

## Case Report

# Oral Squamous Cell Carcinoma Mimicking Medication-Related Osteonecrosis of the Jaws (MRONJ): A Case Series

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**Abstract:** (1) Background: Medication-related osteonecrosis of the jaw (MRONJ) is a potential adverse drug reaction of antiresorptive and/or antiangiogenic treatment. MRONJ is mostly diagnosed by anamnestic data, clinical examination and radiological findings, with signs and symptoms often unspecific. On the other hand, oral squamous cell carcinoma (OSCC) is characteristic for its pleomorphic appearance (e.g., ulcer, mucous dehiscence, non-healing post-extractive socket). We report three cases where OSCC mimicked MRONJ lesions. (2) Patients: Three patients undergoing amino-bisphosphonate treatment for osteoporosis presented with areas of intraorally exposed jawbone and unspecific radiological signs compatible with MRONJ. Due to the clinical suspicious of malignant lesion, incisional biopsy for histological examination was also performed. (3) Results: Histological examination of the tissue specimen revealed the presence of OSCC. All patients underwent cancer treatment. (4) Conclusions: Several signs and symptoms of OSCC may simulate, in patients with a history of anti-resorptive, MRONJ; for these reasons, it is important to perform histologic analysis when clinicians are facing a suspicious malignant lesion.

**Keywords:** osteonecrosis of the jaw; ONJ; MRONJ; oral squamous cell carcinoma; OSCC; bone exposure



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## 1. Introduction

Osteonecrosis of the jaw related to medication (MRONJ) has been defined as “an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease, in the absence of a previous radiation treatment” [1–3].

The diagnosis of MRONJ is commonly based both on clinical and radiographic findings, because patients may present with other common clinical disorders not to be confused with MRONJ; among these are alveolar osteitis, sinusitis, periodontitis, chronic sclerosing osteomyelitis or benign fibro-osseous lesions. However, differential diagnosis may also consider bone metastases and oral squamous cell carcinoma (OSCC) [3–5].

In particular, OSCC can appear through bone exposure, mucous dehiscence, sudden increased dental mobility, lack of post-extractive alveolar repair and pain, mimicking MRONJ [6–8].

The aim of this paper is to report three cases of patients at risk of MRONJ but found to suffer from OSCC and use them to discuss some issues of the current diagnostic workflow of both diseases.

## 2. Case Presentation

### 2.1. Clinical Case 1

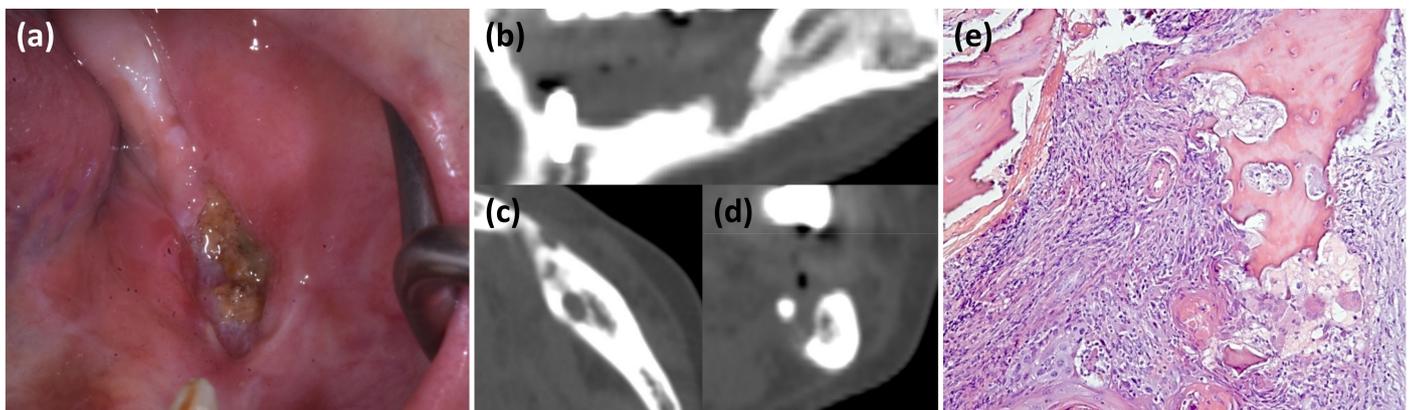
A 62-year-old non-smoker woman was referred to the sector of Oral Medicine at the University Hospital in October 2020 for swelling in his left mandible and severe pain.

In 2006, the patients had been diagnosed with a OSCC (grade 1) on the posterior part of the left body of the mandible in a different institution; afterwards, she underwent marginal mandibular resection.

Additionally, she was affected by chronic drug-induced pancreatitis and osteoporosis, and she had been treated from 2016 to 2018 with alendronate (once-weekly oral alendronate 70 mg), and steroids.

The patient was partially edentulous, she reported mandibular rehabilitative treatment by 3 dental implants in 2019; all of them failed to integrate after 2 months from implant placement. The patient reported that she developed numerous episodes of swelling and pain in the implant site after fixtures' loss.

Intra-oral examination revealed a large area of exposed necrotic bone of the posterior left part of the mandible (Figure 1a). Computed tomography (CT) showed a diffuse osteosclerotic pattern, non-healing post-surgical site and cortical disruption (Figure 1b–d).



**Figure 1.** Left-sided mandibular OSCC: (a) clinical view; (b–d) computed tomography scan sections; (e) magnification of histological findings.

All clinical and radiological features were compatible with a diagnosis of MRONJ; however, due to the clinical aspects of the lesions and the medical history (i.e., previous OSCC), incisional biopsy for histological examination was promptly performed. Histological examination showed a squamous cell carcinoma infiltrating lamellae of cortical bone (Figure 1e).

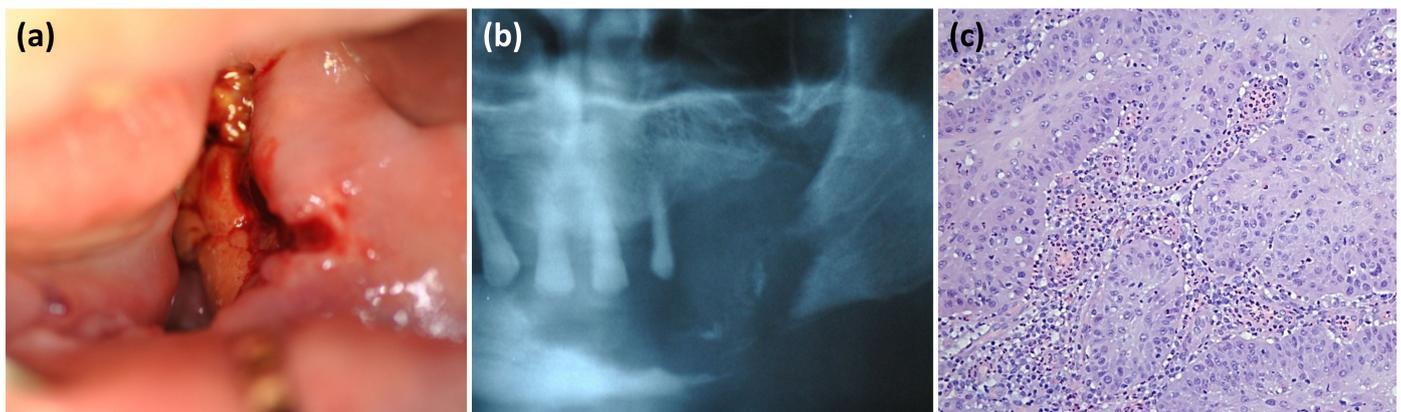
The histological findings confirmed the diagnosis of OSCC; appropriate oncological management has therefore been started.

### 2.2. Clinical Case 2

A 90-year-old non-smoker woman with osteoporosis was treated with ibandronate (once-monthly oral ibandronate 150 mg) for 10 years.

Six months before examination, she underwent dental extraction of tooth 3.6. After this surgery, due to the presence of a non-healing post-extraction socket, she underwent bony curettage and antiseptic mouthwashes at a different institution for 3 months.

In January 2019, she was referred to the Maxillofacial Surgery Unit of Ragusa, where extra-oral examination revealed the presence of soft tissue swelling and high-volume lymph nodes in the left neck. Intra-oral examination highlighted bone exposure and high granulation tissue of the posterior left portion of the mandible; additionally, she referred the paraesthesia of the inferior alveolar nerve (Figure 2a).



**Figure 2.** Left-sided mandibular OSCC: (a) clinical view; (b) detail of panoramic X-ray; (c) magnification of histological findings.

Orthopantomography showed extensive osteolysis, with pathological fracture of the left mandibular body (Figure 2b).

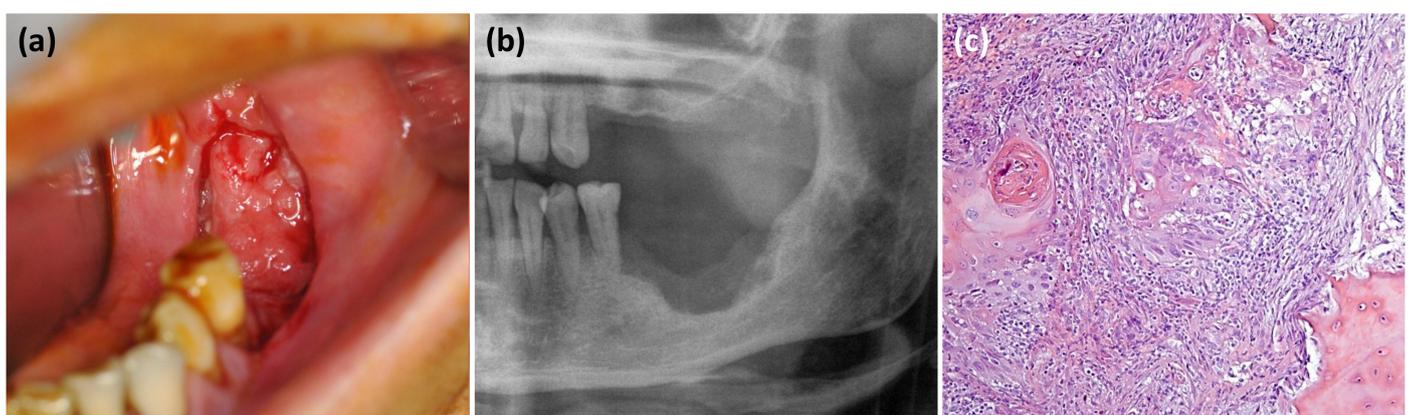
Incisional biopsy was performed; the histological examination showed islets of squamous cell carcinoma surrounded by granulation tissue; bone tissue was not included in the sample (Figure 1c). Subsequently, the patient was referred to the Department of Oncology for management.

### 2.3. Clinical Case 3

A 72-year-old non-smoker woman with osteoporosis was treated with alendronate for more than 15 years (once-weekly oral alendronate 70 mg)

She reported having undergone dental extractions about 5 months before the referral (tooth 3.6 and 3.7). Due to the presence of a non-healing post-extraction socket, she underwent several bony curettage and antiseptic mouthwashes at another institution for 2 months.

Extra-oral examination showed the presence of soft tissue swelling and high-volume lymph nodes in the left neck. Intra-oral examination revealed high granulation tissue of the posterior left portion of the mandible. She did not report the paresthesia of the inferior alveolar nerve (Figure 3a).



**Figure 3.** Left-sided mandibular OSCC: (a) clinical view; (b) detail of panoramic X-ray; (c) magnification of histological findings.

Orthopantomography revealed an extensive osteolysis of the posterior left portion of the mandible (Figure 3b).

Incisional biopsy was carried out; histological examinations detected a squamous cell carcinoma, accompanied by granulation tissue, with focal infiltration of the cortical bone fragments included in the sample (Figure 3c). Subsequently, the patient underwent oncological treatment.

### 3. Discussion

Almost 20 years after the first mention of osteonecrosis of the jaws related to antiresorptive medication (MRONJ) [9], it remains a current topic within the scientific community. Through the last years, increasing information regarding the possible etiology, risk factors, and diagnostic strategy have been obtained.

MRONJ is a potentially severe and debilitating adverse reaction to antiresorptive and/or antiangiogenic agents [3,4,10,11].

The risk of developing MRONJ ranges from 0.01% in patients with osteoporosis, and up to 15% in patients taking antiresorptive and/or antiangiogenic medication for malignancy [3,4].

MRONJ typically manifests as an infected area of necrotic bone, and it may be related to severe chronic pain and facial deformity, which can adversely affect the quality of life [5].

MRONJ is usually diagnosed by clinical examination and radiological findings without performing a biopsy for histological investigations [4,5,10,12]. However, it is important to remember that clinical and radiological criteria of MRONJ are often unspecific. Indeed, patients at risk for or with established MRONJ also can present with other common clinical conditions, both benign and malignant disorders.

Indeed, OSCC that involves the mandibular alveolus may exhibit themselves through several clinical presentations that may mimic MRONJ, such as mucous dehiscence, sudden increased dental mobility, lack of post-extractive alveolar repair, pain and paresthesia [6–8,13,14]. Cancer metastasis should also be included in the differential diagnosis for the bone lesion, especially in cancer patients at risk of MRONJ, as well as OSCC (Table 1) [6,7,15].

**Table 1.** Shared and unshared main clinical features between MRONJ and OSCC (modified from Campisi et al. and Scully et al. [3,16]).

	Shared Clinical Criteria	Unshared Clinical Criteria
<b>MRONJ</b>	<ul style="list-style-type: none"> <li>• Bone exposure</li> <li>• Halitosis</li> <li>• Hypoesthesia/paresthesia of the lips</li> <li>• Jaw pain</li> <li>• Mandibular asymmetry</li> <li>• Non-healing post-extraction socket</li> </ul>	<ul style="list-style-type: none"> <li>• Abscess formation (with/without purulent discharge)</li> <li>• Hyperemia of the mucous membranes</li> <li>• Intra- or extra-oral fistula</li> <li>• Nasal leakage of fluid</li> <li>• Spontaneous sequestrum formation</li> </ul>
<b>OSCC</b>	<ul style="list-style-type: none"> <li>• Soft tissue swelling</li> <li>• Sudden dental mobility or loose tooth</li> <li>• Lymph node enlargement</li> </ul>	<ul style="list-style-type: none"> <li>• Indurated lump/ulcer</li> <li>• Granular ulcer with fissuring or raised exophytic margins</li> <li>• Red lesion (erythroplasia)</li> <li>• Mixed red/white lesion; irregular white lesion</li> <li>• Dysphagia</li> </ul>

Only few studies described OSCC in patients assuming MRONJ-related medication. Gander et al. described three cases of malignancy (OSCC and cancer metastasis) mimicking bisphosphonate-associated osteonecrosis of the jaw [7].

Arduino et al. reported on an OSCC that appeared adjacent to an area diagnosed as MRONJ [13]. Tocaciu et al. showed two cases in which an osteolytic lesion caused a diagnostic dilemma between MRONJ and OSCC; similarly, Terenzi et al. [8,14].

The gold standard for the diagnosis of OSCC is still biopsy and histopathological examination [17,18].

The role of biopsy in MRONJ is controversial; biopsy should be performed only in doubtful cases with confounding patterns for differential diagnosis, because any surgical

procedure may lead to progression of the underlying disease [6]. Some authors proposed that bone fragment investigation may be evaluated to rule out malignancy and confirm MRONJ at the discretion of the surgeon and oncologist [10,15]. Thus, a conservative approach is currently recommended; however, it seems prudent therefore to biopsy only suspicious malignant osteolytic lesions in patients taking MRONJ-related drugs, with MRONJ being reserved as a diagnosis of exclusion [8].

It should also be considered that it may be sometimes difficult to distinguish between mucosal lesions deriving from MRONJ, OSCC or metastasis by primary disease, since the appearance of pseudoepitheliomatous hyperplasia in MRONJ may often mimic OSCC, leading to a misdiagnosis of malignancy [6–8,13]. For this reason, it is important to inform the pathologist about the history of MRONJ-related drugs when a biopsy is sent to them for histopathological analysis. Additionally, the type and amount of tissue submitted should be appropriate: specimens that comprise only necrotic bone are difficult to evaluate; due to the possible presence of pseudoepitheliomatous hyperplasia in MRONJ lesions, a proper biopsy specimen should also contain both abnormal and normal soft tissues [8].

#### 4. Conclusions

In the last decades, an increasing use of MRONJ-related drugs has been documented in the patients' community, and this trend is going to increase in the coming years.

Even if a clinician should be aware of the importance of early diagnosis of MRONJ, it should be reminded that several signs and symptoms of OSCC may simulate MRONJ. Indeed, the rapid onset of high dental mobility or the lack of post-extraction alveolar repair may suggest a diagnosis of MRONJ, especially in the presence of local and systemic confounding factors

For these reasons, it is important to perform mucosal and/or jaw bone biopsies if there is a suspicion of OSCC in any kind of patients or metastases in cancer patients in order to exclude malignant lesions.

A meticulous selection of the biopsy site will be mandatory to reach a correct diagnosis as well as the appropriate communication with the pathologist regarding the patient's medical history.

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