases secondary to breast cancer	Mandible	Yes	Yes	Yes	Yes	Not known
2	69	F	Bone metastases secondary to breast cancer	Maxilla	No	Yes	Yes	Yes	Not known
3	57	M	Multiple myeloma	Maxilla and mandible	No	Yes	Yes	Yes	Not known
4	71	F	Bone metastases secondary to breast cancer	Mandible	No	Yes	Yes	Yes	Perimplantitis
5	71	F	Multiple myeloma	Mandible	No	Yes	Yes	Yes	Dental extraction
6	71	F	Bone metastases secondary to breast cancer	Mandible	No	Yes	Yes	Yes	Dental extraction
7	61	F	Bone metastases secondary to lung cancer	Maxilla	No	Yes	Yes	Yes	Not known
8	76	F	Multiple myeloma	Mandible	No	No	No	No	Dental extraction
9	82	M	Multiple myeloma	Mandible	No	Yes	Yes	Yes	Bone biopsy
10	70	F	Bone metastases secondary to breast cancer	Mandible	No	Yes	Yes	No	Dental extraction
11	78	M	Bone metastases secondary to lung cancer	Maxilla	No	Yes	Yes	No	Pre-prosthesis surgery
12	67	F	Bone metastases secondary to breast cancer	Mandible	No	Yes	Yes	No	Removable prosthodontics trauma

noticed and a single case presented with a cutaneous fistula. In eight subjects the oral symptoms were accompanied by fever (>37.7°C).

A precise dental history revealed the correlation between the bone exposure and dental extraction (n=4), perimplantitis (n=1), bone biopsy (n=1), pre-prosthetic surgery (n=1), and traumatic lesion due to a removable prosthesis (n=1). These potential associated factors occurred from 1 to 8 months prior to the development of clinically evident osteonecrosis. Four subjects were not able to identify any precipitating factor for the onset of the osteonecrosis.

*Histology*

On microscopic examination, all the specimens consisted predominantly of sheets of necrotic bone, showing loss of osteocytes from their lacunae and peripheral resorption (Figure 1). Bacterial colonization composed of *Actinomyces*-like microorganisms was present in all slides apart from one (Figure 2).

In all specimens the periphery of the sequestra and the haversian canals contained necrotic debris and an acute inflammatory infiltrate consisting of polymorphonuclear leukocytes, sometimes with abscess formation. In eight cases, the formation of granulation tissue was evident.

*Radiology*

In all symptomatic patients the orthopantomography showed osteolytic areas in correspondence with the regions of clinical involvement. The radiolucent images were patchy, with occasional radiopaque

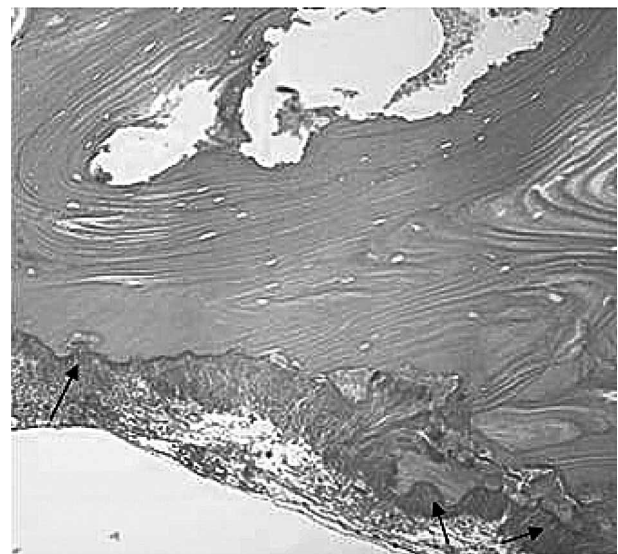


Figure 1. Histological aspect of the necrotic bone showing loss of osteocytes from their lacunae and peripheral resorption. A bacterial infiltrate is also evident on periphery of the bone (black arrows) (hematoxylin-eosin, ×10)



Figure 2. Higher magnification of Figure 1. The necrotic bone is surrounded by a bacterial infiltrate with the appearance of *Actinomyces*-like micro-organisms (hematoxylin-eosin,  $\times 50$ ).

sequestra of necrotic bone and little evidence of healing. It was difficult to sharply identify the border between the necrotic and normal bone. The radiographic imaging of the asymptomatic patient showed a radiolucent lesion corresponding to an empty socket.

CT displayed abnormalities in all symptomatic patients in correlation with the orthopantomographic features. The images showed irregularity of the cortical margins (Figure 3).

In all cases, the MRI showed involvement of the cancellous bone, which produced low signal intensity on T1-weighted images and a mild hyperintensity on T2-weighted and T-STIR images. A mild and irregular enhancement of the lytic areas was noticed after injection of contrast agent. Where present, the bone sequestrum showed a well-defined dark area. In patients with evident swelling, an area of oedema of soft tissues was clearly visible on T-STIR images as high signal intensity.

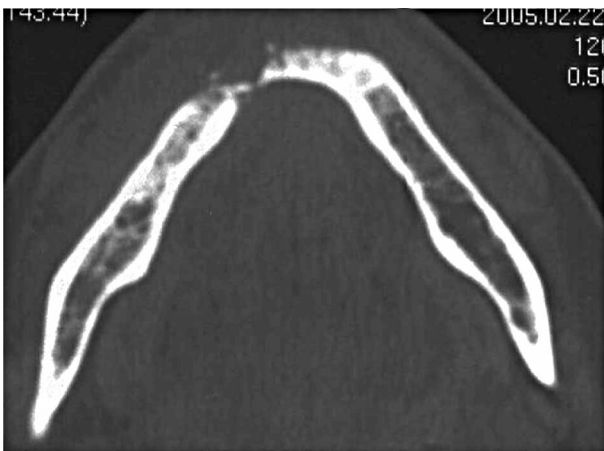


Figure 3. Computed tomography shows the destruction of the cortical bone.

### Nuclear medicine

In all patients the scintigraphy showed focal abnormal activity in comparison with the adjacent jaw regions. In three cases a central spot of decreased uptake was observed within the area of uptake of the radionuclide. The  $^{99m}\text{Tc}$ -MDP 3-phase bone scan raised suspicions of an area of increased activity in the mandible of the asymptomatic patient, and the presence of increased uptake was confirmed through single photon emission computed tomography (SPECT).

All the radiological and scintigraphic images showed a proper correlation with the clinical features in terms of position and severity of the lesion.

### Microbiology

The swab of one patient showed the presence of normal oral flora without evidence of pathogenic micro-organisms. For all the other subjects the swabs revealed the presence of different species of bacteria: *Bacteroides fragilis*, *Enterobacteriaceae* (including *Klebsiellae*), *Beta-haemolytic Streptococcus Group F* and *Haemophilus influenzae*.

Bone cultures showed numerous colonies of *Streptococcus viridans* in seven patients.

### Management

For all the patients the antibiotic therapy, even without the contribution of the hyperbaric oxygen therapy, was useful in obtaining complete remission of the symptoms. However, relapses occurred regularly after 7–15 days starting from withdrawal of the treatment.

The hyperbaric oxygen therapy was efficient in obtaining symptomatic relief but did not improve the clinical aspect of the lesions.

Where attempts were made to cover the exposed bone with a mucosal flap, a good wound healing was obtained in all patients at 1 month from the surgical procedure. At 3 months, however, 3 patients developed a fistula around the flap and a complete dehiscence was noticed in 1 patient.

### Discussion

Osteonecrosis of the jaws (ONJ) can arise as a consequence of radiation therapy [5], chronic osteomyelitis [6], metastases, and, less commonly, Herpes Zoster [7].

In 2003, Marx and Stern described for the first time avascular necrosis of the bone associated with the use of pamidronate in patients with multiple myeloma [8]. Several other cases of ONJ that appeared following therapy with bisphosphonates were then reported [9–23]. In the majority of patients ONJ was associated with intravenous use of pamidronate or zoledronic acid but few cases

described necrosis secondary to the use of oral bisphosphonates [13,22].

Tarassoff & Csermak noted that despite nearly 2.5 million patients treated worldwide with bisphosphonates, the incidence of ONJ remains low [3]. Recently, Bamias demonstrated that among 252 patients who received bisphosphonates, 6.7% developed ONJ [10]. Considering that in Trieste during 2004 hundreds of patients underwent therapy with zoledronic acid for metastases secondary to breast, lung and prostate cancer and our series of patients probably represents all symptomatic cases of ONJ in our region, it can be assumed that this condition presents with a low prevalence. However, our clinical evidence indicates that the incidence of cases of osteonecrosis in patients on therapy with zoledronic acid is rapidly growing. The incidence of ONJ in our patient population who are not receiving bisphosphonates remains exceedingly low. We follow a strict protocol for the prevention of osteonecrosis secondary to radiation therapy and during the past year we have seen a single case of osteoradionecrosis.

The increased indications for use of bisphosphonates and the emergent awareness of the associated complications could lead to a growing number of reported cases of ONJ.

The diagnosis of ONJ is generally established in a late stage of the disease, since patients usually present to the attention of the clinician when the osteonecrosis is already symptomatic. It is essential to recognize subclinical signs of this condition early, as a timely diagnosis can make a significant difference to the outcome of the disease.

It is recommended to take an orthopantomography (OPG) as a first routine radiological investigation. However, a more detailed definition of the bone structure is obtained with computed tomography, which allows a three-dimensional reconstruction of the osteolysis.

The scintigraphy is a very sensitive tool for early recognition of altered bone metabolism. It can therefore be assumed that abnormal uptake of the radionuclide in patients who receive bisphosphonates should always be considered as an indicator of probable ONJ. Bone scan was actually useful in detecting early lesions in the only patient of our series who did not show clinically evident bone involvement. Despite the bone scan being very sensitive, it lacks specificity and it should always be accompanied by accurate radiological and, where possible, histological investigations in order to confirm the diagnosis.

The pathogenesis of ONJ is still not clear and few hypotheses have been proposed on the basis of the clinical evidence and history of this condition. It could be postulated that both reduction in blood supply and the presence of bacteria play a significant

role in the development of the necrosis [16,22]. The histological evaluation in our patients confirmed the avascular nature of the osteonecrosis.

The most important clinical effect of bisphosphonates is the inhibition of bone resorption. The recruitment and the life span of osteoclast are reduced [25], their activity is decreased, and there appears to be modulation of the osteoclast-osteoblast interrelation [26]. Ruggiero proposes that the mechanism by which bisphosphonates could compromise bone vascularity may be related to its effect on the osteoclasts as the inhibition of osteoclast function results in microdamage: dead and dying osteocytes are not replaced and the capillary system in the bone is not maintained, resulting in avascular osteonecrosis [22].

The reduction of blood supply in the necrotic areas could also be correlated with the well-established anti-angiogenic properties of bisphosphonates. In a recent study, bisphosphonates were shown to inhibit endothelial cell function *in vitro* and *in vivo* [27]. In the same study there was a marked decrease in the number of blood vessels in pagetic bone marrow after bisphosphonates treatment compared with pretreatment biopsy results. Santini et al. proposed that the anti-angiogenic properties of bisphosphonates in breast cancer patients with bone metastases could be due to the ability of this drug to significantly decrease circulating levels of vascular endothelial growth factor, a potent angiogenic factor [28].

A possible role of bacteria in the pathogenesis of ONJ still needs to be clarified. In our series of patients, only 1 out of 11 symptomatic subjects had both the swab and the microscopic examination negative for the presence of pathogenic microorganisms. Our findings are in accordance with those of Hellstein [29], who noted that in acutely affected areas, bacteria colonies accompanied by inflammatory cells are often the dominant feature in any given microscopic field. In the series of patients described by Wang, none showed histological evidence of active infection, although laboratory examination demonstrated superficial contamination by oral organisms [23]. In Ruggiero series, on microscopic examination necrotic bone had associated bacterial debris and granulation tissue but cultures revealed normal oral flora [22]. Melo & Lugassy independently described a few cases where the presence of filamentous bacteria in the histological report, consistent with *actinomyces*, was evident [15,21].

We support the hypothesis for which a bacterial component is significant, but it is not well understood whether it actually plays a role in the pathogenesis of this condition or merely represents secondary infections [29].

Although there is evidence suggesting that osteonecrosis can develop independently of minor oral

surgery, in the majority of our cases ONJ was triggered by such procedures. To the best of our knowledge there is no case in the literature that describes osteonecrosis secondary to bisphosphonates in areas different from the jaws.

Osteonecrosis is difficult to treat and the main target should be prevention [30]. It is important to inform the patients about any potential risks correlated with the administration of bisphosphonates, especially when they are given endovenously. An accurate dental examination should precede commencement of bisphosphonates treatment so that any potential risks for dental infections can be recognized and removed.

Dental extractions or other oral surgical procedures should be avoided in patients who are already on treatment with e.v. bisphosphonates. If this is not possible, a preoperative cycle of hyperbaric oxygen therapy and antibiotic cover is always attempted in our clinic. The choice of trying the HBOT as a prophylactic measure is not based on clinical evidence because, at present, there are no guidelines that provide indications on the treatment of such patients. However, since osteonecrosis is typically avascular, it could be assumed that an increase in oxygen concentration together with the growth of new blood vessels could be of benefit for our patients. Follow-up data are necessary to assess the HBOT outcome in the prevention of osteonecrosis in subjects treated with e.v. bisphosphonates.

Once osteonecrosis occurs, surgical debridements are not completely successful in eradicating the necrotic bone. It is difficult to identify viable bleeding bone margins and it cannot be excluded that even apparently healthy bone could be at risk of becoming necrotic following invasive surgery. In accordance with Carter et al., our experience demonstrated that covering exposed bone with tissue flaps has been found ineffective because of the development of fistulae around the flaps and possible complete dehiscence [11].

Hyperbaric oxygen and antibiotics therapy do not limit the progress of the disease, although symptomatic relief can be experienced.

Communication between the oncologist and the dental professional is of essential value in preventing and detecting bisphosphonates-associated osteonecrosis at an early stage.

In conclusion, the pathogenesis of bisphosphonates-associated ONJ is still unknown. Histological, radiological, nuclear medicine, and microbiological investigations are essential diagnostic tools in the management of such patients and can offer interesting information about the origin of this new condition. More scientific data are needed to support the choice of any specific treatment protocol for the management of this new condition.

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