

Malignancy mimicking bisphosphonate-associated osteonecrosis of the jaw: a case series and literature review

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Objective. Bisphosphonate-related osteonecrosis of the jaw (BONJ) is a common complication of bisphosphonate treatment that has been well documented over the past decade. Nevertheless, its pathogenesis is poorly understood, and treatment guidelines are based mostly on expert recommendations. Clinicians must be aware of malignancy mimicking BONJ, of which a few cases have been documented in the literature.

Study Design. Three patients undergoing long-term treatment with intravenous bisphosphonates for malignant disease demonstrated the distinct diagnostic signs of BONJ. Surgical treatment was performed by resecting the affected bone. In all cases, histologic specimens were taken for analysis.

Results. Histologic analysis of the bone specimen with surrounding soft tissue revealed necrotic bone with signs of inflammation, but also with cells of the underlying malignant disease.

Conclusions. Clinical and radiographic diagnosis of BONJ should be confirmed by histologic analysis in patients with underlying malignant disease. (Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:32-36)

Bisphosphonates play a vital role in the management of malignant and nonmalignant diseases with high bone resorption, such as multiple myeloma, osteoporosis, Paget disease, or bone metastases.¹⁻³ Bisphosphonate-associated osteonecrosis of the jaw (BONJ) was first described in 2003 by Robert Marx.⁴ The term “bisphossy jaw of the 21st century” has been suggested by Hellstein and Marek in accordance with findings in 19th century match factory workers.⁵

BONJ has been well documented in the past decade; nevertheless, its pathogenesis remains poorly understood.⁶⁻⁹ The bisphosphonates are nonmetabolized analogs of endogenous pyrophosphates binding to exposed bone mineral around activated osteoclasts. Due to their ability to withstand metabolism, bisphosphonates are maintained within resorbed bone for a long period, inhibiting osteoclast activity or even affecting apoptosis, thereby limiting further bone resorption. It is hypothesized that bisphosphonates are released by invasive dental treatment, such as tooth extractions or implant placement, with possible subsequent direct toxicity to the surrounding soft tissue or periosteum, but there is also strong evidence supporting the hypothesis that BONJ is a special type of osteomyelitis.¹⁰⁻¹³

The clinical findings in most patients involve dehiscence of the oral mucosa with exposed necrotic bone. Furthermore, patients may have pain and oral discomfort; or, less commonly, hypesthesia of the inferior alveolar

nerve or acute soft tissue abscess are observed. All patients present with a local symptom,¹⁴ usually a periodontal or periapical infection, but invasive dental treatment or a pressure ulcer may cause osteopathology with subsequent infectious invasion into the metabolically altered bone and possible sequestration. The exposed bone usually becomes rough and hard.^{6,7} Common radiographic findings are changes in the trabecular pattern with sclerosis, cortical erosion, periosteal reaction, thickening of the lamina dura, and narrowing of the inferior alveolar canal.⁷

Although numerous clinical and radiographic patterns of BONJ have been described, they are not pathognomonic. Malignant lesions may clinically and radiographically mimic BONJ and must be excluded by histologic examination.¹⁵⁻¹⁸ The present article presents 3 cases initially treated for BONJ at our Department of Cranio-Maxillofacial Surgery with an additional, detailed literature review.

MATERIALS AND METHODS

Cases

Patients with BONJ with a histologic malignancy, independent of the type or galenic application of

Statement of Clinical Relevance

Bisphosphonate-related osteonecrosis of the jaw (BONJ) seems to be an apparent clinical and radiologic diagnosis. However, specialists have to be aware of the differential diagnosis, which includes malignancy. This article shows the importance of accurate diagnosis of BONJ.

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bisphosphonates and irrespective of age, gender, or underlying disease, were included in this retrospective analysis. Between December 2004 and July 2012 a total of 121 patients were surgically treated due to BONJ. Of those, 3 patients presented with histologically confirmed malignancy.

Most patients were referred to the Department of Oral and Maxillofacial Surgery, University Hospital of Zürich, Switzerland, with typical clinical and radiographic findings of BONJ. Histologic analysis was performed in each patient who was surgically treated and in all patients with underlying malignant disease, except in patients with a considerably reduced general health status or those who rejected the bone biopsy. The standard treatment was surgical revision, consisting of necrotic bone excision followed by meticulous rinsing with neomycin sulfate 0.5% and dense wound closure. In addition, systemic antibiotics were administered.

All specimens were obtained primarily for medical purposes with patients' informed consent. The study design fulfilled the guidelines of the Declaration of Helsinki regarding ethical principles for medical research involving human subjects.

Literature review

An extensive literature search was performed in current databases such as PubMed, using the terms "osteonecrosis," "bisphosphonates," "mimicking," "malignancy," and "jaw metastasis" independently from the date of publication. Excluded were publications written in languages other than English or German.

Using the first 2 terms, a total of 969 articles were identified. When "mimicking" and "malignancy" were added, 16 publications could be found, only 3 of which dealt with malignancy mimicking BONJ or vice versa. The selected publications were assessed according to the following criteria:

1. Age and gender
2. Underlying disease
3. Criteria of BONJ in accordance to the AAOMS
4. Type and galenic form of bisphosphonate therapy
5. Histologic analysis
6. Treatment strategy

RESULTS

Patient cases

Case I. A 65-year-old man was referred with a submental abscess after interforaminal implant placement, which had been performed 8 months earlier (Figure 1). Due to multiple myeloma, initial stage III A (Durie and Salmon system), the patient received bisphosphonate therapy with zoledronic acid (Zometa; Novartis Pharma, Bern, Switzerland) for a total of 23 months with an



Fig. 1. Patient with typical clinical signs of submental abscess.

intermittent drug withdrawal of almost 2 years, due to stable disease status.² Because of tumor progression, combination therapy with lenalidomide (Revlimid; International Sàrl, Boudry, Switzerland), dexamethasone, and zoledronic acid was initiated.

For treatment of the submental abscess, systemic amoxicillin with clavulanic acid (Augmentin; GlaxoSmithKline, Münchenbuchsee, Switzerland) was initiated, and the submental abscess was incised and drained under general anesthesia. Since computed tomography showed typical signs of BONJ, surgical revision was performed 2 weeks later with explantation of the dental implant. A routine histologic specimen was taken. The histologic analysis revealed necrotic bone with signs of inflammation, but also cells of the underlying multiple myeloma, and the patient was referred to an oncologist for further treatment.

Case II. A 72-year-old woman was referred to our department with persistent pain and swelling of the left submandibular region after abscess treatment with intravenous antibiotics in another hospital. The abscess formation was interpreted as a consequence of implant placement in the region of the first lower molar on the right side, which had been performed 3 weeks earlier. The patient had undergone mass removal and axillary lymphadenectomy in 1994 due to breast cancer, followed by adjuvant radiotherapy and chemotherapy with tamoxifen (Tamec; Sandoz Pharmaceuticals AG, Rotkreuz, Switzerland). After the lesion metastasized to the bone, zoledronic acid therapy was administered for 42 months, until the submandibular abscess occurred.

Because of the typical clinical and radiologic signs of BONJ, antibiotic treatment with amoxicillin/clavulanic acid and bisphosphonate drug withdrawal was initiated, followed by surgical revision 4 weeks later. The histologic specimen showed breast cancer cells within the surrounding soft tissue, and the patient was referred to an oncologist for further treatment.

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