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ORIGINAL ARTICLE

Periosteal reaction of medication-related osteonecrosis of the jaw (MRONJ): clinical significance and changes during conservative therapy

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Abstract

Purpose We previously reported that the periosteal reaction (PR) in medication-related osteonecrosis of the jaw (MRONJ) is a poor prognostic factor in surgical cases, but it is not clear how PR changes during conservative therapy. The purpose of this retrospective study was to compare computed tomography (CT) findings at the first visit and during follow-up visits in MRONJ patients subjected to conservative therapy and to investigate factors associated with the exacerbation of PR during conservative therapy.

Methods Sixteen patients with MRONJ of the lower jaw who underwent conservative therapy and experienced a PR on CT images at the first visit and underwent CT examination again after 6 months or more were enrolled in the study. Clinical features and CT findings (extent of osteolytic lesion, extent of PR, type of PR, and changes during conservative treatment) were investigated.

Results On the second CT scan, the osteolytic lesion improved in 4 patients, had not changed in 5, and deteriorated in 7, whereas the PR improved in 5 patients, had not changed in 4, and deteriorated in 7 patients. PR was significantly deteriorated in patients who continued to receive antiresorptive agents during conservative treatment and in patients with deteriorated osteolytic lesions.

Conclusion PR in MRONJ often expands during conservative therapy and the PR type progresses from the attached type to the gap type, and the irregular type, but discontinuation of antiresorptive agent may improve PR as well as osteolytic lesions.

Keywords Medication-related osteonecrosis of the jaw (MRONJ) · Periosteal reaction · Osteolytic lesion · Conservative treatment · Computed tomography

Introduction

Antiresorptive agents such as bisphosphonates and denosumab are widely used to prevent osteoporotic fractures and for treating skeletal-related events associated with bone metastasis of malignant tumors or multiple myeloma. A serious late-onset adverse event of these drugs is medication-related osteonecrosis of the jaw (MRONJ), which is a cause of marked deterioration in the patient's quality of life. There are conservative and surgical treatments for MRONJ available, but in recent years, many reports have recommended surgical treatment [1–9]. The MASCC/ISOO/ASCO Clinical Practice Guideline for MRONJ [10] describes conservative measures, which comprise antimicrobial mouth rinses, antibiotics if clinically indicated, and conservative surgical interventions, as the initial approach to the treatment of MRONJ. Aggressive surgical interventions (e.g., mucosal flap

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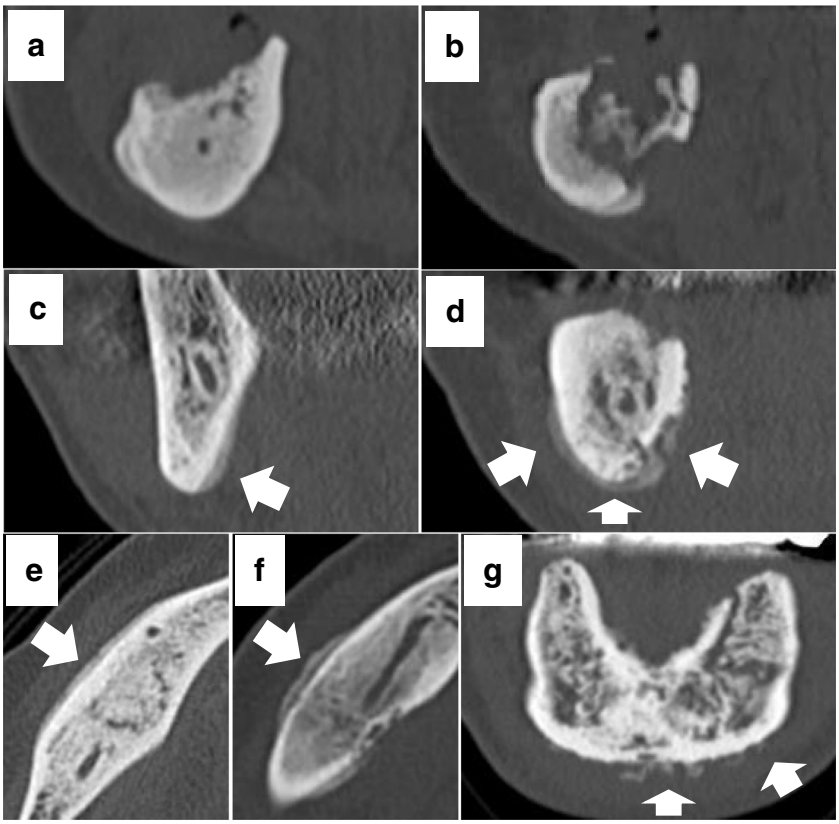

Fig. 1 Findings of the first CT image. **a** Localized type of osteolytic lesion in which osteolysis is localized above the mandibular canal. **b** Extended type of osteolytic lesion in which osteolysis includes the mandibular canal. **c** Localized type of PR in which PR is present on the buccal or lingual side of the mandible only. **d** Extended type of PR in which PR is found on both the buccal and lingual sides beyond the lower margin of the mandible. **e** Attached type of PR defined as new bone formed parallel to the bone surface without any gap between the mandible and new bone. **f** Gap type of PR in which new bone is formed parallel to the bone surface with a gap between the mandible and new bone. **g** Irregular type of PR in which PR develops an irregular-shaped new bone (PR, periosteal reaction)

elevation, block resection of necrotic bone, or soft tissue closure) may be used if MRONJ results in persistent symptoms or affects function despite initial conservative treatment. We previously reported that surgical treatment was superior to conservative treatment in 361 patients with MRONJ using propensity score matching analysis [11]. However, some patients are not cured by surgical treatment alone. We investigated the factors that influence the cure rate of surgical treatment and found that treatment outcomes were poor in cancer patients who received high-dose antiresorptive agents and in patients with evidence of periosteal reaction (PR) on preoperative computed tomography (CT) [12, 13].

PR is often found on CT images in MRONJ, but the details and clinical significance have not been clarified. We recently reported that the PR of MRONJ can be classified into three types according to the morphology on CT. In type 1 PR (attached type), new bone is formed parallel along the mandible, and there is no gap between them. In type 2 (gap type), new bone is formed parallel to the mandible with a gap between them. Type 3 PR (irregular type) develops an irregularly shaped new bone. Patients with grade 1 PRs are expected to be cured even with residual PRs after surgery, but those with grade 3 PR do not heal with residual PRs on surgery [14]. However, the clinical significance of PR in cases of conservative therapy and how it changes over time are unknown. The purpose of this retrospective study was to compare CT findings at the first visit and during follow-up in MRONJ patients who received conservative therapy and to examine factors related to the advancement of PR during conservative therapy.

Materials and methods

Patients

A total of 330 patients with MRONJ were treated at the Kansai Medical University Hospital or Nagasaki University Hospital between 2011 and 2019. Among them, 71 patients received conservative treatment such as oral hygiene guidance, gargling with antibacterial mouthwash, local lavage, and administration of oral antibiotics. The remaining 259 patients underwent surgery. The subjects of this study consisted of 16 of the 71 patients who with MRONJ in the lower jaw, and who underwent conservative therapy, with evidence of a PR on CT images at the first visit, and had undergone CT again after 6 months or more (6–15 months, mean; 9.0 months).

Clinical factors examined

The variables examined were as follows: sex, age, primary disease (osteoporosis/malignant tumor), type of antiresorptive agent (bisphosphonate/denosumab), MRONJ stage according to the AAOMS Position Paper [15], administration of

Table 1 Patient characteristics

Factor		Number of patients/ mean ± SD
Sex	Male	8
	Female	8
Age (years)		76.1 ± 12.6
Primary disease	Osteoporosis	3
	Malignant tumor	13
Sort of antiresorptive agent	Bisphosphonate	9
	Denosumab	4
	Both	3
MRONJ stage	Stage 1	1
	Stage 2	9
	Stage 3	6
Corticosteroid	(−)	14
	(+)	2
Diabetes	(−)	13
	(+)	3
Leukocyte (/μL)		6060 ± 1068
Albumin (g/dL)		3.84 ± 0.480
Creatinine (mg/dL)		1.13 ± 0.585
Duration of administration of antiresorptive agent	< 4 years	11
	≥ 4 years	5

corticosteroids, history of diabetes, minimum leukocyte count, lowest serum albumin, and highest serum creatinine during conservative treatment, duration of administration of antiresorptive agent (< 4 years/≥ 4 years), and drug holiday during treatment.

CT findings

On the first CT image, the extent of the osteolytic lesion, the extent of PR, and the type of PR were determined. The assessment of the CT image was decided by consultation between two dental radiologists and three oral surgeons. The extent of osteolytic lesions was divided into two categories: the localized type in which osteolytic lesions are localized above the mandibular canal and the extended type in which osteolytic lesions include the mandibular canal. The extent of the PR was also divided into two types: the localized type in which the PR is present on the buccal or lingual side of the mandible but does not include the lower edge of the mandible and the extended type in which the PR is present on both the buccal and lingual sides beyond the lower margin of the mandible. The type of PR was classified into three categories, as reported previously [14]: type 1 PR (attached type) defined as new bone formed parallel to the bone surface without any gap between the mandible and new bone. Type 2 PR (gap type) is defined as new bone formed parallel to the bone surface with a gap between the mandible and new bone. Type 3 PR (irregular type) develops an irregularly shaped new bone (Fig. 1). Cases with both type 1 and type 2 were classified as type 2, and cases with type 3 and other types were classified as type 3.

In CT images taken again after 6 months or more, changes in osteolytic lesions and PR were examined. Regarding osteolytic lesions, those with a reduced range, or progression with separation of sequester were classified as "improved," those with no change were classified as "no change," and those with an expanded range were classified as "deteriorated." Changes in the PR were classified into three categories: "Improvement," defined a reduction in PR range, or as changes in PR type from the irregular type to the gap/attached type, or from the gap type to the attached type; "No change," indicating that the range or type did not change; and "Deterioration," defined an expansion in range, or when an attached type changed to a gap/irregular type, or a gap type changed to an irregular type.

Statistical analysis

All statistical analyses were performed using SPSS software (version 26.0; Japan IBM Co., Ltd., Tokyo, Japan). The correlations between each variable and changes in PR were analyzed using Fisher's exact test and one-way ANOVA. In all analyses, two-tailed p values < 0.05 were considered statistically significant.

Ethics

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research involving Human Subjects by the Ministry of Health, Labor and Welfare of Japan. Ethical approval was obtained from the Institutional Review Board (IRB) of Nagasaki University Hospital and the Kansai Medical University Hospital. Japanese law does not require individual informed consent from participants in non-invasive observational trials, such as the present study. Therefore, the need for informed consent was waived. As this was a retrospective study, identifiable information regarding patients was removed, and the research plan was published on the homepages of the participating hospital websites, along with an opt-out option for study participation in accordance with IRB instructions.

Results

Patient characteristics

Demographic features of the 16 patients enrolled in the study are summarized in Table 1. Eight patients were male and 8

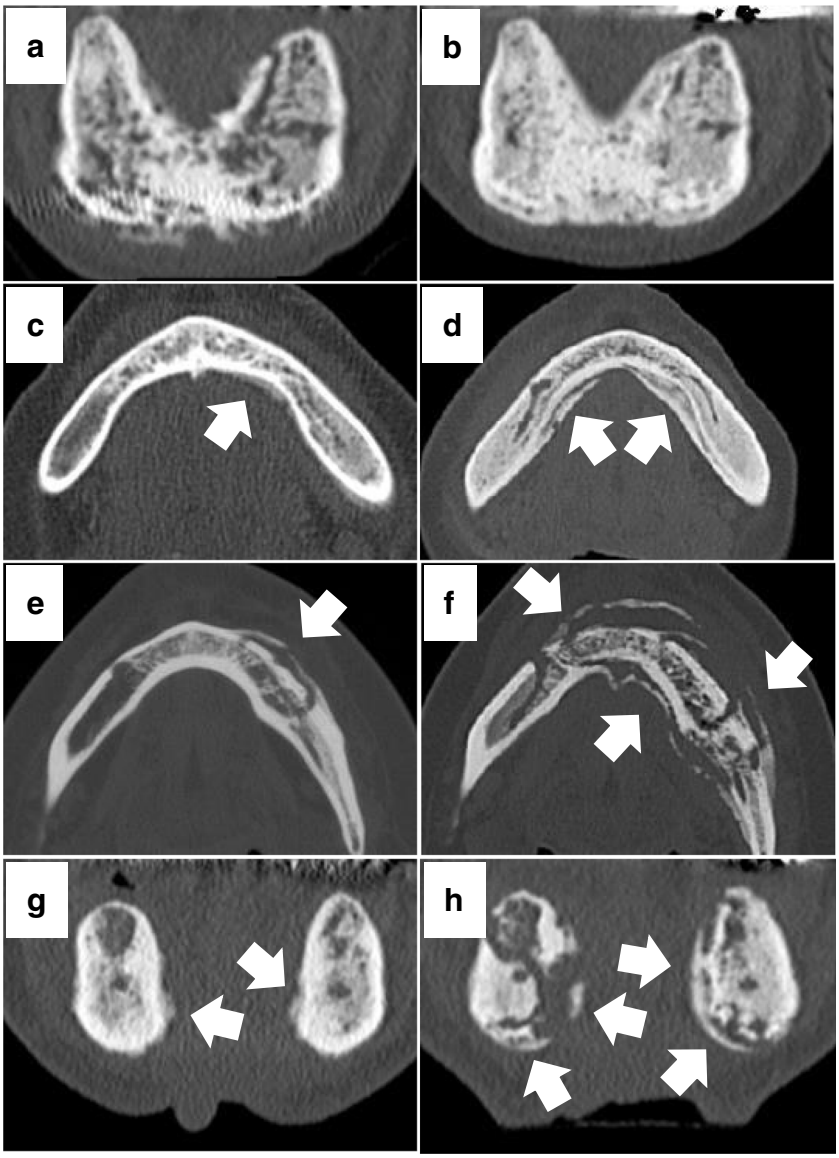

Fig. 2 Changes in PR during conservative treatment **a** A 90-year-old female with osteoporosis. Irregular type PR and osteolytic lesion is observed at the first CT. **b** Ossification is progressing in both the osteolytic lesion and PR 12 months later. **c** A 75-year-old female with osteoporosis. Localized and attached type PR is found. **d** The range of PR is expanded and the type is changed to gap type. **e** A 52-year-old female with breast cancer. Localized and gap type PR is observed. **f** PR is extremely expanded as well as progression of osteolytic lesion. **g** A 88-year-old male with prostate cancer. Attached type PR is observed. **h** The extent of PR is expanded and type is changed to gap type. Osteolytic lesion also increases (PR, periosteal reaction)

were female, with an average age of 76.1 ± 12.6 years. The primary disease was osteoporosis in 3 patients and malignant tumor in 13 patients. Antiresorptive agents were administered for more than 4 years in 5 patients.

Changes in PR during conservative treatment

In the first CT scan, the extent of osteolysis was localized in 9 cases and was extended in 7 cases, and the extent of PR was localized in 8 cases and extended in 8 cases. The type of PR was the attached type in 7 cases, the gap type in 5 cases, and the irregular type in 4 cases. During conservative treatment, the antiresorptive agent was stopped in 11 patients, while it was continued in 5. On the second CT scan, the osteolytic lesion improved in 4 patients, had not changed in 5, and had deteriorated in 7, whereas the PR improved in 5 patients, did not change in 4, and deteriorated in 7 patients (Fig. 2).

Factors related to worsening PR

Table 2 shows the correlation between each variable and worsening PR by univariate analysis. PR significantly worsened in patients who continued to receive antiresorptive agents during conservative treatment ($p = 0.036$) and in patients with deteriorated osteolytic lesions ($p = 0.035$). PR tended to be worse in younger patients, in patients with malignant tumors than in those with osteoporosis, or in patients receiving denosumab rather than bisphosphonate, though the difference was not statistically significant. Multivariate analysis could not be performed because of the small number of cases.

Table 2 Factors related to worsening of periosteal reaction

Factor		Change of PR		*p* Value
		Improved/no change	Deteriorated	
Sex	Male	6	2	0.608
	Female	4	4	
Age (years)		80.4 ± 9.58	69.0 ± 14.7	0.080
Primary disease	Osteoporosis	4	0	0.234
	Malignant tumor	6	6	
Sort of antiresorptive agent	Bisphosphonate	7	2	0.190
	Denosumab	1	3	
	Both	2	1	
MRONJ Stage	Stage 1	1	0	0.660
	Stage 2	5	4	
	Stage 3	4	2	
Corticosteroid	(−)	8	6	0.500
	(+)	2	0	
Diabetes	(−)	8	5	1.000
	(+)	2	1	
Leukocyte (/μL)		6267 ± 821.6	5750 ± 1385	0.378
Albumin (g/dL)		3.79 ± 0.467	3.92 ± 0.531	0.637
Creatinine (mg/dL)		1.11 ± 0.417	1.17 ± 0.823	0.855
Drug holiday before treatment	< 4 years	7	4	1.000
	≥ 4 years ≥ 4 years	3	2	
Duration of administration of antiresorptive agent	Discontinued	9	2	0.036
	Continued	1	4	
Extent of osteolytic lesion	Localized	5	4	0.633
	Extended	5	2	
Extent of PR	Localized	5	3	1.000
	Extended	5	3	
Type of PR	Attached type	4	3	0.833
	Gap type	3	2	
	Irregular type	3	1	
Change of osteolytic lesion	Improved/no change	8	1	0.035
	Deteriorated	2	5	

Discussion

The periosteum is a fibrous capsule on the outside of the cortical bone, which is usually not visible on X-rays. However, when the periosteum is stimulated by a bone tumor, trauma, or osteomyelitis, osteogenesis may occur and is visualized as a shadow on the X-ray, which is called PR. Ida et al. [16] observed various oral and maxillofacial diseases using CT imaging and found that 39 of 97 (40.2%) patients with osteomyelitis, 7 of 236 (3.0%) with trauma, 2 of 409 (0.5%) with cysts, 4 of 279 (1.4%) with benign tumors, and 18 of 121 (14.9%) with malignant tumors of the jaw exhibited PR. Some investigators have reported that PR is often seen in patients with MRONJ. Baba et al. [17] stated that 4/10 (40%) of those receiving denosumab and 7/65 (10.1%) of those receiving bisphosphonate showed PR. Akashi et al. [18] reported that 11 of 61 MRONJ patients (18.0%) had PR, but 27 patients with osteoradionecrosis (ORN) did not. Obinata et al. [19] also reported that PR was observed in 13 of 34 MRONJ patients, but in none of the 16 ORN patients. According to Suei [20], PR was observed in 15 of 25 (60%) MRONJ in 2 of 36 (6%) ORN in 39 of 92 (42%) cases of suppurative osteomyelitis, and in 29 of 34 (85%) of diffuse sclerosing osteomyelitis. Similarly, PR may be observed in inflammatory diseases of MRONJ as in osteomyelitis, but it is unclear whether both share the same pathology.

Ida et al. [16] reported that the average age of osteomyelitis patients with PR was 33 years, which is significantly younger than the average age of 51 years of cases without PR. In contrast, our observational study of 164 patients with MRONJ revealed that the average age of PR (+) patients was 75 years and that of PR (−) was 77 years, with no

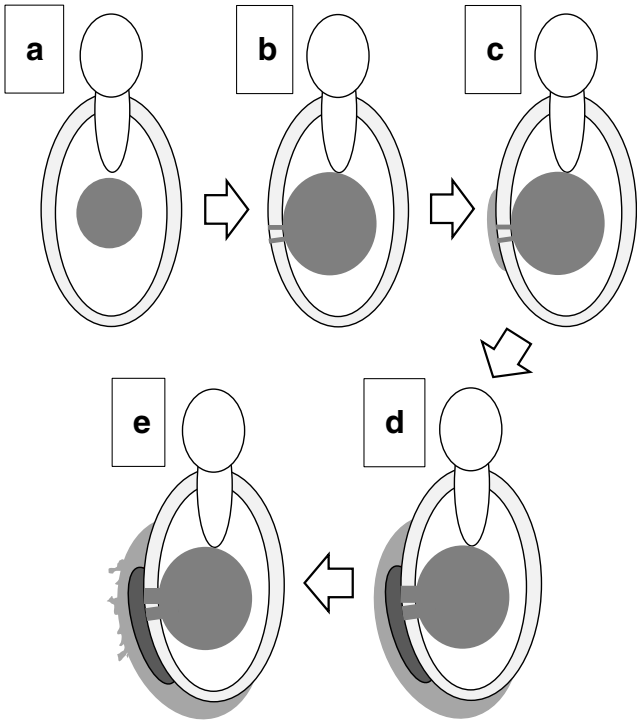

Fig. 3 The possible mechanisms of forming PR. **a** MRONJ arising in the lower jaw. **b** Micro-perforation through the cortical bone. **c** Attached type PR is formed. **d** Gap type PR is formed by abscess or inflammatory granulation tissue. **e** Irregular type PR is formed by perforation of the periosteum (PR, periosteal reaction)

significant differences between the two groups. Since PR in osteomyelitis is common among young people with active bone remodeling activity and is often seen in non-infectious chronic mandibular osteomyelitis, it may be a biologically responsive lesion to an inflammatory stimulus in the bone. Conversely, PR in MRONJ occurs in patients whose bone remodeling is impaired by antiresorptive agents, and it also occurs in elderly patients. We first reported that MORNJ patients with PR achieved significantly poorer treatment outcomes after surgical treatment [12, 13]. Furthermore, the presence of many microorganisms has been identified in the PR by real-time PCR, and histological examination has revealed abscess formation and inflammatory granulation in PR [14]. We believe that PR in MRONJ is an infectious lesion rather than a reactive lesion.

In this retrospective study, we examined the changes in PR during conservative treatment and in factors related to worsening PR. Our findings showed that the extent of PR was expanded and the type of PR changed from the attached type to the gap type and to the irregular type in most patients who continued to receive antiresorptive agents. Although there was no significant difference, PR tended to worsen in younger patients. This was thought to be because older patients were more likely to receive low-dose antiresorptive agent for osteoporosis, whereas younger patients were more likely to receive high-dose antiresorptive agent for malignant tumors.

We proposed the hypothesis that different types of PR were formed [14]. When an infection reaches the cortical bone and micro-perforations through the cortex occur, the attached type of PR is formed as a protective response (Fig. 1b and d). Next, if the infection overwhelms the host immunity, a gap consisting of abscess and inflammatory granulation tissue is formed between the cortical bone and the PR, resulting in a gap type PR (Fig. 1f). Further, if the infection is aggressive and perforates the periosteum, the irregular type of PR is formed (Figs. 1g and 3).

There are two possible routes for the expansion of periosteal reactions. The first is the route by which the lesion in the bone marrow expands and the periosteal reaction expands by

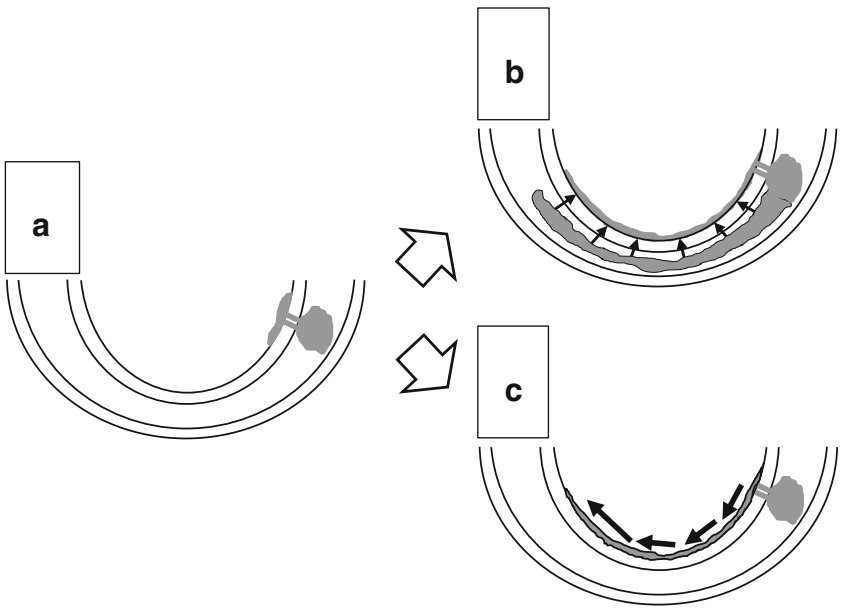

Fig. 4 The possible route of expansion of PR. **a** PR in the lingual side of the lower jaw. **b** Progression via bone marrow. **c** Progression via periosteum (PR, periosteal reaction)

perforating the cortical bone from the lesion. Second, the lesion in the bone marrow does not spread, but it is a route that spreads along the periosteum (Fig. 4). Since magnetic resonance imaging (MRI) was not performed, it was not possible to clarify whether the bone marrow or periosteal route was the main route for the exacerbation of PR.

The study revealed that PR also worsened when osteolytic lesions increased and when antiresorptive agents were continued. Since the effect of conservative treatment is low, it is easy to imagine that MRONJ lesions including osteolytic lesions and PR will worsen if the antiresorptive agent is continued. The withdrawal of antiresorptive agents during MRONJ treatment is controversial. In a multicenter observational study of 427 patients with MRONJ, a drug holiday of antiresorptive agents improved the cure rate with conservative therapy, but it did not affect the cure rate of patients undergoing surgical treatment [21].

The standard treatment for MRONJ is surgery [11], but some patients choose conservative therapy for a variety of reasons. MRONJ lesions with PR are more aggressive and have a higher possibility of exacerbation in a short period of time, but it has been suggested that withdrawal of antiresorptive agents may suppress the progression of PR and leads to improvement of MRONJ lesions. However, since drug holidays have a negative effect on the treatment of the primary disease, it was considered that drug change should be considered rather than drug withdrawal.

This study has some limitations. First, this was a retrospective study with a small number of patients, and detailed statistical analysis was not possible. Second, since this study only included patients who underwent a second CT scan, there may be some selection bias. In the future, we would like to collect a larger number of cases from more institutions and investigate the pathophysiology of PR in MRONJ and its clinical significance.

Conclusion

PR in MRONJ often expands during conservative therapy and the type of PR progresses from the attached type to the gap type and then to the irregular type, although withdrawal of antiresorptive agents may represent a strategy to improve PR and progression of osteolytic lesions.

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(3) Provision of study materials or patients: Sakiko Soutome and Mitsunobu Otsuru
(4) Collection and assembly of data: Sakiko Soutome, Mitsunobu Otsuru, Saki Hayashida, Yuka Kojima, Shunsuke Sawada, Miho Sasaki, Yukinori Takagi, and Misa Sumi
(5) Data analysis and interpretation: Masahiro Umeda and Hiroshi Iwai
(6) Manuscript writing: The first draft of the manuscript was written by Sakiko Soutome and Mitsunobu Otsuru
(7) Revision of the drafted manuscript critically for important intellectual content: All authors
(8) Approval of the version to be published: All authors
(9) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: All authors

Data availability The datasets generated analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval This study was performed in accordance with the 1964 Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB) of Nagasaki University (#21021509).

Consent to participate Because this was a retrospective study, the research plan was published on the homepage of the participating hospitals according to the instructions of the IRB in accordance with the guaranteed opt-out opportunity.

Consent for publication Not applicable

Conflict of interest The authors declare no competing interests.

References

1. Kim HY, Lee SJ, Kim SM, Myoung H, Hwang SJ, Choi JY, Lee JH, Choung PH, Kim MJ, Seo BM (2017) Extensive surgical procedures result in better treatment outcomes for bisphosphonate-related osteonecrosis of the jaw in patients with osteoporosis. J Oral Maxillofac Surg 75:1404–1413. https://doi.org/10.1016/j.joms.2016.12.014
2. Ruggiero SL, Kohn N (2015) Disease stage and mode of therapy are important determinants of treatment outcome for medication-related osteonecrosis of the jaw. J Oral Maxillofac Surg 73 Supplement:S94–S100. https://doi.org/10.1016/j.joms.2015.09.024
3. Schubert M, Klatte I, Linek W, Müller B, Döring K, Eckelt U, Hemprich A, Berger U, Hendricks J (2012) The saxon bisphosphonate register - therapy and prevention of bisphosphonate-related osteonecrosis of the jaws. Oral Oncol 48:349–354. https://doi.org/10.1016/j.oraloncology.2011.11.004
4. Jacobsen C, Metzler P, Obwegeser JA, Zemann W, Graetz KW (2012) Osteopathology of the jaw associated with bone resorption inhibitors: what have we learned in the last 8 years? Swiss Med Wkly 142:w13605. https://doi.org/10.4414/smw.2012.13605
5. Vescovi P, Campisi G, Fusco V, Mergoni G, Manfredi M, Merigo E, Solazzo L, Gabriele M, Gaeta GM, Favia G, Peluso F, Colella G (2011) Surgery-triggered and non surgery-triggered bisphosphonate-related osteonecrosis of the jaws (BRONJ): a retrospective analysis of 567 cases in an Italian multicenter study. Oral Oncol 47:191–194. https://doi.org/10.1016/j.oraloncology.2010.11.007

6. Mücke T, Koschinski J, Deppe H, Wagenpfeil S, Pautke C, Mitchell DA, Wolff KD, Hölzle F (2011) Outcome of treatment and parameters influencing recurrence in patients with bisphosphonate-related osteonecrosis of the jaws. J Cancer Res Clin Oncol 137:907–913. https://doi.org/10.1007/s00432-010-0953-1
7. Rupel K, Ottaviani G, Gobbo M, Contardo L, Tirelli G, Vescovi P, Di Lenarda R, Biasotto M (2014) A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). Oral Oncol 50:1049–1057. https://doi.org/10.1016/j.oraloncology.2014.08.016
8. Fliefel R, Tröltzsch M, Kühnisch J, Ehrenfeld M, Otto S (2015) Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. Int J Oral Maxillofac Surg 44:568–585. https://doi.org/10.1016/j.ijom.2015.01.026
9. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sándor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J (2015) Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 30:3–23. https://doi.org/10.1002/jbmr.2405
10. Yarom N, Shapiro CL, Peterson DE, Van Poznak CH, Bohlke K, Ruggiero SL, Migliorati CA, Khan A, Morrison A, Anderson H, Murphy BA, Alston-Johnson D, Mendes RA, Beadle BM, Jensen SB, Saunders DP (2019) Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO clinical practice guideline. J Clin Oncol 37:2270–2290. https://doi.org/10.1200/JCO.19.01186
11. Hayashida S, Soutome S, Yanamoto S, Fujita S, Hasegawa T, Komori T, Kojima Y, Miyamoto H, Shibuya Y, Ueda N, Kirita T, Nakahara H, Shinohara M, Umeda M (2017) Evaluation of the treatment strategies for medication-related osteonecrosis of the jaws (MRONJ) and the factors affecting treatment outcome: a multicenter retrospective study with propensity score matching analysis. J Bone Miner Res 32:2022–2029. https://doi.org/10.1002/jbmr.3191
12. Kojima Y, Kawaoka Y, Sawada S, Hayashida S, Okuyama K, Yutori H, Kawakita A, Ishida S, Soutome S, Yanamoto S, Umeda M, Iwai H (2019) Clinical significance of periosteal reaction as a predictive factor for treatment outcome of medication-related osteonecrosis of the jaw. J Bone Miner Metab 37:913–919. https://doi.org/10.1007/s00774-019-00994-1
13. Kawaoka Y, Kojima Y, Sawada S, Funahara M, Hayashida S, Yutori H, Murata M, Soutome S, Umeda M (2020) Periosteal reaction as a risk factor for poor outcomes after surgical treatment for medication-related osteonecrosis of the jaw: a retrospective analysis of 205 surgeries. J Oral Maxillofaci Surg Med Pathol 32:8–13. https://doi.org/10.1016/j.ajoms.2019.09.001
14. Soutome S, Yanamoto S, Sumi M, Hayashida S, Kojima Y, Sawada S, Rokutanda S, Iwai H, Saito T, Umeda M (2020) Effect of periosteal reaction in medication-related osteonecrosis of the jaw on treatment outcome after surgery. J Bone Miner Metab. 39:302–310. https://doi.org/10.1007/s00774-020-01154-6
15. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F, American Association of Oral and Maxillofacial Surgeons (2014) 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. https://doi.org/10.1016/j.joms.2014.04.031
16. Ida M, Tetsumura A, Kurabayashi T, Sasaki T (1997) Periosteal new bone formation in the jaws. A computed tomographic study. Dento Maxillo Fac Radiol 26:169–176. https://doi.org/10.1038/sj.dmfr.4600234
17. 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 (2018) CT imaging features of antiresorptive agent-related osteonecrosis of the jaw/medication-related osteonecrosis of the jaw. Dento Maxillo Fac Radiol 47:20170323. https://doi.org/10.1259/dmfr.20170323
18. Akashi M, Wanifuchi S, Iwata E, Takeda D, Kusumoto J, Furudoi S, Komori T (2018) Differences between osteoradionecrosis and medication-related osteonecrosis of the jaw. Oral Maxillofac Surg 22:59–63. https://doi.org/10.1007/s10006-017-0667-5
19. Obinata K, Shirai S, Ito H, Nakamura M, Carrozzo M, Macleod I, Carr A, Yamazaki Y, Tei K (2017) Image findings of bisphosphonate related osteonecrosis of jaws comparing with osteoradionecrosis. Dento Maxillo Fac Radiol 46:20160281. https://doi.org/10.1259/dmfr.20160281
20. Suei Y (2013) Radiographic findings of bisphosphonate-related osteomyelitis of the jaw: investigation of the diagnostic points by comparison with radiation osteomyelitis, suppurative osteomyelitis, and diffuse osteomyelitis. Oral Radiol 29:121–134. https://doi.org/10.1007/s11282-013-0135-3'
21. Hayashida S, Yanamoto S, Fujita S, Hasegawa T, Komori T, Kojima Y, Miyamoto H, Shibuya Y, Ueda N, Kirita T, Nakahara H, Shinohara M, Kondo E, Kurita H, Umeda M (2020) Drug holiday clinical relevance verification for antiresorptive agents in medication-related osteonecrosis cases of the jaw. J Bone Miner Metab 38:126–134. https://doi.org/10.1007/s00774-019-01035-7