



## Symposium: Imaging modalities for drug-related osteonecrosis of the jaw (4), CT and MR imaging findings of antiresorptive agent-related osteonecrosis of the jaws/medication-related osteonecrosis of the jaw (secondary publication)<sup>☆</sup>

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### SUMMARY

Generally, CT and MR images of antiresorptive agent-related osteonecrosis of the jaw (ARONJ)/medication-related osteonecrosis of the jaw (MRONJ) show nonspecific findings as seen in active osteomyelitis. However, there are some characteristics as follows; unilateral maxillary sinusitis adjacent to ipsilateral maxillary ARONJ/MRONJ, DRONJ presenting larger sequestrum and periosteal reaction more frequently than BRONJ, BRONJ resulting from intravenous administration of the drug presenting larger and more frequent buccolingual cortical bone perforations than BRONJ from oral administration, and better diagnostic accuracy of extent of perilesional soft tissue inflammation on MR imaging than CT. The CT and MR imaging features of ARONJ/MRONJ are summarized in this report.

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## 1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is defined as a complication associated with antiresorptive medications and antiangiogenic medications by American Association of Oral and Maxillofacial Surgeons (AAOMS) [1]. This entity is corresponded to antiresorptive agent-related osteonecrosis of the jaws (ARONJ) defined by position paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw in Japan [2]. ARONJ/MRONJ includes bisphosphonate-related osteonecrosis of the jaw (BRONJ) and denosumab-related osteonecrosis of the jaw (DRONJ). The MRONJ staging system recommended by AAOMS assigns patients to different stages based only on clinical manifestations not including

radiological evaluation [1]. Nevertheless the clinical examination cannot usually reveal the disease extent and involvement of ARONJ/MRONJ beneath the mucosa [3,4]. In clinical practice, CT and MR imaging are used for the purpose of the evaluation of lesion extents and activity. The CT and MR imaging features of ARONJ/MRONJ are summarized in this report.

## 2. CT

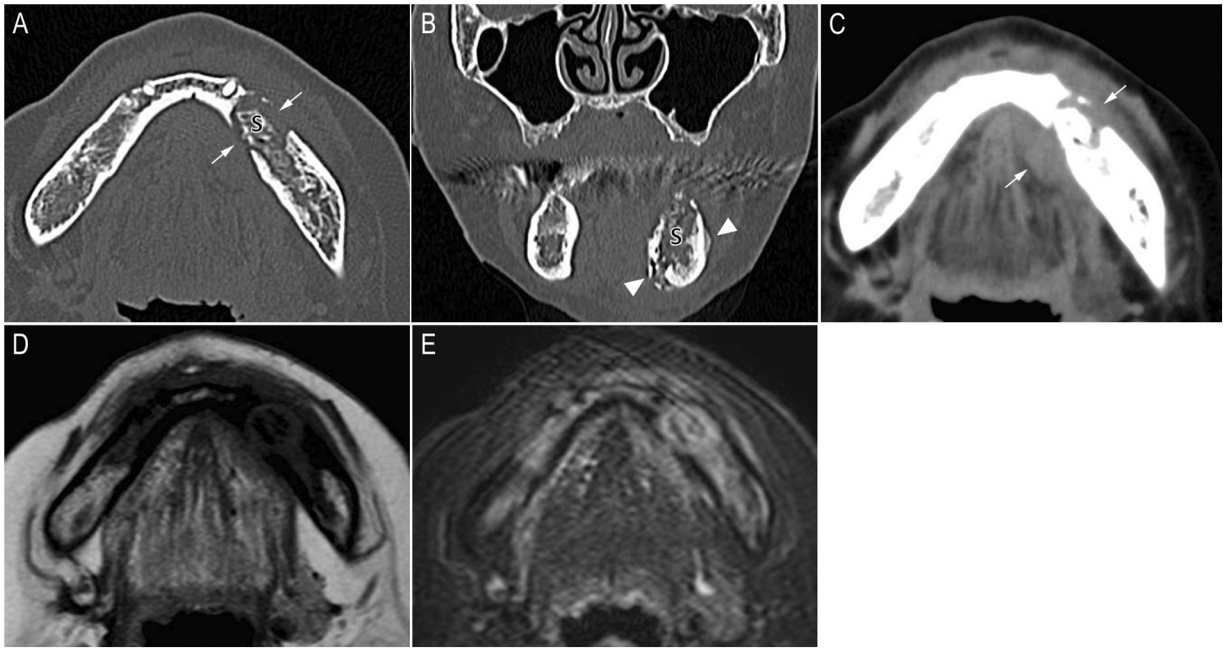
### 2.1. Usefulness

CT is one of the imaging modalities for evaluation of ARONJ/MRONJ. It has a great advantage of morphological evaluation and delineating the extent of this disease [4,5]. CT tends to be chosen secondary to panoramic radiography (PR) in clinical practice. It has been reported that the detectability of ARONJ/MRONJ is 96% in CT compared with 54% in PR [6]. Besides the high sensitivity, CT offers greater information on the extent of bone involvement with better precision than PR for observation of the ARONJ/MRONJ

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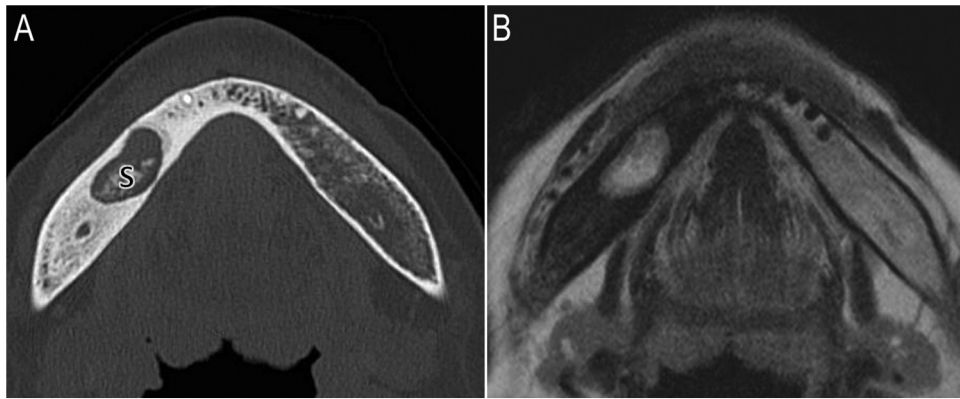
**Fig. 1.** A woman in her 70s diagnosed as BRONJ.

On axial and coronal CT in bone window setting (Fig. 1A, B), sclerotic and lytic lesion with buccal and lingual cortical bone perforation (arrows), periosteal reaction (arrowheads) and sequestrum (S) were detected in the left body of the mandible. On axial CT in soft tissue window setting (Fig. 1C), soft tissue thickening adjacent to the lesion was detected. The lesion was identified as low signal intensity on axial T1-weighted imaging (Fig. 1D) and high signal intensity on STIR MR imaging (Fig. 1E). STIR MR imaging also revealed edematous high signal intensity in adjacent soft tissue which indicates presence of active inflammation.



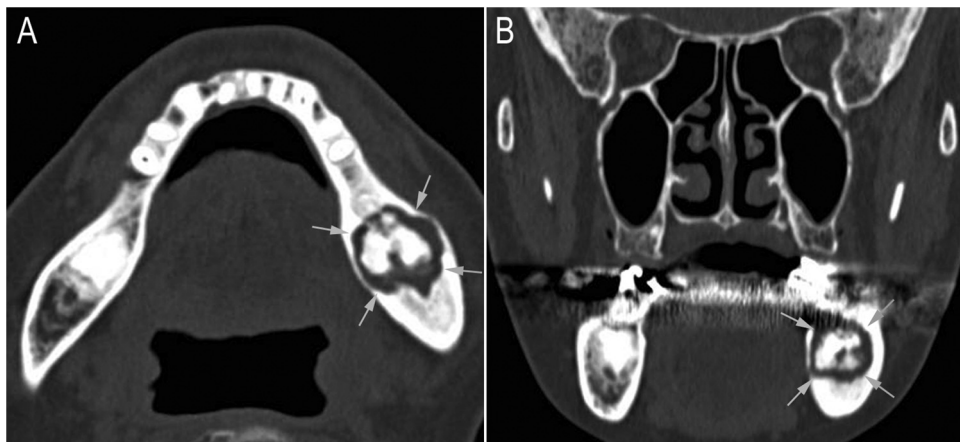
**Fig. 2.** A man in his 60s diagnosed as BRONJ.

On axial CT in bone window setting (Fig. 2A), sclerotic and lytic lesion with buccal and lingual cortical bone perforation (arrows) and periosteal reaction (arrowhead) were detected in the right body of the mandible. On axial CT in soft tissue window setting (Fig. 2B), soft tissue thickening was detected (arrows). The right body of the mandible was low signal intensity on axial T1-weighted imaging (Fig. 2C) and high signal intensity on STIR MR imaging (Fig. 2D). STIR MR imaging also revealed edematous high signal intensity in soft tissue adjacent to the lesion which indicates presence of active inflammation.



**Fig. 3.** A woman in her 60s diagnosed as BRONJ.

On axial CT in bone window setting (Fig. 3A) revealed sclerotic changes with cystic low density lesion in the right body of the mandible. A high density structure with ill-defined margin (S) in the cystic low density area was considered as sequestrum formation. T2-weighted imaging (Fig. 3B) revealed high signal intensity cystic area without detectable sequestrum.



**Fig. 4.** A woman in her 50s diagnosed as BRONJ.

On axial and coronal CT images in bone window setting (Fig. 4A, B), expansive lytic lesion with a dense (arrows) sequestrum resulting in a “bone-within-bone appearance” was detected in the left body of the mandible.

[4,7]. PR serves as the baseline imaging and possibly depicts signs that may serve as predictors for the disease extent including sclerosis, thickening of the lamina dura, prominent mandibular canal, and delayed healing of extraction sockets [7,8]. CT shows higher sensitivity than PR, particularly with regard to soft tissue swelling, periosteal bone reaction, and sequestrum as previously reported [6,8–10].

## 2.2. Location

The mandibular ARONJ/MRONJ was the most frequently presented site (95%) [11]. In the study we reported, the mandibular ARONJ/MRONJ was also detected more frequently than maxillary ARONJ/MRONJ (78.7% vs 21.3%) [12]. When including all mandibular and maxillary ARONJ/MRONJ, posterior parts of the jaws were the more involved more (86%) than anterior [12]. There was no location laterality in ARONJ/MRONJ [12].

## 2.3. CT imaging findings

In general, CT findings of ARONJ/MRONJ are not specific and can also be similar to ordinary osteomyelitis of the jaw. Previous studies reported that the CT evaluation for ARONJ/MRONJ showed lytic and/or sclerotic lesion, periosteal reaction, cortical perforation, periosteal reaction, mandibular fractures, and soft tissue inflamma-



**Fig. 5.** A woman in her 70s diagnosed as BRONJ.

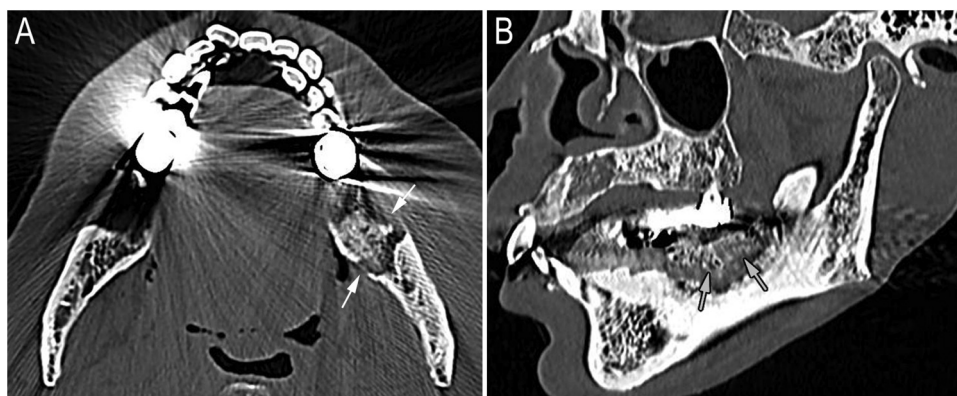
On coronal CT in bone window setting demonstrated sclerotic/lytic changes and sequestrum (arrow) of left maxilla. These findings were compatible with BRONJ. Left unilateral maxillary sinusitis (M) adjacent to the left maxillary BRONJ lesion was detected. This sinusitis was expected to result from ARONJ/MRONJ of maxilla.



**Fig. 6.** A woman in her 60s diagnosed as BRONJ resulting from intravenous bisphosphonate administration. On axial coronal CT in bone window setting (Fig. 6A, B), buccal and lingual cortical bone perforation (arrows) of right mandible were identified.



**Fig. 7.** A woman in her 70s diagnosed as DRONJ. On axial coronal CT in bone window setting (Fig. 7A, B), periosteal reaction (arrows) along both buccal and lingual cortices was detected.



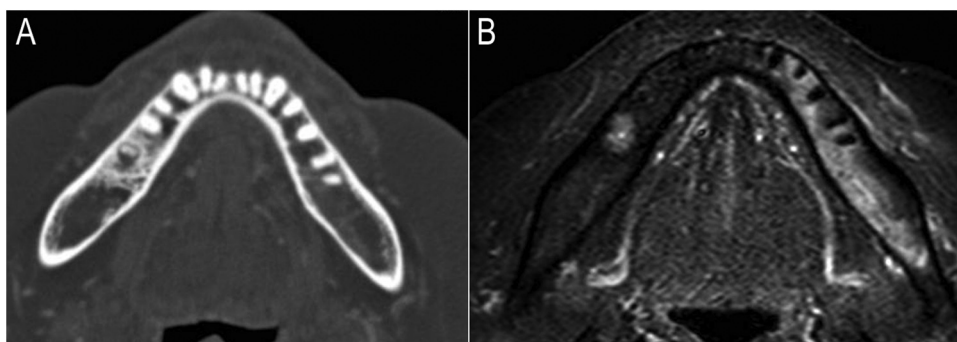
**Fig. 8.** A man in his 70s diagnosed as DRONJ. On axial and parasagittal CT in bone window setting (Fig. 8A, B), relatively large (2.8 cm) sequestrum (arrows) was noted in the left body of mandible.

tion [7,9,10,13,14] (Figs. 1–8). In a previous study, the presence of expansive lytic lesions with a dense sequestrum resulting in a bone-within-bone appearance has been reported as the characteristic image finding [14] (Fig. 4).

It was reported that ARONJ/MRONJ tends to show thicker cortical bones, more sclerotic bone marrow [15–17], and narrower neurovascular canals including nasopalatine and mandibular canal [17] in the studies with assessment using cone beam CT (CBCT).

CT findings of patients with ARONJ/MRONJ in our study [12] are presented in Table 1. The internal texture of ARONJ/MRONJ were mainly mixture of lytic and sclerotic type (61.3%) (Figs. 1–7).

Sequestrum was seen in about a half (52%) of the cases (Figs. 1, 3–6, 8). Swelling of soft tissue including gingiva was detected in relatively high frequency (81.3%) on CT (Figs. 1, 2). Periosteal reactions adjacent to ARONJ/MRONJ were detected in relatively low frequency (17.3%) (Figs. 2, 7). Cortical perforation was detected in more than half of the cases (57.3%) (Figs. 1, 2, 6). The frequency of cortical perforation at both buccal and lingual aspects (51.2%) (Figs. 1, 2, 6) was slightly greater than that of buccal aspects only (39.5%), while that of lingual one was only 9.3%. Bone expansions were detected in one third (33.3%) (Fig. 4). Pathological fractures were uncommon, presenting in only 5.3%.



**Fig. 9.** A woman in her 70s diagnosed as BRONJ.

On axial CT in bone window setting (Fig. 9A), no focal abnormality was detected in the left body of mandible. STIR MR imaging (Fig. 9B) revealed high signal intensity in the left body of mandible, which was compatible with ARONJ/MRONJ.

**Table 1**  
CT Findings of patients with ARONJ/MRONJ (N = 74, 75 jaws).

Location	
Maxilla	16 (21.3)
Mandible	59 (78.7)
Anterior	8 (10.7)
Posterior	63 (84.0)
Whole	4 (5.3)
Right	32 (42.7)
Left	35 (46.7)
Bilateral	8 (10.6)
Internal texture	
Normal	3 (4.0)
Sclerotic	26 (34.7)
Lytic and sclerotic	46 (61.3)
Sequestrum	
Present	39 (52.0)
Absent	36 (48.0)
Sequestrum size	
Large (>20 mm)	6 (15.4)
Small (<20 mm)	33 (84.6)
Periosteal reaction	
Present	11 (14.7)
Absent	64 (85.3)
Cortical perforation	
Present	43 (57.3)
Absent	32 (42.7)
Buccal	17 (39.5)
Lingual	4 (9.3)
Buccal and lingual	22 (51.2)
Soft tissue swelling	
Present	60 (80.0)
Absent	15 (20.0)
Bone expansion	
Present	25 (33.7)
Absent	50 (66.7)
Pathological fracture	
Present	4 (5.3)
Absent	71 (94.7)
Unilateral maxillary sinusitis adjacent to upper MRONJ	
Present	16 (100)
Absent	0

Note. — Data are number of findings, percentages.

ARONJ/MRONJ of the maxilla adjacent to the maxillary sinus is known to show mucoperiosteal thickening, air-fluid levels, and fistula formation [4,10,18]. Similar to those reports, all patients of upper ARONJ/MRONJ (100%) in our study showed maxillary sinusitis on the same side [12].

#### 2.4. Comparison between BRONJ and DRONJ

DRONJ showed larger sequestrum and periosteal reaction more frequently than BRONJ in our study [12] (Figs. 7, 8). Underlying pathophysiological mechanisms of these phenomena are still uncertain. There has been a report that DRONJ tended to be detected in higher stage [19] which may be related to the sequestrum size. Difference of sequestrum formation between DRONJ and BRONJ might be affected by separation speed of bony sequestrum. Considering different periosteal reactions between DRONJ and BRONJ, drug distributions and pharmacokinetics might have some influences on the jaws in relative mechanisms. Although denosumab, compared with bisphosphonate, has significantly greater reductions in bone turnover markers, it does not accumulate on bones. It also has shorter half-life, rapid offset of action and reversibility of its antiresorptive effect, and displays low-cytotoxicity or antiangiogenic profiles [20–23]. In addition, Denosumab primarily inhibits remodeling-based bone formation and permits modeling-based bone formation whereas bisphosphonate tends to cease both pathways [24]. These differences may make DRONJ more prone to advanced separation of necrotic bones from surrounding bony tissue and periosteal expansion. The CT findings of large sequestrum and periosteal reaction would be a characteristic for DRONJ.

#### 2.5. Comparison between BRONJ resulting from oral bisphosphonate administration and intravenous administration

The patients of BRONJ resulting from intravenous bisphosphonate administration showed larger and more frequent buccolingual cortical bone perforations than BRONJ resulting from oral bisphosphonate administration in our study [12] (Fig. 6). Cortical perforation was detected in about half of the cases (47%) in the patients of BRONJ resulting from intravenous bisphosphonate administration. The lesions were mostly presented both buccal and lingual cortical perforation (87%) [12]. Previous studies showed higher incidence rates of BRONJ with intravenous administration than with oral administration [5,11,25,26]. Based on previous reports as well as our study, BRONJ resulting from intravenous bisphosphonate tended to show more progressive disease compared to those with oral bisphosphonate. The CT findings of buccolingual cortical perforation would be a characteristic for BRONJ with intravenous administration.

#### 2.6. Imaging features of BRONJ among different clinical stages

When focusing on relationship between radiological findings and clinical stages, studies in the past describe some correlations. One report said that stage 0 and stage 1 BRONJ patients tended to show osseous sclerosis, stage 2 patients periosteal reaction and cor-

tical bone perforation, and stage 3 patients mandibular fractures in addition to all other findings [7]. It has also been described that early-stage BRONJ may present predominantly osteolytic change with cortical bone destruction [13]. On the other hand, advanced BRONJ may present with increased bone density, periosteal reactions, and bone sequestrations [4,10]. However, according to our study, there were no statistically significant differences among stage 0, 1 and 2, 3 nor between 0–2 and 3 in patients with BRONJ [12]. Compared to our study, the size of the previous studies were rather small and no statistical evaluation was performed [4,10,13]. This discrepancy suggests that there probably are only weak relationship between specific CT findings and BRONJ clinical stage.

### 2.7. Comparison among medications in BRONJ

Hydroxyapatite (HAP) adsorption affinity is different for bisphosphonate medications such as alendronate, zoledronate, risedronate and minodronate [27]. It is likely that differences in HAP adsorption affinity influence imaging findings, however, according to our study, no significant statistical differences of CT findings along different BRONJ medications were observed [12].

### 2.8. Comparison between BRONJ with long-term administration and short-term administration

Although BRONJ was more prevalent in patients who were under longer medication duration [2], there were no statistically significant differences between BRONJ with long-term (more than 4 years) administration and short-term (less than 4 years) administration [12].

## 3. MR imaging

### 3.1. Usefulness

MR imaging provides supportive information a diagnosis and accurate disease extent in ARONJ/MRONJ. Occasionally, MR imaging reveal ARONJ/MRONJ lesion which is undetectable on CT. As well as evaluation for ordinary osteomyelitis of the jaw, MR sequence, such as short-tau inversion recovery (STIR), can assess the activity of the disease by detecting bone marrow edema. Although the detectability of ARONJ/MRONJ in MR imaging is superior to that in PR [28], it was reported that the detectability of ARONJ/MRONJ is 96% in CT superior to 92% in MR imaging [6]. Particularly, the detectability of sequestrum, cortical bone perforation and periosteal reaction on MR imaging is expected to be inferior to that on CT.

### 3.2. MR imaging findings

A few reports stated that MR imaging findings of ARONJ/MRONJ is nonspecific as seen in active osteomyelitis [29,30]. Findings of patients with ARONJ/MRONJ of MR imaging in our study [31] are presented in Table 2. The signal intensity on T2-weighted imaging was mainly low or intermediate (73%) rather than high (27%). The signal intensity on T1-weighted imaging was mostly low (94%) (Figs. 1D, 2C). All ARONJ/MRONJ lesions presented high signal intensity on STIR MR imaging (100%) (Figs. 1E, 2D). Soft tissue swelling was detected in almost all lesions (94%) (Figs. 1, 2). Such MR imaging features are compatible with ordinary osteomyelitis of the jaw. This is consistent with previous reports that early-stage ARONJ/MRONJ may present high signal intensity on T2-weighted imaging and low signal intensity on T1 weighed imaging, and advanced ARONJ/MRONJ may present low signal intensity on T2-weighted imaging and T1 weighed imaging [29]. The detectability of soft tissue swelling is 94% on MR imaging compared with 80% on

**Table 2**  
MR imaging Findings of patients with ARONJ/MRONJ (N = 33, 34 jaws).

T2-weighted imaging	
Low	15 (44)
Intermediate	10 (29)
High	9 (27)
T1-weighted imaging	
Low	32 (94)
Intermediate	2 (6)
STIR	
High	34 (100)
Swelling of soft tissue	
Present	32 (94)
Absent	2 (6)

Note.— Data are number of findings, percentages.

CT [12]. Higher contrast resolution of MR imaging compared with CT might have influences on this result. In our study, there was no significant correlation among MR imaging findings, and method of administration (oral or intravenous), term of administration (shot or long), and clinical stages of BRONJ.

## 4. Conclusions

CT and MR imaging are often need as imaging modalities in assessment of ARONJ/MRONJ. CT is considered as a standard one and evaluation in MR imaging is complementary. CT imaging findings of ARONJ/MRONJ are identified as ordinary osteomyelitis of the jaw. In our retrospective review, DRONJ tends to showed large sequestrum and periosteal reaction and BRONJ resulting from intravenous bisphosphonate administration tends to show buccolingual cortical bone perforations. All patients of upper ARONJ/MRONJ in our study showed maxillary sinusitis on the same side. MR imaging findings of ARONJ/MRONJ is identified as active osteomyelitis of the jaw. Adjacent soft tissue swelling could be evaluate more precisely than CT.

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### Conflict of interest

The authors declare that there is no conflict of interest.

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