Characteristic Image Findings of Medication-related Osteonecrosis of the Jaw Using Computed Tomography

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Running title: Characteristic Image Findings of MRONJ Using CT

Key words: medication-related osteonecrosis of the jaw, computed tomography, the submandibular lymph nodes, the mandibular canal

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Abstract

The purpose of this study was to determine the characteristic image findings indicating bone and soft tissue involvement in patients with medication-related osteonecrosis of the jaw (MRONJ) using computed tomography (CT).

125 patients (35 men, 90 women) with MRONJ were evaluated for jaw pain. The patients, whose mean age was 76.4 ± 10.1 years (range 36 - 94 years), underwent CT examination of the jawbone at our hospital from August 2006 to December 2018 and were included in this study.

CT findings of MRONJ included i) location [maxilla (29.6%), mandible (70.4%); anterior (21.6%), posterior (76.0%), entire of the jaw (2.4%); right (48.8%), left (34.4%), bilateral (16.8%)], ii) internal texture [normal (2.4%), sclerotic (28.8%), lytic and sclerotic (68.8%)], iii) sequestrum (87.2%), iv) periosteal reaction (52.8%), v) bone expansion (60.0%), vi) cortical bone thinning (97.6%), vii) cortical perforation (95.2%) [buccal (35.3%), lingual (6.7%), buccal and lingual (58.0%)], viii) pathological fracture (5.6%), ix) soft tissue swelling (88.0%), x) swelling of the submandibular lymph nodes (51.2%), xi) unilateral maxillary sinusitis adjacent to upper MRONJ (83.8%) and xii) contact with the mandibular canal (93.2%).

CT findings in MRONJ were characterized by bone and soft tissue involvement.

These characteristic CT findings are useful in detecting MRONJ in a clinical situation.

Introduction

Bisphosphonates, have been used in clinical place for about 30 years (1). Marx was the first to report osteonecrosis of the jaw due to administration of BPs in 2003. Since then, many studies have showed that bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a side effect of BP therapy (2, 3).

Recently, many studies have showed that long interval use of bisphosphonates and other antiresorptive medications may cause osteonecrosis of the jaws (medicine-related osteonecrosis of the jaws [MRONJ]) (4, 5). MRONJ has been determined as a complication associated with antiangiogenic medications and antiresorptive medications by american association of oral and maxillofacial surgeons (AAOMS) (6). And, MRONJ is defined by present or past treatment with antiresorptive or antiangiogenic agents, exposed bone or bone that can be probed through an extraoral or intraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks, and no history of radiation therapy to the jaws or obvious metastatic disease to the jaws (6, 7).

The incidence of MRONJ reported in past literature is 0.8% to 18.5% (8). Also, the mandible was the site most frequently influenced by MRONJ (9). Therefore, many previous studies worldwide have been reported about MRONJ (10, 11).

The MRONJ staging system was determined by AAOMS assigns patients to

different stages based on clinical symptoms including few radiological assessments (6). However, the clinical examination cannot usually disclose the disease involvement and extent of MRONJ (12).

Computed tomography (CT) is the imaging methods for assessment of MRONJ. It has a greatest advantage of delineating the extent and morphological assessment of this disease. CT affords greater information on the extent of bone involvement with precision for detection of the MRONJ (13). And, as previously reported that CT shows high sensitivity, particularly with regard to swelling of soft tissue and sequestrum (14, 15). However, few studies have used CT to systematically evaluate MRONJ (4, 16). Thus, the purpose of this study was to determine the characteristic image findings indicating bone and soft tissue involvement in patients with MRONJ using CT.

Materials and Methods

Subjects

The university ethics committee approved this study (EC19-009). Altogether, 125 patients (35 men, 90 women) were examined in this retrospective study. The patients (mean age 76.4 ± 10.1 years, range 36 - 94 years) complained of jaw pain and underwent CT examination of the jawbone at our hospital from August 2006 to December 2018. They comprised the study groups in this study. They all had been diagnosed with MRONJ according to established diagnostic criteria (e.g., AAOMS criteria).

Image Assessment

CT imaging was performed with a 64-multi-detector row CT (MDCT) system (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan). All patients were scanned using the routine clinical protocol for osteomyelitis examination at our hospital as follows: tube voltage, 120 kV; tube current, 100 mA; field of view, 240 × 240 mm; helical pitch, 41. The protocol consisted of axial acquisition (0.50 mm) with axial (3.0 mm), coronal (3.0 mm) and sagittal and oblique (1.0mm) on multi-planar reconstruction (MPR) images. The MDCT images were interpreted using a medical liquid crystal display monitor (RadiForce G31; Eizo Nanao, Ishikawa, Japan).

The following characteristics of the MRONJ were evaluated on CT images: location, internal texture, sequestrum, periosteal reaction, bone expansion, cortical bone thinning, cortical perforation, pathological fracture, soft tissue swelling, swelling of the submandibular lymph nodes, unilateral maxillary sinusitis adjacent to upper MRONJ and contact with the mandibular canal.

The scoring options were presence or absence. Swelling of the submandibular lymph nodes was identified when the glands were larger than the maximum diameter ($>$10.0 mm) (17). All images were independently evaluated by 2 specialists in oral radiology; any differences were resolved by forced consensus.

Results

Table 1 shows characteristic CT findings of MRONJ: i) location [maxilla (29.6%), mandible (70.4%); anterior (21.6%), posterior (76.0%), entire of the jaw (2.4%); right (48.8%), left (34.4%), bilateral (16.8%)], ii) internal texture [normal (2.4%), sclerotic (28.8%), lytic and sclerotic (68.8%)], iii) sequestrum (87.2%) (Figs.1, 3), iv) periosteal reaction (52.8%) (Figs.1, 2), v) bone expansion (60.0%) (Fig. 2), vi) cortical bone thinning (97.6%), vii) cortical perforation (95.2%) [buccal (35.3%), lingual (6.7%), buccal and lingual (58.0%)] (Figs.1, 3), viii) pathological fracture (5.6%), ix) soft tissue swelling (88.0%) (Figs. 2, 3), x) swelling of the submandibular lymph nodes (51.2%) (Fig.3), xi) unilateral maxillary sinusitis adjacent to upper MRONJ (83.8%) and xii) contact with the mandibular canal (93.2%) (Figs. 1, 3).

Discussion

The characteristic CT findings of MRONJ in the present study included location, internal texture, sequestrum, periosteal reaction, bone expansion, cortical bone thinning, cortical perforation, pathological fracture, soft tissue swelling, swelling of the submandibular lymph nodes, unilateral maxillary sinusitis adjacent to upper MRONJ and contact with the mandibular canal.

CT is the optimal imaging modalities for assessment of MRONJ. CT is very useful in evaluating both hard and soft tissue changes of MRONJ (18). And, pantomography is one of the imaging modalities most commonly used by dentists and oral and maxillofacial surgeons (4, 5). However, its assessment is lower than that of CT, with regard to swelling of soft tissue and sequestrum as previously reported (10, 11).

Regarding the location involved in MRONJ in this study, the mandible was detected more than maxilla. This result was consistent with past studies that mandible was the most presented site (9). MRONJ was observed in 76% of the posterior part of the maxilla and mandible. And, there was no location laterality in MRONJ. Previous studies reported that the CT assessment for MRONJ showed periosteal reaction, pathological fracture, etc (14, 15). In this study, the internal texture of MRONJ were mainly lytic and sclerotic type. Sequestrum was detected in high frequency on CT. Periosteal reactions

adjacent to MRONJ were seen in approximately 52.8% of the cases. Bone expansions were detected in more than half of the cases. Cortical bone thinning was detected in high frequency on CT. Cortical perforation was detected in high frequency on CT. The frequency of cortical perforation at both buccal and lingual aspects was greater than that of buccal aspects 35.3%, while that of lingual aspects was only 6.7%. Pathological fractures were rare, presenting in only 5.6%. These result was consistent with past studies that internal texture, sequestrum, periosteal reaction, bone expansion, cortical bone thinning, cortical perforation and pathological fracture. In this study, swelling of soft tissue was detected in high frequency on CT. And, studies have reported about relationship with soft tissue in the past (14, 15). However, no studies have used CT to evaluate the relationship between MRONJ and submandibular lymph nodes. In this study, swelling of the submandibular lymph nodes was detected in a half of MRONJ. This study is the first paper to mention its swelling of the submandibular lymph nodes. MRONJ of the maxilla adjacent to the maxillary sinus is known to occur mucoperiosteal thickening and fistula formation. Similar to those studies, the patients of upper MRONJ in this study showed maxillary sinusitis on the same side (16). When MRONJ contact the mandibular canal, previous studies have shown that it needed attention as it can cause symptoms such as inferior alveolar nerve palsy (19). However, no studies have

used CT to evaluate the relationship between MRONJ and the mandibular canal. In this study, the patients of lower MRONJ showed contact with the mandibular canal on the same side. And, this study showed contact between the most patients of lower MRONJ and the mandibular canal. This study is the first paper to mention its contact with the mandibular canal.

In conclusion, CT findings of MRONJ were characterized by bone and soft tissue involvement, including location, internal texture, sequestrum, periosteal reaction, bone expansion, cortical bone thinning, cortical perforation, pathological fracture, soft tissue swelling, swelling of the submandibular lymph nodes, unilateral maxillary sinusitis adjacent to upper MRONJ and contact with the mandibular canal. Our findings suggest that these characteristic CT findings are useful aid for assessing MRONJ in a clinical situation.

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Conflict of interest:

There are no conflicts of interest for this study.

References

1. Kunchur R, Need A, Hughes T, Goss A: Clinical Investigation of C-terminal Cross-linking Telopeptide Test in Prevention and Management of Bisphosphonate-associated Osteonecrosis of the Jaws. J Oral Maxillofac Surg, 67: 1167-1173, 2009.
2. Nomura T, Shibahara T, Uchiyama T, Yamamoto N, Shibui T, Yakushiji T, Watanabe A, Muramatsu K, Ogane S, Murayama M, Sekine R, Nakata E, Fujimoto Y: Bisphosphonate-related Osteonecrosis of Jaws (BRONJ) in Japanese Population: A Case Series of 13 Patients at our Clinic. Bull Tokyo Dent Coll, 54: 117-125, 2013.
3. Marx RE: Pamidronate (Aredia) and Zoledronate (Zometa) Induced Avascular Necrosis of the Jaws: A Growing Epidemic. J Oral Maxillofac Surg, 61: 1115-1117, 2003.
4. Guo Y, Wang D, Wang Y, Peng X, Guo C: Imaging Features of Medicine-related Osteonecrosis of the Jaws: Comparison between Panoramic Radiography and Computed Tomography. Oral Surg Oral Med Oral Pathol Oral Radiol, 122: e69-76, 2016.
5. Klingelhöffer C, Klingelhöffer M, Müller S, Ettl T, Wahlmann U: Can Dental Panoramic Radiographic Findings Serve as Indicators for the Development of

Medication-related Osteonecrosis of the Jaw? Dentomaxillofac Radiol, 45: 20160065, 2016.

6. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, ORyan F; American Association of Oral and Maxillofacial Surgeons: American Association of Oral and Maxillofacial Surgeons Position Paper on Medication-related Osteonecrosis of the Jaw — 2014 Update. J Oral Maxillofac Surg, 72: 1938-1956, 2014.
7. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL: Osteonecrosis of the Jaws Associated with the Use of Bisphosphonates: A Review of 63 Cases. J Oral Maxillofac Surg, 62: 527-534, 2004.
8. Uyanne J, Calhoun CC, Le AD: Antiresorptive Drug-related Osteonecrosis of the Jaw. Dent Clin North Am, 58: 369-384, 2014.
9. Huang YF, Chang CT, Muo CH, Tsai CH, Shen YF, Wu CZ: Impact of Bisphosphonate-related Osteonecrosis of the Jaw on Osteoporotic Patients after Dental Extraction: a Population-based Cohort Study. PLoS One, 10: e0120756, 2015.
10. Mizohata K, Sano T, Oishi K, Morita S: Successful Treatment of MRONJ in the Palatal Torus with Teriparatide. J Oral Maxillofac Surg, 30: 500-503, 2018.

11. Matsui A, Kurihara J, Morishima H, Suzuki H, Sato S, Yamauchi K, Takahashi T: Medication Related Osteonecrosis of the Jaw (MRONJ): A Retrospective Survey of a Series of Patients Treated According to the AAOMS Guidelines. J Oral Maxillofac Surg, 27: 757-763, 2015.

12. Wilde F, Heufelder M, Lorenz K, Liese S, Liese J, Helmrich J, Schramm A, Hemprich A, Hirsch E, Winter K: Prevalence of Cone Beam Computed Tomography Imaging Findings According to the Clinical Stage of Bisphosphonate-related Osteonecrosis of the Jaw. Oral Surg Oral Med Oral Pathol Oral Radiol, 114: 804-811, 2012.

13. Bedogni A, Blandamura S, Lokmic Z, Palumbo C, Ragazzo M, Ferrari F, Tregnaghi A, Pietrogrande F, Procopio O, Saia G, Ferretti M, Bedogni G, Chiarini L, Ferronato G, Ninfo V, Lo Russo L, Lo Muzio L, Nocini PF: Biphosphonate-associated Jawbone Osteonecrosis: A Correlation between Imaging Techniques and Histopathology. Oral Surg Oral Med Oral Pathol Oral Endod, 105:358-364, 2008.

14. Phal PM, Myall RW, Assael LA, Weissman JL: Imaging Findings of Bisphosphonate-associated Osteonecrosis of the Jaws. AJNR Am J Neuroradiol, 28: 1139-1145, 2007.

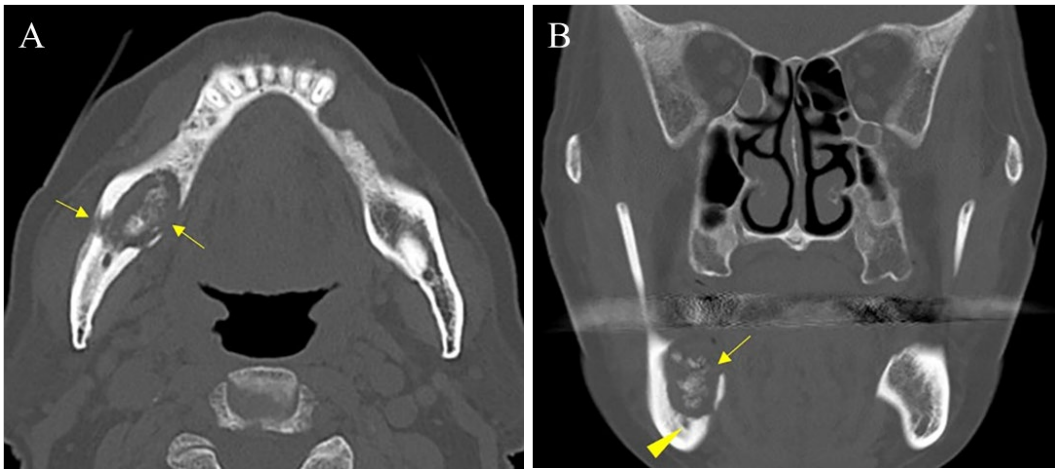
15. Bisdas S, Chambron Pinho N, Smolarz A, Sader R, Vogl TJ, Mack MG:

Biphosphonate-induced Osteonecrosis of the Jaws: CT and MRI Spectrum of Findings in 32 Patients. Clin Radiol, 63: 71-77, 2008.

16. Baba A, Goto TK, Ojiri H, Takagiwa M, Hiraga C, Okamura M, Hasegawa S, Okuyama Y, Ogino N, Yamauchi H, Kobashi Y, Yamazoe S, Munetomo Y, Mogami T, Nomura T: CT Imaging Features of Antiresorptive Agent-related Osteonecrosis of the Jaw/ Medication-related Osteonecrosis of the Jaw. Dentomaxillofac Radiol, 47: 20170323, 2018.
17. Giacomini CP, Jeffrey RB, Shin LK: Ultrasonographic Evaluation of Malignant and Normal Cervical Lymph Nodes. Semin Ultrasound CT MR, 4: 236-247, 2013.
18. Stockmann P, Hinkmann FM, Lell MM, Fenner M, Vairaktaris E, Neukam FW, Nkenke E: Panoramic Radiograph, Computed Tomography or Magnetic Resonance Imaging: Which Imaging Technique Should Be Preferred in Bisphosphonate-associated Osteonecrosis of the Jaw? A Prospective Clinical Study. Clin Oral Investig, 14: 311-317, 2010.
19. Poort LJ, van Neck JW, van der Wal KG: Sensory Testing of Inferior Alveolar Nerve Injuries: a Review of Methods Used in Prospective Studies. J Oral Maxillofac Surg, 67: 292-300, 2009.

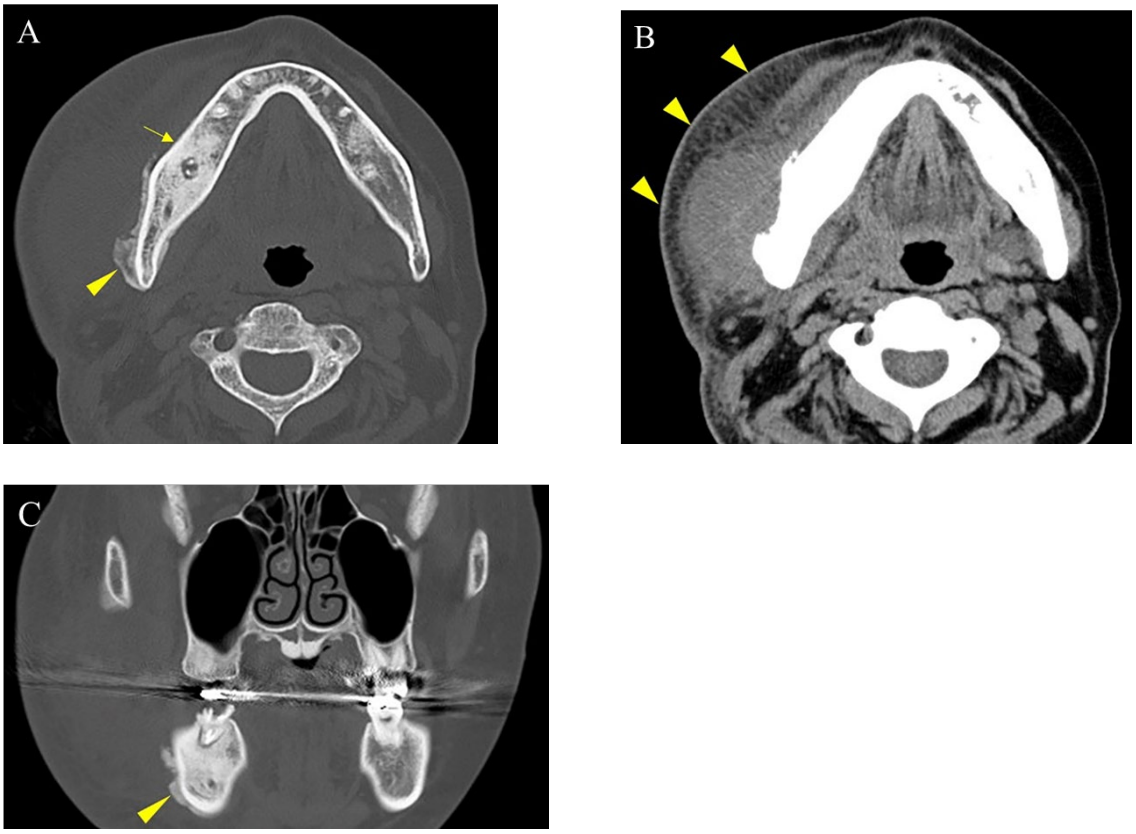
Figure Legends

Fig. 1 MRONJ in a 76-year-old man.



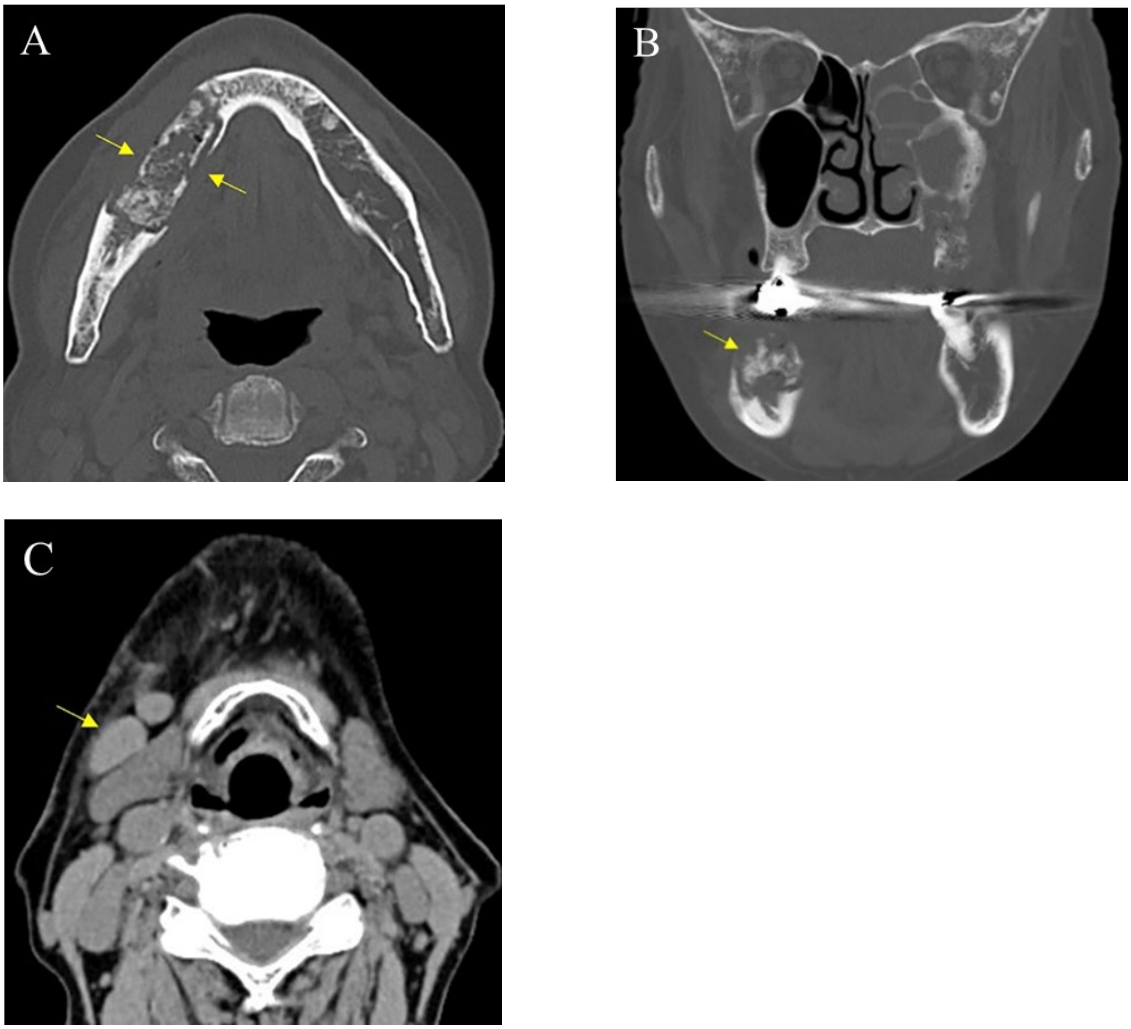
On axial CT in bone window setting (Fig. 1A), sclerotic and lytic lesion with buccal and lingual cortical bone perforation, periosteal reaction and sequestrum were detected in the right body of the mandible (arrows). On coronal CT in bone window setting (Fig. 1B), sequestrum (arrow) and contact with the mandibular canal (arrowhead) were found in the right body of the mandible.

Fig. 2 MRONJ in a 37-year-old woman.



On axial and coronal CT in bone window setting (Figs. 2A, C), sclerotic lesion, bone expansion (arrow) and periosteal reaction (arrowhead) were confirmed by the right body of the mandible. On axial CT in soft tissue window setting (Fig. 2B), soft tissue swelling (arrowheads) adjacent to the lesion was indicated.

Fig. 3 MRONJ in a 78-year-old man.



On axial CT in bone window setting (Fig. 3A), sclerotic and lytic lesion with buccal and lingual cortical bone perforation and sequestrum were showed in the right body of the mandible (arrows). On coronal CT in bone window setting (Fig. 3B), sequestrum and contact with the mandibular canal (arrow) were evinced the right body of the mandible. On axial CT in soft tissue window setting (Fig. 3C), swelling of the submandibular lymph nodes (arrow) was exhibited.

Table 1 CT findings of medicine-related osteonecrosis of the jaws (125 cases)

		No.	%
Location	Maxilla	37	29.6
	Mandible	88	70.4
	Anterior	27	21.6
	Maxilla	8	29.6
	Mandible	19	70.4
	Posterior	95	76.0
	Maxilla	28	29.5
	Mandible	67	70.5
	Entire of the jaw	3	2.4
	Maxilla	1	33.3
	Mandible	2	66.7
	Right	61	48.8
	Maxilla	14	23.0
	Mandible	47	77.0
	Left	43	34.4
	Maxilla	20	46.5
	Mandible	23	53.5
	Bilateral	21	16.8
	Maxilla	3	14.3
	Mandible	18	85.7
Internal texture	Normal	3	2.4
	Sclerotic	36	28.8
	Lytic and sclerotic	86	68.8
Sequestrum		109	87.2
Periosteal reaction		66	52.8
Bone expansion		75	60.0
Cortical bone thinning		122	97.6

Cortical perforation		119	95.2
	Buccal	42	35.3
	Lingual	8	6.7
	Buccal and lingual	69	58.0
Pathological fracture		7	5.6
Soft tissue swelling		110	88.0
Swelling of the submandibular lymph nodes		64	51.2
Unilateral maxillary sinusitis adjacent to upper MRONJ		31	83.8
	Right	11	35.5
	Left	17	54.8
	Bilateral	3	9.7
Contact with the mandibular canal		82	93.2