



Review Article

Symposium: Imaging modalities for drug-related osteonecrosis of the jaw (1), role of imaging in drug-related osteonecrosis of the jaw: An up-to-date review (secondary publication)[☆]

Makoto Tsuchimochi^{a,*}, Tohru Kurabayashi^b

^a The Nippon Dental University (Emeritus Professor), Formerly, Oral and Maxillofacial Radiology, The Nippon Dental University School of Life Dentistry at Niigata, 1-8 Hamaura-cho, Chuo-ku, Niigata 951-8580, Japan

^b Department of Oral and Maxillofacial Radiology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8549, Japan

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SUMMARY

MRONJ/ARONJ is a serious adverse effect of medication, although the incidence of the disease is rare, and there are still controversial issues regarding the pathogenesis of MRONJ/ARONJ. Medications that can lead to MRONJ/ARONJ are commonly used to treat osteoporosis and to prevent bone fractures caused by bone metastasis of malignancies. The long-standing disease state of ONJ deteriorates the quality of life of affected patients. Early detection and prevention of the disease are key to alleviating pain and discomfort. To date, several imaging modalities have been introduced to depict the lesions. Imaging modalities, radiography, CT, MRI and nuclear medicine provide important information for managing this challenging disease.

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1. Introduction

Medication-related and difficult-to-treat jaw bone necrosis has been brought to the attention of health care practitioners, especially to dentists, since Marx et al. reported cases with exposed bone and necrosis of the mandible and maxilla among bisphosphonate-treated patients. To date, not only bisphosphonates but also other anti-bone-resorptive drugs (e.g., denosumab) or antiangiogenic agents (e.g., bevacizumab) can cause jaw bone necrosis. Since then, the terminology of bone necrosis has been changed from bisphosphonate-related osteonecrosis of the jaw (BRONJ) to medication-related osteonecrosis of the jaw (MRONJ) or antiresorptive agent-related osteonecrosis of the jaw (ARONJ) [1,2].

The incidence of the disease in Japan is 0.01–0.02% (bisphosphonate related, oral) and 1–2% (bisphosphonate related, iv). A similar incidence has also been reported in patients treated with denosumab [3] (refer to the symposium article, Shibahara et al.). Although the incidence is low, patients suffer pain and discom-

fort in the jaw for a prolonged course with decreased oral function, including mastication and deglutition, and osteonecrosis of the jaw deteriorates their quality of life.

MRONJ/ARONJ differs from other conventional osteomyelitis with osteonecrosis in jaws because of the difficulty of treating MRONJ/ARONJ and chronicity of the disease, which can progress to severe osteonecrosis and result in the resection of jaw bones. Many imaging modalities are available for diagnosing the disease. The aims of imaging examinations are to determine the extent of the disease, define the area of inflammation, provide useful imaging findings for surgical procedures, follow the disease course, and predict disease prognosis (Tables 1 and 2).

2. Determining the extent of disease

Histopathologic findings of MRONJ/ARONJ are characterized by a large amount of necrotic bone and surrounding thick trabecular bones with intertrabecular fibrous tissues accompanying abundant vasculature and inflammation. Lamellar bone-containing viable osteocytes are surrounded by woven bone. At sites where osteogenesis is evident, bone trabeculae are rimmed by osteoblasts [4]. Plain radiographs can reveal alterations in bone structure and density changes in trabeculae, cancellous bone, and cortical bone with high spatial resolution. In stage I, the lesion is restricted to the alve-

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* Corresponding author.

E-mail address: tsuchimochi@ngt.ndu.ac.jp (M. Tsuchimochi).

Table 1
Stages of ARONJ: clinical symptoms and imaging findings [2].

Stage 0*	Clinical symptoms: no bone exposure/necrosis, deep periodontal pocket, loose tooth, oral mucosal ulcer, swelling, abscess formation, trismus, hypoesthesia/numbness of the lower lip (Vincent's symptom), nonodontogenic pain Imaging findings: sclerotic alveolar bone, thickening and sclerosis of the lamina dura, remaining tooth extraction socket
Stage 1	Clinical symptoms: asymptomatic bone exposure/necrosis without signs of infection or a fistula in which the bone is palpable with a probe Imaging findings: sclerotic alveolar bone, thickening and sclerosis of the lamina dura, remaining tooth extraction socket
Stage 2	Clinical symptoms: bone exposure/necrosis with infection, or fistula in which the bone is palpable with a probe. Pain in the bone-exposed site associated with redness with/without pus discharge Imaging findings: mixed diffuse osteosclerosis and osteolysis from the alveolar bone to the jaw bone, thickening of the mandibular canal, periosteal response, maxillary sinusitis, and sequestration
Stage 3	Clinical symptoms: bone exposure/necrosis associated with pain, infection or at least one of the following symptoms, or a fistula in which bone is palpable with a probe; bone exposure/necrosis over the alveolar bone (e.g., reaching the mandibular inferior edge or mandibular ramus, or reaching the maxillary sinus or mandibular ramus or the cheek bone). As a result, pathologic fracture or extraoral fistula, nasal/maxillary sinus fistula formation, or advanced osteolysis extending to the mandibular inferior edge or maxillary sinus. Imaging findings: osteosclerosis/osteolysis to the surrounding bone (cheek bone, palatine bone), pathologic mandibular fracture, and osteolysis extending to the maxillary sinus floor

*Note: Care should be taken to avoid overdiagnosis because half of stage 0 ARONJ cases do not progress to ONJ.

Table 2
Imaging characteristics of MRONJ/ARONJ. Partly referred to [27–30].

	Morphological anatomy		Physiological tissue characteristics				
	Soft tissue	Bone	Adipose tissue	Edema	Bone marrow	Bone remodeling	Blood flow, bone
Dental, panoramic X-ray	–	++	–	–	–	–	–
CBCT	–	+++	–	–	–	–	–
CT	++	+++	+	Soft tissue +	±	–	Enhanced ++
MRI	+++	++	++	Inflammation ++	++	–	++
Bone scintigraphy	–	– (SPECT/CT ±)	–	–	±	+++	3-phase ++
PET/CT(FDG)	+	±	–	Inflammation ++	–	–	–

olar bone, and intraoral imaging can show bone changes in the trabeculae of the alveolar bone around teeth and the lamina dura. To examine the whole mandible and maxilla, panoramic examination is available as a screening method. X-ray examinations are performed daily in dental clinics. However, plain radiographs need changes of 30%–50% in bone mineral content before detecting bone lesions, and these changes have low sensitivity even in digital imaging. CT and cone-beam CT (CBCT) offer high quality tomographic images to reveal MRONJ/ARONJ lesions [5–10] (refer to the symposium article, Baba et al.). Diffuse osteosclerosis, bone resorption, degenerated cortical bone, periosteal reaction, and bone fistulas are findings for diagnosing the spread of osteonecrosis of the jaw.

Although CBCT has higher spatial resolution than conventional CT does, the field of view is small and unable to accurately measure Hounsfield units. CBCT is preferred to CT because of its higher resolution in the alveolar bone and the jaw bones. CT is recommended to examine the mandible, maxilla, base of the maxillary sinus, and around the facial bone area as a whole. MRI scans are less accurate in skeletal information than CT scans are. Many studies have shown the usefulness of bone scintigraphy, which is highly specific for detecting bone formation or bone remodeling in a physiological manner [11–13] (refer to the symposium articles, Watanabe et al. and Ohbayashi et al.). Bone scintigraphy offers less information about anatomical configuration than the information from CT or MRI. Increasing use of SPECT/CT has been observed for bone scintigraphy, which can provide better localization of physiological changes in bone in patients with MRONJ/ARONJ. The site of increased pathologic bone remodeling is clearly shown by ^{99m}Tc phosphate compound uptake. This radioactive-phosphate compound accumulates in the region of bone formation of the remodeled bone and some in nonphysiological skeletal tissue. Lesions that extend deeply to the facial bones are easily detected as well-contrasted black-and-white images. Similar to bone scintig-

raphy, ¹⁸F-fluoride PET/CT is also available for bone lesion imaging [14,15].

3. Defining the area of inflammation

Bisphosphonate-related MRONJ/ARONJ is basically osteomyelitis associated with bone necrosis [2]. Histopathological examination in specimens shows severe infiltration of inflammatory cells, especially in nonexposed bone, and actinomyces species are often found in necrotic lesions. In the early stage of the disease, MRI shows a decrease in bone marrow signal intensity on T1-weighted images. T2-weighted images and short T1 inversion recovery (STIR) may show increased signal intensity. Inhomogeneous gadolinium enhancement reflects inflammation in the soft tissue. In advanced diseases, the bone marrow signal intensity of T2-weighted images and STIR can decrease in necrotic areas, and in contrast, increasing intensity can represent nonnecrotic areas [6]. These high signal intensities reflect inflammation of the bone marrow, edema and circulatory disturbances in bone. Tomographic information depicting inflammation of the soft tissue is also observed.

FDG PET/CT is also used to diagnose MRONJ/ARONJ [16] (refer to the symposium article, Kitagawa et al.). FDG PET/CT is useful for diagnosing osteomyelitis [17] and also helpful for diagnosing inflammation in patients with MRONJ/ARONJ.

4. Following the disease course

It is critical to closely follow patients with MRONJ/ARONJ via imaging modalities for the assessment of spread or remission. Repeat imaging examinations provide important information to evaluate the response to treatment and to select treatment options. When the lesion is confined to the alveolar bone, periodic intraoral X-ray imaging and panoramic examination are useful for assessing changes in the alveolar bone surrounding teeth under caution

of excess radio-exposure. In stage II, III, or advanced stage I, CBCT, CT, MRI, and bone scintigraphy can offer additional and more precise information to follow patients. MRI and FDG PET/CT are useful for assessing inflammation of the disease state. Bone scintigraphy is well suited to reflect changes in bone metabolism during the disease course and after surgery. FDG PET/CT can be available to evaluate the treatment response after surgery [18].

5. Providing useful imaging findings for surgery

Surgical intervention can result in improved outcomes, although conservative treatment has been widely accepted [19–21]. Patients may undergo surgical procedures including debridement, marginal resection, partial resection, en bloc or segmental resection of the mandible, hemi-mandibulectomy, maxillectomy, or excision of the whole mandible, depending on the severity of MRONJ/ARONJ. The success rate of surgery varies from 15% to 100% [19]. Complete excision of sequestered and nonregenerative bone is mandatory to improve the success rate. Total coverage of the viable bone by soft tissue and improvement in symptoms are important to maximize the patient's quality of life. To ensure successful surgical excision of the nonviable bone CT, CBCT, MRI, and bone scintigraphy provide useful information to set a surgical margin. Sclerosing bone and tissues that indicate negative regenerative capacity can be identified by CT and CBCT, and the status of inflammation in the bone and soft tissue can be assessed by MRI. Bone scintigraphy clearly demarcates the bone lesion boundaries. Sufficient blood supply is necessary for bone repair and regeneration. Three-phase bone scintigraphy (vascular phase, blood pool phase) or measurement of the blood flow index may help to assess blood circulation [22,23]. Fluorescence imaging-guided debridement is also reported for MRONJ/ARONJ treatment [24].

6. Predicting disease prognosis

MRONJ/ARONJ often develops after tooth extraction. Advanced periapical and marginal periodontitis is a common cause of extraction. Intraoral X-ray examination and panoramic radiography are the standard imaging techniques for detecting periodontitis. However, it is difficult to predict the future onset of the disease by imaging results among people with antiresorptive therapy because periodontitis is very common. Detection and treatment of dental diseases is important to decrease the possible risk of future development of the osteonecrosis of the jaw. Especially for non-symptomatic intravenous bisphosphonate users, intraoral X-ray examination and panoramic radiography should be routinely performed because of the high occurrence rate of the disease. Close examination of intraoral and panoramic X-ray images also must be studied in oral bisphosphonate users without MRONJ/ARONJ symptoms, because when patients have a history of more than 4 years of bisphosphonate use, the onset rate of the disease rises. Bone scintigraphy is useful for predicting the onset of the disease [25,26,13]. O'Ryan, et al. reported that bone scintigraphy showed positive uptake before the development of BRONJ in 67.5% of patients who had no clinical evidence of osteonecrosis [11]. A parameter of the computer-aided diagnosis system was higher in patients who developed MRONJ/ARONJ than in those who did not [13] (refer to the symposium article, Watanabe et al.).

Radiopharmaceuticals including methylene diphosphonate (MDP) and hydroxymethylene diphosphonate (HMDP), used for bone scintigraphy, have a P–C–P bond in their chemical structures, which is the same basic structure as that in bisphosphonate drugs. These radiotracers are thought to accumulate in identical sites in the bone as bisphosphonate drugs concentrate. When radiotracers show high uptake in the alveolar bone (suspected periodontitis),

bisphosphonate drugs accumulate at high concentrations in the same region, in contrast to the normal uptake region, which may induce higher toxic damage to osteoclasts than in non-high-uptake cases. Radiotracers accumulate increasingly in tooth extraction sites. Bisphosphonate use may be postponed for nonsymptomatic patients with increased uptake in jaws on bone scintigraphy until a decrease to normal uptake levels is observed.

7. Conclusion

Although there are no specific imaging findings for MRONJ/ARONJ, various imaging modalities provide valuable information. Intraoral and panoramic X-ray examinations reveal important findings that relate the risk factors for developing future disease. In stage I, repeat oral and panoramic X-ray examinations are useful for detecting bone changes and for assessing disease progression and response to treatment. In stage II, III, or advanced stage I, CBCT, CT, MRI, and bone scintigraphy can offer additional helpful information to manage MRONJ/ARONJ.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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