

Short Communication

Osteonecrosis of the Jaw Associated with Bisphosphonates. A Histopathological Study of 24 Cases

María Luisa Paparella^{1*}, Daniel Brandizzi², Eduardo Santini-Araujo³, Rómulo Luis Cabrini⁴

¹María Luisa Paparella, Laboratory of Orthopedic Pathology, Buenos Aires, Argentina

²Daniel Brandizzi, Department Radiobiology, Radiation Pathology Division, National Atomic Energy Commission, Argentina

³Eduardo Santini-Araujo, Laboratory of Orthopedic Pathology, Buenos Aires, Argentina

⁴Rómulo Luis Cabrini, Department Radiobiology, Radiation Pathology Division, National Atomic Energy Commission, Argentina

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***Corresponding author**

María Luisa Paparella, Laboratory of Orthopedic Pathology, Buenos Aires, Argentina, Paraguay 2302, 11º, 1., Buenos Aires, Argentina, Fax: 5411 49661224; Email: mluisapaparella@yahoo.com.ar

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Abstract

The aim of this work is to report the histopathological features of jaw bone in 24 cases of bisphosphonate-related osteonecrosis of the jaw. In all cases, lamellar bone trabeculae were thicker (bone sclerosis), had no osteocytes in the lacunae (bone necrosis), and exhibited a Paget-like structure with marked signs of bone remodeling and formation of multiple trabecular compartments that were not connected to the trabecular surface. The Paget-like trabecular structure would result in a loss of trabecular vitality and in the onset of an inflammatory process due to microbial invasion. Bisphosphonate-related osteonecrosis of the jaw would initially be an aseptic process and osteomyelitis would develop after microbial infection. The results obtained from this series of cases would seem to confirm that bisphosphonates cause Paget-like bone regeneration, which would explain the likely aetiopathogenic mechanism and the association between bisphosphonate administration and the development of necrosis with secondary infection.

INTRODUCTION

We recently found and reported a peculiar microscopic finding in 8 cases of bisphosphonate-related osteonecrosis of the jaw, based on which we suggested a possible aetiopathogenic mechanism of this complex condition. The microscopic finding was the formation of a Paget-like trabecular structure with multiple compartments [1]. It seemed important to analyze a larger number of cases in order to define this morphological feature and its regularity. Therefore, the aim of this study was to present the histopathological features of 24 cases now available in our files at the Laboratory of Orthopedic Pathology.

MATERIALS AND METHODS

The histopathological features of 24 cases of bisphosphonate-related osteonecrosis of the jaw were studied in bone specimens demineralized in nitric acid and embedded in paraffin. The histological sections were stained with hematoxylin-eosin and Harris hematoxylin. All the patients had received bisphosphonates for at least 2 years, none had had radiation therapy, 12 had a history of cancer (bone metastasis of adenocarcinoma), and 12

had osteoporosis. The oncology patients (8 men and 4 women; age range: 49 to 85 years) had received or were receiving intravenous zoledronic acid. The osteoporotic patients (women; age range: 54 to 83 years) were receiving oral alendronic acid or ibandronic acid. Eighty percent of cases were located in the mandible. Twenty patients (83%) had exposed bone. Four patients (17%) – with bone metastasis – had no exposed bone but radiographic images exhibited alterations in bone density; puncture biopsy was therefore indicated in order to rule out jaw metastasis.

RESULTS

The 24 analyzed cases, including those with no exposed bone, exhibited similar histopathological features to those previously described by our research group. The mature lamellar bone trabeculae were thicker than normal (bone sclerosis), had no osteocytes in the lacunae (bone necrosis), showed marked signs of remodeling and formation of multiple trabecular compartments, giving rise to a mosaic, Paget-like trabecular structure. Many of the compartments showed no connection with medullary spaces, as evidenced by the histological sections. The medullary spaces

were smaller and occupied by mixed inflammatory infiltrate, cell detritus, and microbial colonies (Figure 1).

In addition to exhibiting the Paget-like trabecular structure, one of the cases with no clinical lesion but with radiographic images showing alterations in bone density, exhibited isolated osteocytes inside lacunae (an indication of bone tissue vitality) and medullary spaces with fibrous tissue containing chronic inflammatory cells (Figure 2).

None of the cases displayed osteoclast-like giant multinucleated cells.

Bone metabolism (F-Ca) serum levels were normal in all cases.

DISCUSSION

In the last decade, osteonecrosis of the jaw has emerged as a complication of bisphosphonate treatment. Most cases are associated with intravenous administration of high-potency bisphosphonates to cancer patients [2-4]. Nevertheless, there are also reports of patients receiving this drug for osteoporosis treatment [4]. The clinical criterion for diagnosis of this condition is the presence of exposed, necrotic bone in the maxillofacial region that has persisted for more than eight weeks, and no history of radiation therapy to the head and neck region [2]. More recently, non-exposed variants have been described. These

variants have been thought to be early stages of bisphosphonate associated osteonecrosis of the jaw; they manifest as fistulae, gingival enlargement, and alterations in bone density [5]. There are few works in the literature describing the histopathological aspects of the disease [3,6,7]. A recent study by our research group reported previously unknown microscopic findings in jaw bone specimens from cases of patients with bisphosphonate-related osteonecrosis of the jaw [1].

The present study extends the histopathological analysis to 24 cases. All specimens showed similar features, with a Paget-like trabecular structure and formation of multiple compartments, which differentiates them from conventional osteomyelitis. It is noteworthy that patients with Paget's disease frequently develop osteomyelitis in the jaw.

On the other hand, necrosis do not occur in other skeletal localizations of bisphosphonates treated patients. As in the case of the bone diseases, the jaw localization induce a different behaviors. This could be due to the sum of multiple factors, such as exposure to specific stimuli, given the presence of teeth, the masticatory function, and the oral microflora, added to the action of the bisphosphonate.

CONCLUSION

In view of the histopathological findings described above, we suggest that the formation of sectors or compartments inside the bone trabeculae, with no contact with the bone marrow (source of nutrition), which would result in loss of vitality and the onset of inflammation due to microbial infection, is a possible aetiopathogenic mechanism involved in bisphosphonate-related osteonecrosis of the jaw.

The study of this series confirm that bisphosphonates produce a Paget-like bone regeneration, which would explain the aetiopathogenic mechanism and the direct relationship between bisphosphonate administration and development of necrosis with secondary infection. The histopathological finding of a vital trabecular structure (as shown by the presence of osteocytes inside lacunae) in the case with no exposed bone confirms this mechanism. The latter case could be considered an early stage of the process, prior to necrosis and bone exposure.

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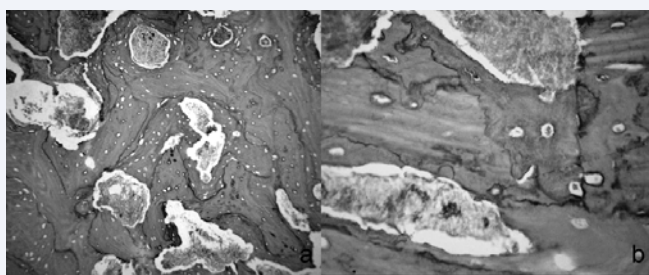


Figure 1 Sclerotic and necrotic lamellar bone trabeculae with signs of remodeling and a Paget-like appearance. The decreased medullary spaces are occupied by cell detritus and microbial colonies. a- H-E Orig. Mag. x10 and b- H-E Orig. Mag. x40.



Figure 2 Patient receiving bisphosphonates for bone metastasis of adenocarcinoma of the breast, with no bone exposure or mucosal fenestration. Panoramic X-ray; note the alteration in bone density at the level of the 2nd lower left molar. Microscopic image, H-E Orig. Mag. x40; note the Paget-like trabecular structure with osteocytes inside lacunae.

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