

# Oral osteonecrosis induced by drugs in a multiple myeloma patient

Claudio Maranhão Pereira,<sup>1</sup> Maria Elvira Pizzigatti Corrêa,<sup>2</sup> Patrícia Freire Gasparetto<sup>2</sup>

## Abstract

Bisphosphonates are effective in the prevention and treatment of bone disease in multiple myeloma (MM) and other bone destructive malignancies. Avascular bone necrosis of the jaw is increasingly recognized as a serious complication of long-term bisphosphonate therapy. The anti-angiogenic effect of the bisphosphonate and its capacity of causing avascular bone necrosis were well recognized. However, the associated avascular bone necrosis with the systemic disease or the other drugs that patients were receiving were not reported. A case of spontaneous mandible avascular necrosis in a multiple myeloma patient is reported herein. For three months, the patient was observed periodically for regional debridement and control of the infectious component with partial improvement. Spontaneous avascular necrosis of the jaws in site without osteolytic lesions is not common.

**Key-words:** Osteonecrosis; Multiple Myeloma; Abnormalities, Drug-Induced

## Introduction

Cancer patients who have undergone chemotherapy and bisphosphonate therapy can present with avascular bone necrosis. Most cases are associated with treatment of cancers involving bone, such as multiple myeloma or metastatic cancers.<sup>1,2,3</sup> The treatment of these tumors may

also comprise of many drugs of osteoclast inhibiting function, with an anti-angiogenic potential, which is important for their anti-tumoral effects<sup>4</sup>. On the other hand, inhibition of angiogenesis can predispose to the development of avascular necrosis. These drugs have been recently included in cancer treatment protocols and the number of reported cases of oral avascular necrosis is increasing. The aim is to report a case of oral avascular bone necrosis in multiple myeloma patient undergoing chemotherapy.

## Case Report

An 84-year-old woman was referred to the Dentistry Section of the Hematology Center, UNICAMP, in October 2003, with the complaint of a painful and spontaneous bone exposure on the right side of the mandible lasting one month. The patient had been diagnosed of multiple myeloma seven years earlier, and had been receiving

<sup>1</sup> Oral Pathology, School of Dentistry of Paulista University, GO-DF, Brazil and Department of Pathology, Estácio de Sá University, Goiás, Brazil

<sup>2</sup> Hematology Center, UNICAMP, São Paulo, Brazil

## Corresponding Author:

Claudio Maranhão Pereira. Faculdade de Odontologia da Universidade Paulista, campus Brasília. Coordenação de Odontologia, SGAS Quadra 913, s/nº - Conjunto B - Asa Sul Brasília-DF/BRAZIL, CEP 70390-130. + 55 (61) 2192-7080 e-mail: claudiomaranhao@hotmail.com; odontologiabrasilia@unip.br



**Figure 1:** Clinical examination revealed an extensive exposure of necrotic bone on the right mandible, extending from first bicuspid area to the second molar.



**Figure 2:** Radiographs exams showed no bone involvement, only a small osteolytic area on the second molar due to periodontal disease.

therapy with pamidronate (Aredia® - intravenously, once a month), thalidomide (also a potent anti-angiogenic drug) (200 mg once a day), and dexamethasone (Decadron® - 15 mg 3 X day for 4 days in the month). The patient complained of difficulty in eating and speaking. In the last month, she received metronidazole (400 mg 3X day for two weeks), ciprofloxacin (500 mg 2 X day for ten days), rifamycin (intramuscularly – 300 mg) with poor improvement of pain and infection.

Oral clinical examination revealed an extensive exposure of necrotic bone measuring 3.0 X 3.5 cm on the right lower alveolar ridge, extending from first bicuspid area to the second molar (Figure 1). The exposed necrotic bone was infected, and the area was slightly painful. The second molar associated with exposed bone showed medial inclination with moderate periodontal disease. Radiographs of the mandible showed no bone involvement, only a small radiolucid area on the second molar due to periodontal disease (Figure 2).

For medical indications, all systemic therapy (pamidronate, thalidomide and dexamethasone) was suspended. Prophylaxis of local and systemic infections was performed with oral administration of metronidazol (500 mg) and amoxilin (1 g) one hour before surgical treatment. The exposed bone was curetted with aim of removal of the necrotic bone. In the course of the procedure, we were decided to extract the second molar due to alveolar bone involvement.

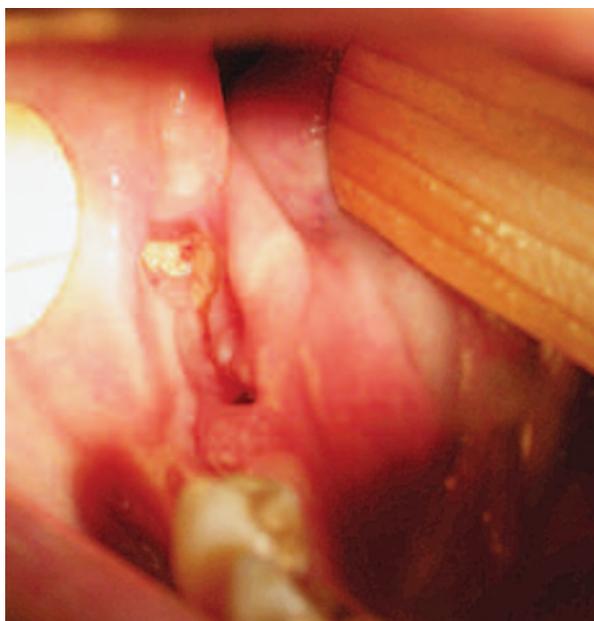
Therapeutic doses of metronidazol (250 mg) and amoxilin (500 mg) were administered to the patient three times a day for seven days after the procedure. Two weeks

thereafter, a moderate improvement in the oral clinical status was observed (Figure 3), and the patient had no complaints of pain. Radiographic exams showed an extensive osteolytic area (Figure 4). After three months, the patient was seen for a recall visit and the lesion remained unchanged. The patient died 3 weeks later due to generalised systemic complications.

## Discussion

Multiple myeloma is a malignant disease caused by the proliferation of abnormal plasma cells. The neoplasm usually arises in hematopoietic bone marrow, and multiple osteolytic lesions are characteristic radiographic findings. Although any bone may be affected, the jaws have been reported to be involved in as many as 30% of cases. Spontaneous avascular necrosis of the jaws in site without radiographic osteolytic lesions is not common.<sup>1, 3, 4</sup>

Recently, several cases have been reported about bone necrosis induced by drugs. The bisphosphonates, especially the pamidronate, plays a role as etiological agent in the process of drug induced avascular bone necrosis. It may cause oral avascular necrosis due to anti-angiogenic effect leading to inhibition of osteoclasts. The decrease in bone cellularity and blood flow resulting from bisphosphonate therapy could lead to a generalized impairment of bone remodeling and of the response to skeletal injury. Although prolonged use of oral bisphosphonates has not increased skeletal fragility or impaired fracture healing in osteoporotic patients, a loss of forearm bone density has been described after intravenous pamidronate treatment in patients with Paget disease.<sup>7</sup> Aseptic necrosis of bone at typical sites such



**Figure 3: The improvement in the oral clinical status was observed after two weeks.**



**Figure 4: After the bone curettage and tooth extraction, radiographic exams showed an extensive osteolytic area.**

as the head of the femur or humerus has not been reported as a complication of bisphosphonate therapy. Indeed, bisphosphonates have been used to treat this condition, although no clear benefit has been established.<sup>2</sup>

The profound effects of the bisphosphonates on calcium metabolism were discovered over 30 years ago, and they are now well established as the major drugs used for the treatment of bone diseases associated with excessive resorption. Bisphosphonates are structural analogues of inorganic pyrophosphate but are resistant to enzymatic and

chemical breakdown. Bisphosphonates inhibit bone resorption by selective adsorption to mineral surfaces and subsequent internalization by bone-resorbing osteoclasts where they interfere with various biochemical processes.<sup>7,8</sup> The simpler, non-nitrogen-containing bisphosphonates can be metabolically incorporated into nonhydrolysable analogues of adenosine triphosphate (ATP) that may inhibit ATP-dependent intracellular enzymes. In contrast, the more potent, nitrogen-containing bisphosphonates (eg, pamidronate, alendronate, risedronate, ibandronate, and zoledronate) inhibit a key enzyme, farnesyl pyrophosphate synthase, in the mevalonate pathway, thereby preventing the biosynthesis of isoprenoid compounds that are essential for the post-translational modification of small guanosine triphosphate (GTP)-binding proteins (which are also GTPases) such as Rab, Rho, and Rac. The inhibition of protein prenylation and the disruption of the function of these key regulatory proteins explains the loss of osteoclast activity.<sup>7, 8, 9</sup>

Several reports demonstrated the anti-angiogenic effect of the bisphosphonate<sup>2,4</sup> and its capacity of causing avascular bone necrosis.<sup>1,2</sup> However, none of them associated the avascular bone necrosis with the systemic disease or the other drugs that patients were receiving. It is clear that various drugs may induce avascular bone necrosis, direct or indirectly, and some of them are commonly used in association with bisphosphonate for cancer therapy.<sup>5, 6</sup> Migliorati<sup>2</sup> (2003) and Marx<sup>1</sup> (2003) reported 4 and 36 cases of painful bone exposure in the jaws of patients with pamidronate therapy. All cases were diagnosed as avascular bone necrosis induced by pamidronate. In the series reported by Marx<sup>1</sup> (2003), some patients also received dexamethasone, but this fact was not considered.

Avascular bone necrosis is a potentially disabling complication of cancer treatment. Although its etiopathogenesis is not fully established, steroids, as dexamethasone or prednisone, are considered one main cause.<sup>5</sup> This effect is dose dependant and should be mentioned; furthermore the most common site for this avascular necrosis is in the femur head. Thalidomide, like pamidronate, also has an anti-angiogenic effect on bone.<sup>6</sup> Thalidomide inhibits vascular endothelial growth factor and basic fibroblast growth factor but the exact mechanism is not straightforward.<sup>6</sup>

In most patients with oral avascular necrosis, the lesions initially occurred after dental extraction. In other instances, accidental trauma by the patient to the involved area was identified. Some patients, however, could not recall a

possible causative event. The involved areas were often secondarily infected. Some patients already had been treated with local surgical procedures and antibiotic therapy, following the same protocol used in the treatment of osteomyelitis. At the time of onset of avascular bone necrosis, all patients with cancer were receiving chemotherapy for the treatment of a primary malignancy.<sup>1,2,3</sup>

Although bisphosphonates have been associated with avascular bone necrosis, their role in its pathophysiology remains to be defined.<sup>7,8</sup> Interference of normal bone homeo-stasis by bisphosphonates may result in the accumulation of microdamage, there-by affecting the mechanical integrity of the bone. The anti-angiogenic effects of bisphosphonates might also be contributory. However, the predilection of avascular bone necrosis for the maxilla and the mandible cannot be due solely to the vascularity of the bone because the maxilla, unlike the mandible, has an abundant vascular supply and is often involved. Instead, the lack of repair of physiologic microdamage, high masticatory forces, the demand placed on bone remodeling because of infection and following extractions, and exposure of tooth socket to a contaminated environment may all contribute to the development of avascular bone necrosis. Current recommendations to avoid avascular bone necrosis therefore focuses on the avoidance of invasive dental procedures and careful maintenance of dental and periodontal health in patients on bisphosphonates.<sup>7,8,9</sup>

Our patient had blood cell count alterations due to multiple myeloma disease. Furthermore, she was taking three drugs simultaneously (pamidronate, dexamethasone, thalidomide) that may cause avascular bone necrosis.<sup>1-6</sup> Systemic disease, such as stem cell cancer, may cause blood cell alterations that can support bone infections. Chemotherapy drugs, such as steroids and thalidomide, may also contribute to the avascular bone necrosis.<sup>1,4-6</sup> We believe that bisphosphonates may cause oral avascular bone necrosis and also that medical oncologists must be aware of avascular bone necrosis when treating cancer patients with these drugs. On the other hand, our present case report suggests that other factors must be analyzed and considered.

## References

1. Marx RE. Pamidronate (Aredia) and Zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 61: 1115-1118, 2003.
2. Migliorati CA, Schubert MM, Peterson DE, Seneda LM. Bisphosphonate-associated osteonecrosis of mandibular and maxillary bone. An emerging oral complication of supportive cancer therapy. *Cancer* 104:83-93, 2005.
3. Ruggiero SL, Mehrotra B, Rosenberg TJ, et al. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 62: 527-534, 2004
4. Raje N, Woo SB, Hande K, Yap JT, Richardson PG, Vallet S, et al. Clinical, radiographic, and biochemical characterization of multiple myeloma patients with osteonecrosis of the jaw. *Clin Cancer Res*. 15;14(8):2387-95, 2008.
5. Arico M, Boccalatte MFP, Silvestri D, et al. Osteonecrosis: an emerging complication of intensive chemotherapy for childhood acute lymphoblastic leukemia. *J Hematol* 88: 747-753, 2003.
6. Rayman S, Almas K, Dincer E. Bisphosphonate-related jaw necrosis: a team approach management and prevention. *Int J Dent Hyg*. 7(2):90-5, 2009.
7. Gutteridge DH, Retallack RW, Ward LC, et al. Bone density changes in Paget's disease 2 years after iv pamidronate: profound, sustained increases in pagetic bone with severity-related loss in forearm nonpagetic cortical bone. *Bone*; 32: 56-61, 2003.
8. Scoletta M, Arduino PG, Dalmaso P, Broccoletti R, Mozzati M. Treatment outcomes in patients with bisphosphonate-related osteonecrosis of the jaws: a prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 110(1):46-53, 2010.
9. Thumbigere-Math V, Sabino MC, Gopalakrishnan R, Huckabay S, Dudek AZ, Basu S, et al. Bisphosphonate-related osteonecrosis of the jaw: clinical features, risk factors, management, and treatment outcomes of 26 patients. *J Oral Maxillofac Surg*. 67(9):1904- 8, 2009.