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Multiple myeloma in the lower jaw developing subsequently after mandibular medication-related osteonecrosis of the jaw: a case report

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Abstract

Multiple myeloma is a hematologic malignancy characterized by the presence of abnormal clonal plasma cells in the bone marrow, with the potential for uncontrolled growth causing destructive bone lesions, kidney damage, anemia, and hypercalcemia. Bisphosphonates are a group of drugs that have been used successfully in the treatment of diseases associated with osteoclast-mediated bone loss, e.g. for the treatment of bone metastases in malignant diseases including Multiple Myeloma.

However, in multiple myeloma patients taking bisphosphonates, an incidence of Bisphosphonate-associated osteonecrosis of the jaw (BAONJ) of 1.8-12.8% has been reported.

BAONJ occurs only in the jawbones, and MM can also affect the jaw. The two diseases have similar clinical and radiological manifestations. There are several cases in the literature of MM masquerading as BAONJ, which were initially clinically diagnosed as BAONJ but were later histologically confirmed as MM. The simultaneous diagnosis of MRONJ and MM at the same site is rarely reported. In our report, the patient was clinically and histologically diagnosed as BAONJ, but 2 years later, MM was detected radiographically at the site of BAONJ development.

Keywords: multiple myeloma, bisphosphonates, Bisphosphonate-associated osteonecrosis of the jaw

Introduction

Multiple myeloma is a hematologic malignancy characterized by the presence of abnormal clonal plasma cells in the bone marrow, with the potential for uncontrolled growth causing destructive bone lesions, kidney damage, anemia, and hypercalcemia (1). Among the patients with multiple myeloma, approximately 79% have osteolytic bone disease at the time of diagnosis (1). MM occurs predominantly in middle-aged and elderly men, most commonly affecting men aged from 50 to 60 years (2). Treatment approaches are aimed at relieving pain and slowing disease progression and include stem cell transplantation, chemotherapy, and

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administration of new agents such as thalidomide, lenalidomide, and bortezomib (3). According to some authors, oral manifestations associated with multiple myeloma are rare and often associated with a poor prognosis, as they are usually indicative of an advanced stage of the disease (4, 5). Others have reported an incidence of MM in the jaw bones of 14% to 30% (6, 7).

Bisphosphonates are a group of drugs that have been used successfully in the treatment of diseases associated with osteoclast-mediated bone loss, e.g. for the treatment of bone metastases in malignant diseases including Multiple Myeloma (8, 9, 10, 11). However, in multiple myeloma patients taking BF, an incidence of Bisphosphonate-associated osteonecrosis of the jaw (BAONJ) of 1.8-12.8% has been reported (10).

BAONJ occurs only in the jawbones, and MM can also affect the jaw. The two diseases have similar clinical and radiological manifestations. There are several cases in the literature of MM masquerading as BAONJ, which were initially clinically diagnosed as BAONJ but were later histologically confirmed as MM (4, 7, 12, 13, 14, 15). The simultaneous diagnosis of MRONJ and MM at the same site is rarely reported (16). In our report, the patient was clinically and histologically diagnosed as BAONJ, but 2 years later, MM was detected radiographically at the site of BAONJ development.

Case description

A 62-year-old male patient was referred to us in December 2019 with complaints of a non-healing extraction wound accompanied by severe radiating pain and exudation. Complaints appeared after extraction of tooth 46 one month ago. The patient was diagnosed with Bence-Jones/kappa multiple myeloma in March 2015 and underwent therapy (first line) 6 courses of CBorDex (Cyclophosphamid+Bortezomib+Dexamethasone) and Zometa, with subsequent monthly administration of Zometa. A complete response to the treatment was registered - absence of a monoclonal component in serum and urine from the control electrophoresis, absence of plasmacytic infiltration in the bone marrow from the control myelogram, reverse development of the bone lesions from the control bone scintigraphy in the absence of pain symptoms. Zometa therapy continues monthly. From November 2018 an evidence of MM relapse was found. The patient underwent CBorDex chemotherapy (Cyclophosphamid+Bortezomib+Dexamethasone) with good partial response data after 8 courses, then MM progression was registered. Followed by RD therapy (Lenalidomide+Dexamethasone) 6 courses (second line) from 02-08.2020. In 09. 2020 progression of MM was found-increase in Kappa/Lambda ratio more than 50% and residual bone marrow infiltration present from trepanobiopsy. The subsequent therapy was 3 courses (third line) of IxaRD treatment (Ixazomib+Lenalidomide+Dexamethasone) from 11.2020. until 02.2021 followed by progression of MM. A fourth line of therapy was administered with 3 courses of MonoDaratumab (Darzalex+Methylprednisolone) from 03-06.2021. MM progression is established. A fourth line of therapy follows with 3 courses of MonoDaratumab (Darzalex+Methylprednisolone) from 03-06.2021. MM progression is established. Fifth line of treatment: from 07.2021. until 01.2022 the patient was enrolled in a clinical trial with Pomalidomide, with evidence of MM progression. Sixth line: Treatment according to the CKd protocol from 24.02.2022 to 26.05.2022 with data on disease progression. Seventh line: 6 courses with Bendamustine+Dexamethasone from 07.2022 to 03.2023. with PET/CT data for complete metabolic and partial morphological response to therapy. Involved lymph nodes and soft tissue lesions are greatly reduced in size and suppressed to background metabolic activity. Generalized lesions in the skeleton had suppressed to background metabolic activity, except for a few lesions in the femur with above-background activity. Rated as a very good partial answer. Eighth line of therapy was conducted with Cyclophosphamide from 04-06.2023. with reported disease progression not affected by conservative treatment. Dexamethasone and Xgeva therapy was decided upon. In 08.2023 - lethal outcome.

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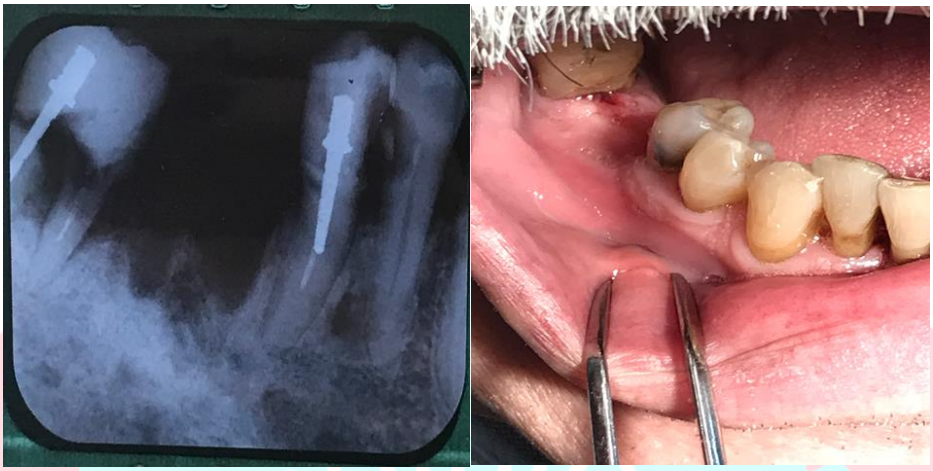

Fig. 1. State of the post-extraction wound and periapical X-ray 1 month after tooth extraction 46- 12.2019

During the primary examination on 04.12.2019 we found a non-healing extraction wound from tooth 26 with a scant amount of purulent exudate, the mucosa in this area was hyperemic. The patient reported severe constant spontaneous pain in this area, radiating along the inferior alveolar nerve. Tooth 47 had second-degree mobility (in medio-distal and vestibulo-oral directions), and there was pain on vertical and horizontal percussion and palpation. In the X-ray taken, we found osteosclerosis and osteolysis in the area of the extracted tooth 46, chronic periodontitis and separation of the roots due to the carious lesion of tooth 47. Based on the medical history, clinical examination, and imaging findings, the patient was diagnosed with stage II MRONJ according to the guidelines outlined in the American Association of Oral and Maxillofacial Surgeons position statement published in 2014 (17). Conservative-surgical treatment was performed: tooth 47 was extracted under local anesthesia, surgical debridement, curettage of granulation tissue and necrotic bone, and smoothing of sharp bone edges were performed. Sutures were placed using 3/0 non-absorbable synthetic sutures, removed on the 7th postoperative day. Medical treatment included the use of chlorhexidine solution 0.2%, antibiotic Augmentin 1g 2 times a day for 14 days. At the control examination of the first month, we found epithelialization of the wound and disappearance of the patient's pain symptoms and subjective complaints.

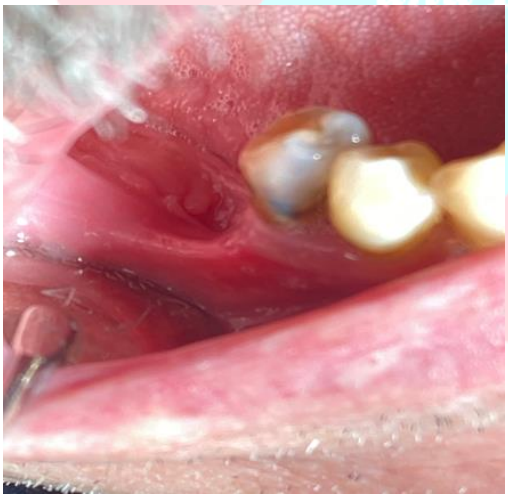

Fig. 2. State of the post-extraction wound 1 month after the operative intervention - 01.2020

The histological result showed inflammatory infiltrates in the bone-marrow spaces, rich vascular proliferation of granulation tissue type and focal necrosis. No vital myeloma tumor was identified.

We conducted regular monthly follow-up examinations, remission had occurred regarding BAONJ. After 6 months, a removable partial prosthesis was made, which the patient used without complaints.

In 03.2022 the patient came to us again with complaints of pain involving the lower right quadrant of the jaw, as well as loss of

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sensation along the course of the right inferior alveolar nerve. During the intraoral examination, the mucosa in this area was found intact, there was pain on palpation in the area of the body of the lower jaw and the mandibular ramus on the right. An imaging study was performed - orthopantomography followed by CBCT, on which we found a large number of osteolytic lesions involving the mandibular body on the left and right and the mandibular ramus on the right. In the area of the body of the mandible on the right, in the area of the extracted molars and the periapical area around and distal to the second premolar, we observed three osteolytic bony lesions with scalloped borders, multicentric. One of these lesions, involving the area with the preceding BAONJ, extends beyond the lower edge of the mandible, and involves the passing neurovascular bundle. Based on the clinical and radiographic data, we concluded that it is not a recurrence of BAONJ, but an impetus in the development of the main disease - MM with manifestation in the jaw bones. We did not proceed with an excisional biopsy, due to the risk of developing subsequent osteonecrosis or contamination with pathogenic microorganisms when the integrity of the oral mucosa is affected. The patient was referred to his treating oncologist. As a result of his applied treatment, at a control examination 9 months later - 12.2022 the clinical symptomatology had decreased - there was no complaint of pain, although the lack of sensitivity along the course of inferior alveolar persisted.

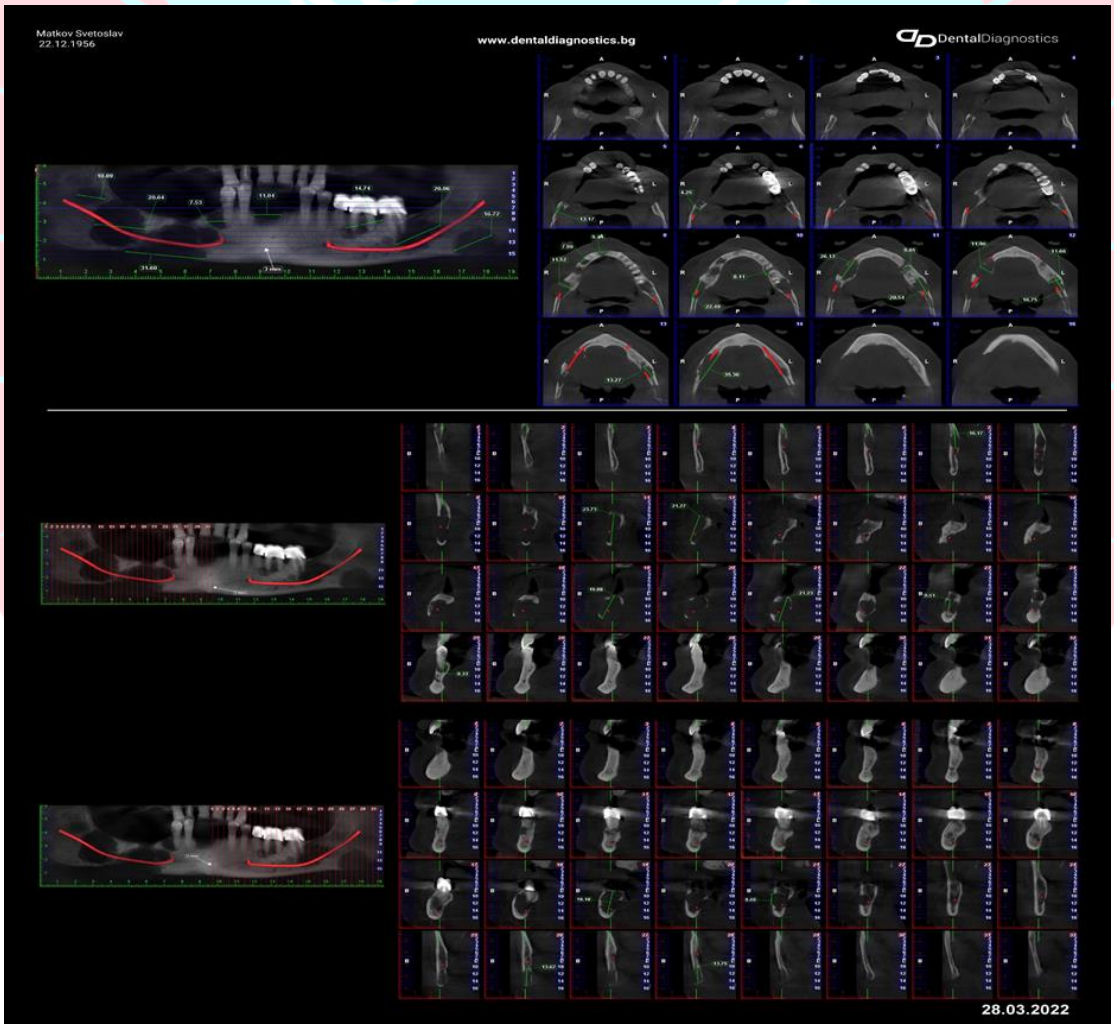

Fig. 3. CBCT of the mandible 03.2022. Osteolytic lesions are clearly visible

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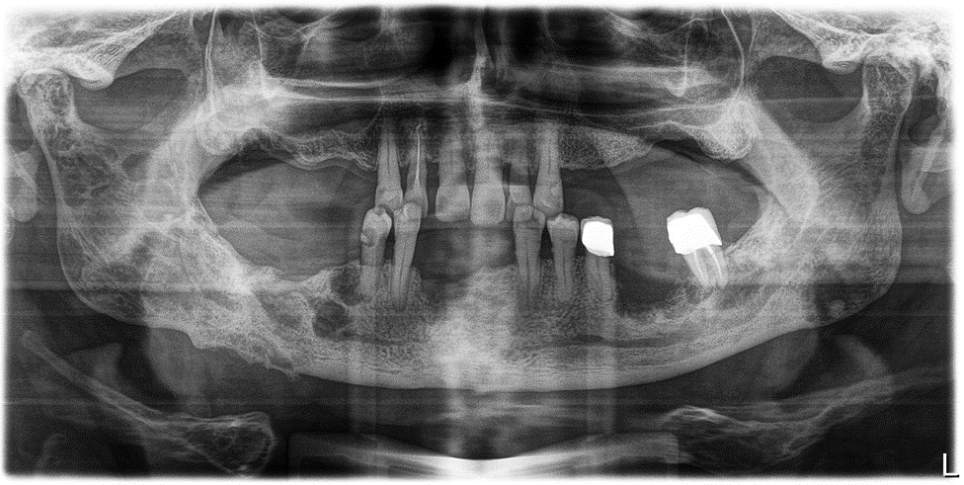

Fig. 4. Panoramic X-ray 12.2022

In the imaging study – panoramic x-ray, we found a reduction in the size of the osteolytic lesions and the formation of new bone tissue (Fig. 4). We also observed osteogenesis in the areas of osteolysis during the CBCT examination performed in June 2023. (Fig. 5)

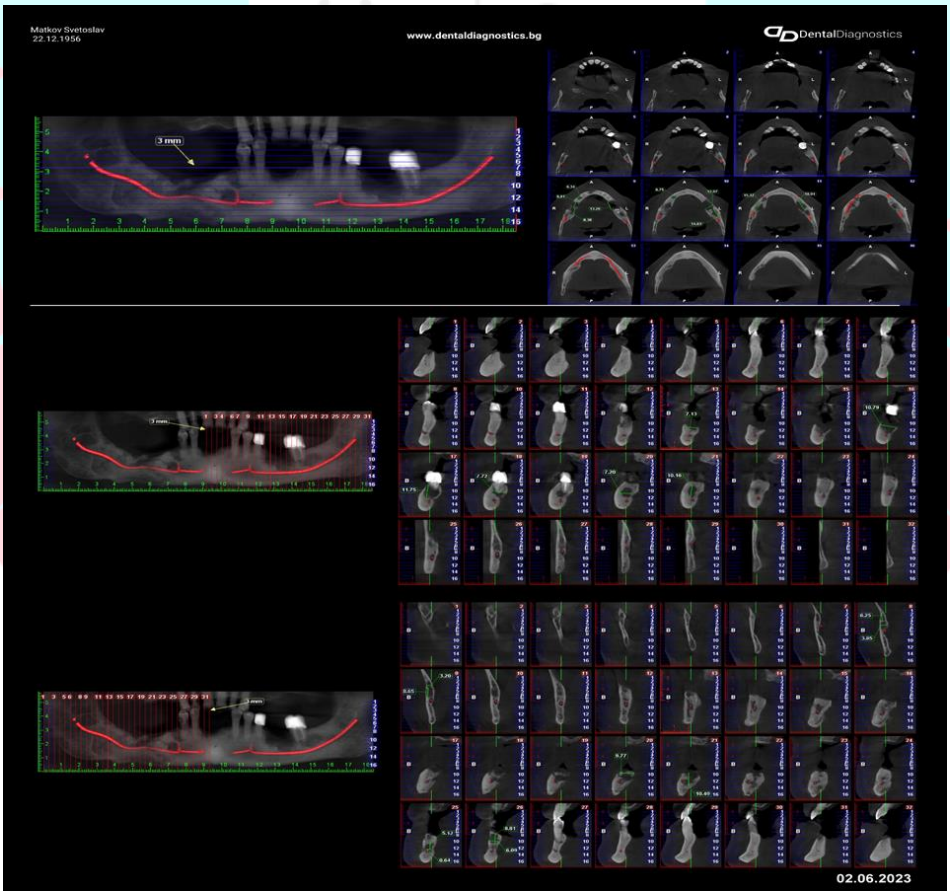

Fig. 5. CBCT of the mandible 06.2023.

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Discussion

Bisphosphonates are highly effective antiresorptive drugs that have been used successfully to treat bone metastases in malignancies (18, 19, 20), including multiple myeloma (8, 9, 10, 11). Although rare, avascular osteonecrosis of the jaw has been recognized as a complication of bisphosphonate use. In 2003, Marx first described "painful bone exposure" of the upper and lower jaws in patients taking pamidronate (Aredia; Novartis Pharmaceuticals, EastHanover, NJ) and zoledronate (Zometa; Novartis Pharmaceuticals)(21). Medication related osteonecrosis of the jaw (MRONJ) is defined as: current or previous treatment with antiresorptive or antiangiogenic agents resulting in exposed bone or bone that can be probed through an intra- or extraoral fistula in the maxillofacial region that persisted for more than 8 weeks, in the absence of evidence of radiation therapy to the jawbones or obvious metastatic disease of the jawbones (4). BAONJ is a multifactorial disease, and the risk factors for the development of the disease are divided into risk factors related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors (22). The clinical presentation of BAONJ includes the presence of "exposed nonvital bone" (21, 22, 23). This symptom may be preceded by vague pain or discomfort in the affected area (21, 22, 23). Inflammation and superimposed infection are seen in advanced cases and are the leading causes of the symptomatic manifestations of BAONJ (23, 24).

MM can appear in the jaw as a single lesion or part of MM, especially in the late stage of the disease. The main symptoms are pain, swelling, tooth loosening, paresthesia, soft tissue formation, bleeding or pathological fracture (25).

The radiographic and clinical features of the oral presentation of MM are vague and variable, making early diagnosis challenging. The radiographic picture of MM may present as lesions that may be single or multiple, have diffuse or well-defined borders, and may have a sclerotic, osteolytic, osteoporotic, or mixed appearance, with or without cortical destruction (26).

It appears that the two diseases can present with similar clinical and radiographic symptoms, which leads to difficulties in differential diagnosis. However, the treatment approach for both diseases is different, which shows that timely and accurate diagnosis is of utmost importance.

Several researchers have reported cases of MM misdiagnosed as MRONJ (4, 7, 12, 14, 15). This is partly due to the fact that biopsies are usually not always performed for jaws affected by MRONJ. When MM with jaw bone involvement is suspected, histological analysis after gingival and/or bone biopsy is warranted. However, clinicians must weigh the benefits of biopsy against the risk of developing MRONJ.

Conclusion

Distinguishing MM with oral presentation from MRONJ is challenging because of the similarity in their clinical and paraclinical (radiographic) picture. The dental practitioner should be aware of MRONJ as a condition that can potentially mask oral metastases and vice versa. Early diagnosis is crucial for timely intervention and relief of patients' symptoms. Tissue biopsy should be considered when MM with oral presentation is suspected. Dental practitioners are placed in a strategic position in patient care for early diagnosis of such oral manifestation associated with multiple myeloma.

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