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Several issues regarding the diagnostic imaging of medication-related osteonecrosis of the jaw

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ABSTRACT

This review presents an overview of some diagnostic imaging-related issues regarding medication-related osteonecrosis of the jaws (MRONJ), including imaging signs that can predict MRONJ in patients taking antiresorptive drugs, the early imaging features of MRONJ, the relationship between the presence or absence of bone exposure and imaging features, and differences in imaging features by stage, between advanced MRONJ and conventional osteomyelitis, between oncologic and osteoporotic patients with MRONJ, and depending on the type of medication, method of administration, and duration of medication. The early diagnosis of MRONJ can be made by the presence of subtle imaging changes such as thickening of the lamina dura or cortical bone, not by the presence of bone exposure. Most of the imaging features are relatively non-specific, and each patient's clinical findings and history should be referenced. Oral and maxillofacial radiologists and dentists should closely monitor plain radiographs of patients taking antiresorptive/antiangiogenic drugs. ***(Imaging Sci Dent 2020; 50: 273-9)***

KEY WORDS: Bisphosphonate-Associated Osteonecrosis of the Jaw; Radiography; Osteomyelitis; Radiography; Review

Introduction

Since Marx[1] in 2003 published 36 cases of painful bone exposure in the jaw of patients taking bisphosphonates (BPs), similar cases have been reported worldwide, and the condition been referred to using a variety of names, including BP-related osteonecrosis of the jaw (BRONJ), denosumab-related osteonecrosis of the jaw (DRONJ), antiresorptive drug-related osteonecrosis of the jaw (ARONJ), and medication-related osteonecrosis of the jaw (MRONJ).

When discussing MRONJ, it is important to refer to its stage, which is largely determined by bone exposure and infection. The American Association of Oral and Maxillofacial Surgeons (AAOMS) proposed a system for classifying and staging MRONJ in 2014, and the AAOMS system has been generally used subsequently (Table 1).[2] As seen in Table 1, exposed and necrotic bone is the most important feature for the initial diagnosis of MRONJ. However, in the advanced stage, an imaging-based diagnosis is very important as it indicates the absence or presence of bone change as well as its extent. It is known that advanced cases of MRONJ show non-specific imaging features of jaw infection. However, the imaging features that can predict MRONJ or the early-stage imaging features of MRONJ have not yet been clarified. In addition, it is not yet clear whether there is a relationship between bone exposure or stage and imaging features, and little is known regarding differences in imaging features depending on the underlying disease, type of drug, method of administration, and duration of administration.

In this review, the results of studies that investigated the above topics were summarized and the collected results were introduced to help in the diagnosis and treatment of MRONJ and to suggest directions for future research on the imaging-based diagnosis of MRONJ.

Are there any imaging signs that predict MRONJ in patients taking antiresorptive drugs?

Since antiresorptive drugs are known to inhibit osteo-

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Table 1. Staging of medication-related osteonecrosis of the jaw by the American Association of Oral and Maxillofacial Surgeons

Stage	Findings
At risk	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates
Stage 0	No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms
Stage 1	Exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection
Stage 2	Exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage
Stage 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and $\geq$1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor

clast activity, thereby interfering with bone resorption and bone remodeling, it is reasonable to assume that there may be some changes in the jaw bone of patients taking these drugs. In order to confirm whether such subtle bone changes take place, many researchers have investigated the bone thickness, density, and structure of tooth-supporting structures, trabecular bone, and cortical bone.

Changes in tooth-supporting structures: Olutayo et al.[3] reported a case in which a lesion presented as a linear sclerosis of uniform thickness limited to the lamina dura. The patient had intact oral mucosa and did not present with any oral symptoms or discomfort in the sclerotic region. Kubo et al.[4] aimed to clarify which panoramic radiographic features can predict the development of BRONJ. They evaluated thickening of the lamina dura in BRONJ patients, a BP-treated group, and an unmedicated group on panoramic radiographs, and found that thickening of the lamina dura was observed significantly more frequently in the BP-treated groups than in the unmedicated group.

Changes in trabecular bone: Hamada et al.[5] sought to establish a simple method for the early detection of BRONJ using computed tomography (CT). Significant differences in cancellous bone radiodensity on CT were observed among the stage 0 BRONJ, stage 1-3 BRONJ, non-BRONJ, and control groups. However, no significant differences were found between the non-BRONJ area and the controls. Yajima et al.[6] reported no significant difference between the cancellous bone mineral density (BMD) of a BP group and a non-BP group. They measured trabecular BMD using quantitative CT. Barngkgei and Khattab[7] investigated the effects of BP on the jaw bones using multidetector CT. They concluded that BP treatment for osteoporosis for 5 years showed no influence on the trabecular parts of the jaw bones. Barngkgei et al.[8] explored potential jaw bone changes secondary to BP treatment of osteoporosis using digital panoramic and periapical radiography, and found no statistically significant differences in the trabecular bone structure and fractal dimension (FD) after BP use for mean intervals of 4.3 and 5 years. They concluded that dental radiographs should not be considered as a method to monitor BP-induced jaw bone alterations in patients with osteoporosis. Kubo et al.[4] also reported that there was no significant difference in the sclerosis of trabecular bone between a BP-medicated group and an unmedicated group on panoramic radiographs. However, another study reported the contradictory result that FD analysis can predict MRONJ in advance. Demiralp et al.[9] evaluated the trabecular pattern of patients with cancer taking BPs on panoramic images using FD analysis in comparison with healthy subjects. The FD values of the patients with cancer taking BPs were higher than those of controls. FD analysis showed the potential for examining bone structure on panoramic radiographs.

Changes in cortical bone: Many studies have compared the thickness of cortical bone using panoramic radiography, cone-beam CT (CBCT), or CT in patients taking antiresorptive drugs and those not. Most of these studies reported that the cortical bone thickness of patients taking antiresorptive drugs was significantly greater than that of the control group.[5,7,10-13] However, other studies showed no significant difference between the 2 groups,[8,14] and 1 study[4] even reported that the cortical bone thickness of patients taking antiresorptive drugs was significantly smaller than that of the control group. However, because these studies were conducted in patients with osteoporosis, it is not clear whether the findings of thin cortical bone were due to osteoporosis or antiresorptive drugs. When investigating changes in cortical bone thickness, researchers should en-

sure that the analysis focuses on patients with osteoporosis in whom the cortical bone has already become thinner. In the future, it will be necessary to study the effects of anti-resorptive medication on cortical bone thickness both in patients where the cortical bone is normal and in patients with osteoporosis who already have thinner cortical bone. Two other papers studied cortical bone density, but reported different results. Hamada et al.[5] reported that there was no significant difference of cortical bone density between at-risk patients and controls on CT. However, Yajima et al.[6] reported that cortical BMD was significantly higher in the BP group than the control group on quantitative CT.

Although reliable imaging features that can predict MRONJ in advance in patients taking antiresorptive drugs are still unclear, thickening of the lamina dura (Fig. 1) and the mandibular cortex may be clues that predict MRONJ in patients taking antiresorptive drugs.

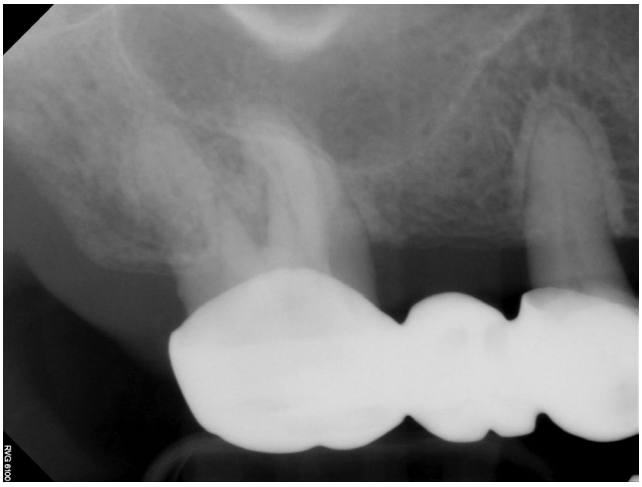

Fig. 1. Bisphosphonate-induced lamina dura thickening of the upper second premolar.

What are the early imaging features of MRONJ?

Since it is difficult to predict MRONJ in advance in patients taking antiresorptive drugs, knowing what bone changes appear in the early stages of MRONJ can help clinicians diagnose this disease promptly and provide effective treatment.

When MRONJ becomes infected, it can be relatively easy to diagnose, as it shows several imaging features seen in osteomyelitis. However, if bone changes can be noticed before infection, an early diagnosis can be made, which is especially helpful if there is no clinical bone exposure.

According to the results of authors who studied bone changes before infection using CT, trabecular bone density was significantly higher in stage 0 MRONJ patients than in the control group or in the at-risk group.[5,11] Their conclusion was that measuring trabecular bone CT radiodensity values has the potential to be a simple quantitative method to detect the early stages of MRONJ. Torres et al.[15] studied trabecular bone changes by fractal analysis on CBCT and reported that MRONJ patients had higher FD values than controls in regions close to the alveolar process.

Studies comparing cortical bone thickness on CBCT or CT showed that cortical bone thickness was greater in stage 0 patients and early MRONJ patients than in the control and at-risk groups.[5,14,16,17]

According to those studies, the early radiologic signs of MRONJ seem to be cortical bone thickening and increased trabecular bone density (Fig. 2).

Is there a relationship between the presence or absence of bone exposure and imaging features?

The current AAOMS definition of MRONJ does not include any diagnostic imaging features; instead, it is essentially based on exposed and necrotic bone or fistulae

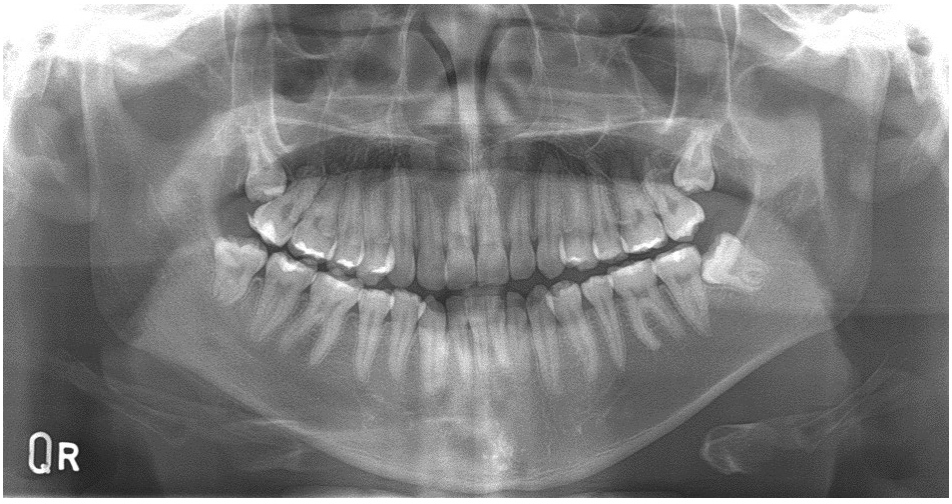

Fig. 2. Trabecular bone density is increased in the lower right mandibular body on a panoramic radiograph.

probing to the bone. Many studies have suggested that the reason for the refractory behavior of MRONJ is that the diagnosis based on bone exposure is too late.[18-22] Nonetheless, many cases of MRONJ without exposed bone have been reported, suggesting the urgent need to include radiographic criteria. Radiographic studies may be of some utility in the detection of early lesions that do not present with clinically exposed bone.[5,21,23,24] However, absence of clinically evident exposed bone is not a sign of low-stage MRONJ, and the presence of exposed bone, pain, and suppuration does not necessarily indicate a more severe stage of disease, since these findings can occur in association with limited extension.[25,26] For reference, it has been reported that the time from first diagnosis to bone exposure was about 1 to 7 months.[21,27]

In conclusion, the presence or absence of bone exposure is not necessarily related with imaging features.

Are there any differences in imaging features by stage?

The staging of MRONJ proposed by the AAOMS, which is currently in widespread use, is based on bone exposure and infection. The question therefore arises: as the stage progresses, will the degree and extent of imaging features increase accordingly?

Şahin et al.[28] reported that signs of focal and diffuse sclerosis, sequestrum, and enhancement of the inferior alveolar canal were observed significantly more frequently in patients with bone exposure than in those without bone exposure. Additionally, no significant difference was detected in FD values among the tested regions, except for the cancellous bone above the mandibular canal on the distal side of the mental foramen.

Wilde et al.,[29] in a study using CBCT study, reported that cancellous bone destruction, cortical bone erosion, sequestration, and osteosclerosis could be seen across all stages, and the prevalence of these findings seemed to decrease with decreasing severity of BRONJ. The occurrence of periosteal new bone formation seemed to start in high-stage BRONJ.

Studies using CT have shown no significant difference between stage and imaging features, except for some features in advanced-stage disease. For instance, no significant differences in cancellous bone CT radiodensity values were found between stage 0 and stage 1-3 BRONJ groups.[5]

The features of diffuse bone disease were identified on CT in all AAOMS stages. Patients classified as stage 0 had diffuse disease on CT, and approximately one-third of patients with CT evidence of diffuse bone disease were misclassified by the AAOMS system as having stage 0 or 1 osteonecrosis. In addition, more than a third of patients with AAOMS stage 2 disease had focal bone disease on CT. These findings led to the conclusion that the AAOMS staging system does not correctly identify the extent of bony disease in patients with osteonecrosis of the jaw.[25] Furthermore, Baba et al.[30] reported that there was no significant correlation between CT findings and the clinical stages of BRONJ.

However, Bagan et al.[31] reported different results; specifically, they found significant differences in sclerosis among the different stages of BRONJ, with the highest values found in stage III. They concluded that the degree of sclerosis increases with the clinical stage of BRONJ, and is correlated with the depth of lucency.

Although the results of several studies were somewhat different, there seems to be no significant relationship between stage and imaging features, except for some features in advanced-stage disease.

Are there any differences in imaging features between advanced MRONJ and conventional osteomyelitis?

One study compared the imaging features of infected MRONJ and conventional osteomyelitis. Shin et al.[32] analyzed the CT imaging features of 133 medication-related osteomyelitis (MROM) patients and 137 medication-unrelated osteomyelitis (MUOM) patients. The MROM group exhibited sequestra and periosteal new bone formation more frequently on CT images than the MUOM group. Other CT imaging features (trabecular defects, cortical defects, sclerosis, and soft tissue changes) showed no significant differences between the MROM and MUOM groups.

Although little research has been done on this subject, sequestrum (Fig. 3) and periosteal new bone formation (Fig. 4) seem to be observed more frequently in advanced MRONJ than in conventional osteomyelitis.

Does MRONJ in oncologic and osteoporotic patients show different imaging features?

The main groups of patients taking drugs that can cause MRONJ are those with osteoporosis and cancer. Thus, differences in imaging features between these 2 groups may be expected.

Walton et al.[33] explored whether differences existed in the clinical and radiographic presentation of oncologic and osteoporotic patients with MRONJ. They retrospectively assessed panoramic radiographs and CBCT examinations of 29 osteoporotic patients and 41 oncologic patients with

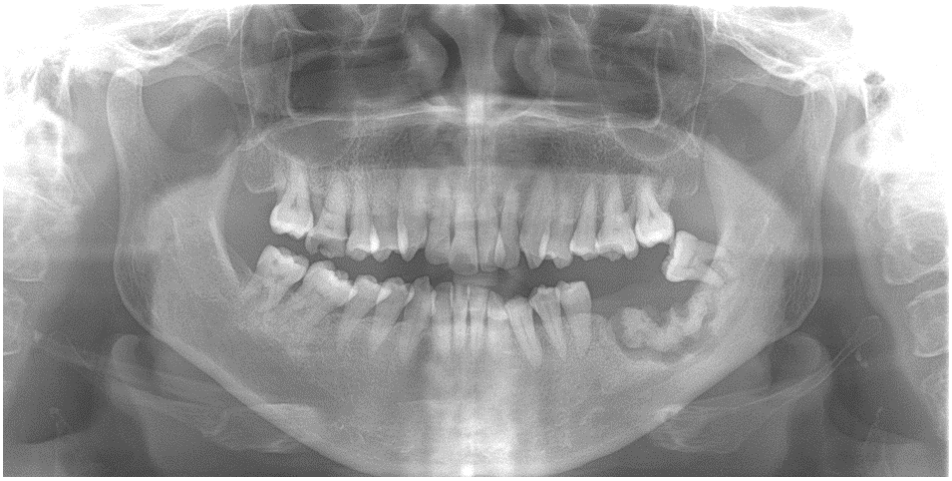

Fig. 3. A large sequestrum is seen in the lower left mandibular body.

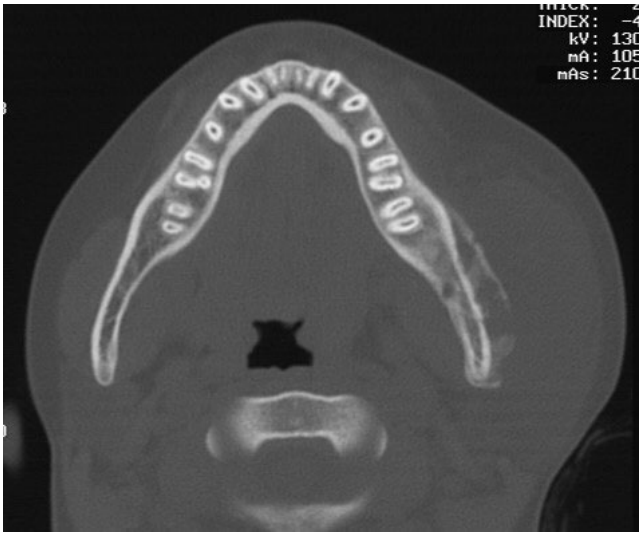

Fig. 4. Massive periosteal new bone formation is seen on the left mandibular ramus on an axial bone-setting computed tomographic image.

MRONJ. Patients with osteoporosis presented more frequently with stage 2 MRONJ, while patients with malignancies presented mostly with stage 1 MRONJ. Most of the patients with minimal radiographic changes were cancer patients, while moderate or more severe bone changes were evenly observed in both groups.

Shin[34] retrospectively compared the panoramic radiographs and CT images of 120 osteoporotic patients and 41 oncologic patients with infected MRONJ. Both groups exhibited the characteristic features of advanced osteomyelitis. The presence and severity of most pathognomonic radiologic features of MROMJ did not differ between the 2 groups, except for sequestrum size and mandibular cortical index (MCI) values. The mean sequestrum size was significantly larger in the patients with cancer than in those with osteoporosis, while on panoramic radiographs, the MCI values were significantly higher in the osteoporosis group.

Although this is difficult to confirm because not many relevant studies have been conducted, MRONJ is often found early in oncologic patients, and once infection occurs, it is difficult to distinguish the 2 groups by imaging features.

Are there any differences in imaging features depending on the type of medication, method of administration, and duration of medication?

Type of medication: Many kinds of drugs can cause MRONJ. The MROMJ-causing agents known to date are BPs, RANKL inhibitors, antiangiogenic agents, and mTOR inhibitors.

Zhang et al.[35] analyzed 17,119 cases of MRONJ and the associated drugs in the US Food and Drug Administration's Adverse Event Reporting System and calculated odds ratio (ORs) for MRONJ based on medication use. The drugs with the highest likelihood of MRONJ were BPs - pamidronate (OR = 498.9), zoledronate (OR = 171.7), and alendronate (OR = 63.6) - whereas denosumab had a lower OR than all the BPs except for etidronate. This then leads to the question of whether there are any differences in imaging features depending on the type of medication. Baba et al.[36] reported that patients with DRONJ showed a large sequestrum and periosteal reaction more frequently than those with BRONJ. In contrast, Heim et al.[37] reported that the bone density values were significantly higher in patients taking BPs than in those taking denosumab. Pichardo et al.[38] reported that in patients with DRONJ, sequestra and lysis of the cortical border of the jaw were significantly

less common than in patients with BRONJ. Subperiosteal bone formation did not differ between the groups.

Method of administration: Patients with BRONJ resulting from intravenous (IV) BP administration showed larger and more frequent buccolingual cortical bone perforations than those with BRONJ resulting from oral BP administration.[36]

Duration of medication: No significant correlation was found between CT imaging features and long/short-term administration.[36] In an investigation of the effect of duration of treatment, no measurements of bone density showed significant differences between the denosumab and BP groups.[37]

Although few studies have investigated these subjects and their results vary, the imaging features may differ depending on the drug, and IV administration is considered to be associated with more severe imaging features.

Conclusion

The early diagnosis of MRONJ can be made by the presence of subtle imaging changes such as thickening of the lamina dura or cortical bone, not the presence of bone exposure. Most of the imaging features are relatively non-specific and the patient's clinical findings and history should be referenced. Oral and maxillofacial radiologists and dentists should closely monitor plain radiographs of patients taking antiresorptive/antiangiogenic drugs. If MRONJ is suspected, advanced imaging modalities such as CBCT or CT should be used to accurately diagnose the presence and extent of the lesion.

Conflicts of Interest: None

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