

# Diagnosis and Staging of Medication-Related Osteonecrosis of the Jaw



Salvatore L. Ruggiero, DMD, MD<sup>a,b,\*</sup>

## KEYWORDS

- Osteonecrosis • Medication-related osteonecrosis of the jaw • Jaw necrosis
- Antiresorptive therapy • Antiangiogenic therapy

## KEY POINTS

- The association of antiangiogenic therapy with osteonecrosis of the jaw has prompted a change in nomenclature to medication-related osteonecrosis of the jaw (MRONJ).
- The diagnostic criteria for MRONJ has expanded to include fistulas that can be probed to bone.
- The imaging characteristics of MRONJ are helpful in defining the extent of the process but are not diagnostic.
- Obtaining a complete patient history and clinical examination remains the most effective mode of establishing a diagnosis of MRONJ.
- Proper staging of MRONJ is essential for directing stage-specific treatment guidelines.

## INTRODUCTION

Medication-related osteonecrosis of the jaw (MRONJ) is now a well-known complication associated with antiresorptive and antiangiogenic therapies that is affecting a growing number of patients. In response to our specialty's expanding clinical experience in the management of MRONJ, updated treatment guidelines were required in 2009 and most recently in 2014. MRONJ patients often present with challenging clinical problems requiring varying degrees of intervention and oral and maxillofacial surgical care. Stage-specific treatment protocols have been created, and recently modified, to guide oral surgeons and other health care professionals in selecting the appropriate operative or nonoperative treatment strategy. Establishing the correct diagnosis and properly stratifying these patients is crucial in

providing necessary care in a timely fashion. Moreover, this approach will permit us to guide our medical and dental colleagues, who will often modify the patient management plan if a diagnosis of MRONJ is suspected.

The aim of this article is to review the recently modified diagnostic criteria for MRONJ with a focus on the clinical, histopathologic, and imaging characteristics of this disease process. Elements of the staging criteria are also examined along with the rationale for the various changes that been implemented since the original American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper in 2007.

## NOMENCLATURE AND DIAGNOSTIC CRITERIA

Standardization of diagnostic criteria and nomenclature for this clinical entity is important to

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Disclosure: Consultant for Amgen Inc.

<sup>a</sup> Department of Oral and Maxillofacial Surgery, School of Dental Medicine, SUNY, Stony Brook, NY 11794-8705, USA; <sup>b</sup> Hofstra North Shore - LIJ School of Medicine, Division of Oral and Maxillofacial Surgery, 270-05 76th Ave, New Hyde park, New York, NY 11040, USA

\* Corresponding author. New York Center for Orthognathic and Maxillofacial Surgery, 2001 Marcus Avenue, Suite N10, Lake Success, NY 11042.

E-mail address: [drruggiero@nycoms.com](mailto:drruggiero@nycoms.com)

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facilitate future clinical and epidemiologic research. In addition, a uniform definition for osteonecrosis of the jaw (ONJ) will serve to distinguish this new clinical entity from other delayed intraoral healing conditions. Since it was first described, various organizations have proposed clinical definitions for ONJ, all of which are analogous to each other; and this has resulted in some degree of confusion. This condition is known in the literature by several acronyms, including BRONJ (bisphosphonate-related osteonecrosis of the jaw), BRON (bisphosphonate-related osteonecrosis), BON (bisphosphonate osteonecrosis), BAONJ (bisphosphonate-associated osteonecrosis of the jaw), and simply ONJ. The emergence of jaw necrosis in bisphosphonate-naïve patients receiving monoclonal therapy with RANKL inhibitors<sup>1-4</sup> prompted the American Dental Association to introduce the more generic term ARONJ (antiresorptive-associated osteonecrosis of the jaw).<sup>5</sup> MRONJ (medication-related osteonecrosis of the jaw) is the most recent nomenclature change that was proposed in the current AAOMS position paper.<sup>6</sup> This modification, though broad in its scope, was considered necessary to address the growing number of osteonecrosis cases affecting jaws that were associated with antiangiogenic therapies.

Despite the variations in nomenclature, the clinical finding of exposed, necrotic bone remains the consistent hallmark of the diagnosis; therefore, a physical examination is the most effective method of establishing the diagnosis of jaw necrosis.

The AAOMS established a working definition for MRONJ since it was first defined in 2006. The recent position paper contained 2 modifications to the definition. More specifically, antiangiogenic agents were added to the list of medications, and “bone that can be probed” was considered equivalent to exposed bone. These changes were implemented so that MRONJ could be more accurately distinguished from other delayed healing conditions and address evolving clinical observations and concerns about underreporting of disease. A diagnosis of MRONJ should be considered if a patient presents with all of the following criteria:

1. Current or previous treatment with antiresorptive and/or antiangiogenic agents
2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) in the maxillofacial region that has persisted for more than 8 weeks
3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

The differential diagnosis of MRONJ should exclude other common clinical conditions such as alveolar osteitis, sinusitis, gingivitis/periodontitis, periapical disorder, and temporomandibular joint disorders. In those rare situations where exposed bone is present in patients exposed to bisphosphonates and radiation therapy to the jaw, osteoradionecrosis should be strongly considered. Although bone inflammation and infection is typically present in patients with advanced MRONJ, this is typically a secondary event. The exposed bone and surrounding soft tissue become secondarily infected, presenting a clinical scenario similar to that of osteomyelitis. However, the histologic analysis of these bone specimens rarely demonstrates the criteria required to establish a diagnosis of acute or chronic osteomyelitis. Analyses of the physical properties of the resected necrotic bone have also failed to demonstrate any unique features that would serve as a reliable biomarker for this disease process.<sup>7,8</sup> A heightened level of awareness for MRONJ should exist among patients with cancer receiving antiresorptive or antiangiogenic medication, as these patients are significantly more likely than those with osteoporosis to develop this complication.<sup>6,9</sup>

## CLINICAL PRESENTATION

The patient's history and clinical examination continues to be the most sensitive diagnostic tools for this condition. Obtaining an accurate exposure history to the various antiresorptive and antiangiogenic medications is a critical first step in assessing for MRONJ. Cancer and non-cancer patients will often present with complicated antiresorptive medication schedules as their physicians attempt to modulate therapy according to disease activity and risk. Patients are often unaware of the specific type of medications they are receiving, especially patients with cancer who are typically receiving multiple chemotherapy medications.<sup>10</sup> For the clinician evaluating these patients, it is important to obtain an accurate assessment of the continuous total drug-exposure history because often there will be a hiatus in therapy (intentional or because of noncompliance) that will affect the probability of establishing a diagnosis of MRONJ. Reviewing the medication history with the treating oncologist or endocrinologist is often required to obtain the necessary information.

Regions of exposed and necrotic bone may remain asymptomatic for weeks, months, or even years. These lesions are most frequently symptomatic when surrounding tissues become

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