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ORIGINAL ARTICLE

Clinical significance of periosteal reaction as a predictive factor for treatment outcome of medication-related osteonecrosis of the jaw

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Abstract
Regarding treatment strategies for medication-related osteonecrosis of the jaw (MRONJ), surgical therapy has recently been reported to be more effective than conservative therapy. However, some patients did not achieve complete healing, even when extensive surgery was performed. Periosteal reaction in MRONJ patients is often observed by the CT examination. Tssshe purpose of this study was to investigate the relationship between periosteal reaction and treatment outcome of MRONJ. A total of 164 surgeries in 136 patients with MRONJ at two hospitals were included in the study. Correlations between various clinical and radiographic factors and treatment outcome were examined with Cox regression analysis. The results showed that the presence of periosteal reaction, as well as primary disease involving malignant tumor, were independent risk factors related to poor outcome. Furthermore, we examined factors related to the occurrence of the periosteal reaction and found that 4 variables were significantly correlated with periosteal reaction by multivariate analysis: gender (female), site (lower jaw), primary disease (malignant tumor), and osteosclerosis (severe). The present study clarified that the cure rate after surgical treatment decreased in cases with periosteal reaction, suggesting that it is necessary to review the treatment method.

Keywords Medication-related osteonecrosis of the jaws (MRONJ) · Periosteal reaction · Surgery · Outcome

Introduction

Antiresorptive agents, such as bisphosphonate (BP) and denosumab (Dmab), are widely used as the first-line therapies for patients with osteoporosis or metastatic bone tumors. Since Marx [1] first described patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) in 2003, case reports of BRONJ have increased. Recently, osteonecrosis among patients receiving Dmab or angiogenesis inhibitors has also been reported; therefore, the term BRONJ was replaced by medication-related osteonecrosis of the jaw (MRONJ), described in the American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper 2014 [2]. Treatment strategies for MRONJ are controversial regarding a nonsurgical versus surgical approach for the first-line therapy. The AAOMS position paper 2014 [2] and Japanese position paper 2012 [3] recommended conservative therapies, such as antibiotic administration, oral rinse, and local washing, for stages 1–2 MRONJ. In contrast, several recent systematic reviews have shown that surgical therapy is more effective than conservative therapy [4–6]. In a multicenter retrospective study of 361 patients with MRONJ, we reported that the outcome of surgical therapy was significantly better than that of conservative therapy, minimizing background factor bias by propensity score method; moreover, extensive surgery, which removes necrotic bone with surrounding bone, was superior to conservative surgery, which removes only necrotic bone [7]. However, some patients did not achieve complete healing, even when extensive surgery was performed.

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Recently, some investigators have reported that a periosteal reaction was frequently detected by the CT examinations among patients with MRONJ [8–11], although its clinical significance and the treatment outcome of patients exhibiting a periosteal reaction were not clearly described. We have experienced MRONJ cases with periosteal reactions; these often did not achieve a cure, despite extensive surgery. The purposes of this study were to investigate the relationships between various clinical factors, including CT findings, and treatment outcome of patients with MRONJ undergoing surgical therapy, and to clarify the clinical significance of the periosteal reaction.

Materials and methods

Patient

We enrolled 136 patients who underwent surgery for MRONJ at the Department of Dentistry and Oral Surgery, Kansai Medical University Hospital between 2014 and 2017, or at the Department of Oral and Maxillofacial Surgery, Nagasaki University Hospital between 2011 and 2017. Patients who were followed up for less than 3 months were excluded from the study. When surgery was performed on both the maxilla and the mandible, or when multiple surgeries were performed at different times, each surgery was counted separately. Finally, we performed the following examinations of 164 surgeries.

Variable

The following factors were examined from medical records or CT data: age, gender, site (upper or lower jaw), MRONJ stage [2], trigger of MRONJ (tooth extraction or others), primary disease (osteoporosis or malignant tumor), type of antiresorptive agent (BP or Dmab), duration of administration of antiresorptive agent, discontinuation of antiresorptive agent for more than 3 months, administration of corticosteroid, diabetes, number of leukocytes, serum albumin, creatinine, operation method (conservative or extensive surgery) [7], wound status (primary suture or open), CT findings, and treatment outcome. Regarding CT findings, separation of sequester (absent/present), osteosclerosis (mild/severe), and periosteal reaction (absent/present) were investigated (Fig. 1).

Osteosclerosis from the alveolar bone to the lower edge of the mandible or maxillary sinus was defined as "severe" osteosclerosis, and partial or no sclerosis was defined as "mild". Treatment outcome was divided into two types: healing or no healing. Healing meant the absence of all symptoms, including swelling, pain, redness, pus discharge, and bone exposure.

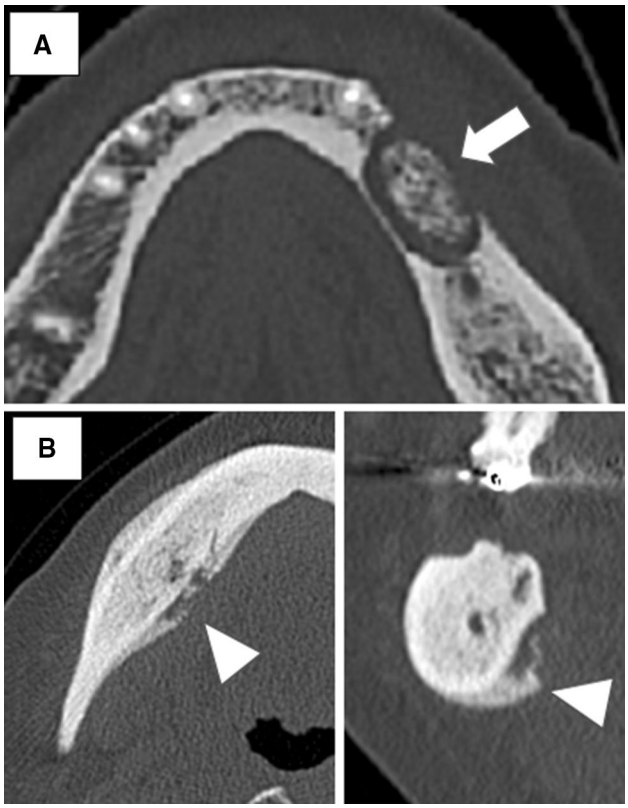

Fig. 1 CT findings of MRONJ: **a** separation of sequester (arrow), and **b** severe osteosclerosis and periosteal reaction (arrowhead)

Statistical analysis

All statistical analyzes were performed using the SPSS software (version 24.0; Japan IBM Co., Tokyo, Japan). Correlations between each variable and treatment outcome were analyzed by univariate and multivariate Cox regression. Kaplan–Meier curves were drawn for some categorized data that were significantly correlated with treatment outcome. Then, factors related to periosteal reaction were analyzed by Fisher's exact test or the Mann–Whitney *U* test, followed by multivariate logistic regression.

Ethics

This study conformed to the tenets of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Boards (IRB) of Kansai University Hospital and Nagasaki University Hospital. This was a retrospective study, and therefore, we published research plan and guaranteed opt-out opportunity by the homepage of our hospital according to the instruction of IRB.

Results

Background factors of the patients are summarized in Table 1. 46 patients were males and 118 were females; the average age of all patients was 74.1 years. The site of MRONJ was upper jaw in 47 patients and lower jaw in 117. Type of antiresorptive agent was BP in 123 patients, and Dmab in 41. The primary disease was osteoporosis in 94 patients and malignant tumor in 70. Surgery was performed without discontinuing the antiresorptive agent for more than 90 days in 85 patients, while 79 patients discontinued medication for more than 90 days before surgery.

Table 1 Background factors of the patients. Values are expressed as median (25–75% tile)

Variable	Category	Number of patients
Gender	Male	46
	Female	118
Age	(years)	77 (66–82)
Site	Upper jaw	47
	Lower jaw	117
Stage	Stage 1	13
	Stage 2	104
	Stage 3	47
Type of antiresorptive agent	BP	123
	Dmab	41
Separation of sequester	Absent	119
	Present	45
Osteosclerosis	Mild	70
	Severe	94
Periosteal reaction	Absent	129
	Present	35
Trigger	Tooth extraction	73
	Others	91
Primary disease	Osteoporosis	94
	Malignant tumor	70
Administration period	< 4 years	91
	≥ 4 years	72
Administration of corticosteroid	Absent	123
	Present	41
Diabetes	Absent	140
	Present	24
Leukocytes	(/μL)	6000 (5100–7500)
Albumin	(g/dL)	3.8 (3.5–4.2)
Creatinine	(mg/dL)	0.78 (0.64–1.05)
Drug holiday before surgery for more than 90 days	Absent	85
	Present	79
Wound	Primary sutured	147
	Opened	17
Total		164

1- and 2-year cumulative cure rates of the 164 cases were 75.2% and 83.2%, respectively (Fig. 2). In univariate analysis, 7 variables were significantly correlated with poor treatment outcome: gender (male), separation of sequester (absent), osteosclerosis (severe), periosteal reaction (present), primary disease (malignant tumor), low albuminemia, and drug holiday (absent). In multivariate analysis, 2 variables were independent risk factors that reduced the cure rate: periosteal reaction (present) and primary disease (malignant tumor) (Table 2, Figs. 3, 4). The 1- and 2-year cumulative cure rates in patients with periosteal reaction were 37.9% and 53.4%, which were significantly lower than 85.1% and 90.8% in those without periosteal reaction. Similarly, the 1- and 2-year cumulative cure rates in patients with malignant tumor were 50.1% and 64.9%, which were significantly lower than 93.2% and 96.4% in those with osteoporosis.

Since it was clear that the periosteal reaction is an important factor related to the cure rate, factors related to the periosteal response were investigated. In univariate analysis, three variables were significant factors related to the periosteal reaction: site (lower jaw), osteosclerosis (severe), and primary disease (malignant tumor). In multivariate analysis, four variables were significant factors associated with the periosteal reaction: sex (female), site (lower jaw), osteosclerosis (severe), and primary disease (malignant tumor) (Table 3).

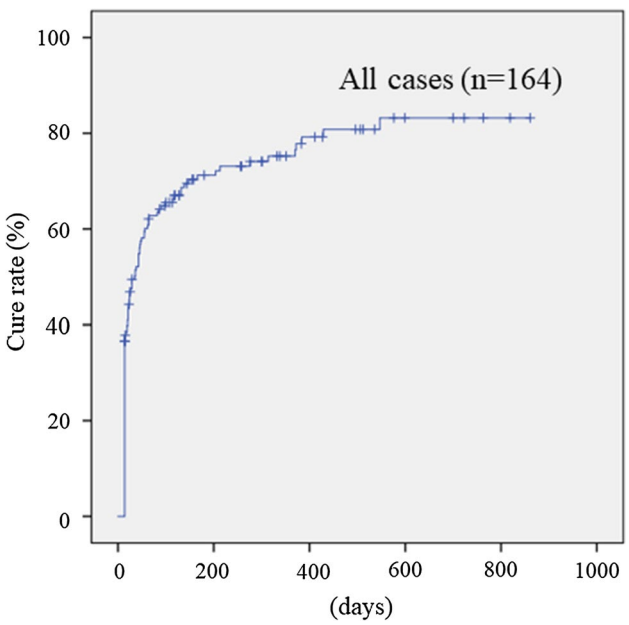

Fig. 2 Cumulative cure rates of all 164 patients. The *X* axis indicates the period (days) from the first visit to the day when the treatment outcome was judged

Table 2 Factors related to treatment outcome

Variable	Univariate analysis	Multivariate analysis*		
	p value	*p* value	Hazard ratio	95% CI
Gender (male/female)	0.023*	0.833		
Age	0.196	0.874		
Site (upper/lower)	0.212	0.459		
Stage (1/2/3)	0.728	0.693		
Type of antiresorptive agent (Dmab/BP)	0.242	0.764		
Separation of sequester (−/+)	0.014*	0.131		
Osteosclerosis (mild/severe)	0.017*	0.92		
Periosteal reaction (−/+)	< 0.001*	< 0.001*	0.326	0.184–0.577
Trigger (others/extraction)	0.721	0.643		
Primary disease (osteoporosis/malignancy)	< 0.001*	< 0.001*	0.419	0.277–0.635
Administration period (<4 years/≥4 years)	0.756	0.675		
Corticosteroid (−/+)	0.512	0.159		
Diabetes (−/+)	0.239	0.172		
Leukocytes	0.230	0.398		
Albumin	0.022*	0.213		
Creatinine	0.492	0.259		
Drug holiday before surgery for more than 90 days (−/+)	0.001*	0.074		
Wound (suture/open)	0.060	0.087		

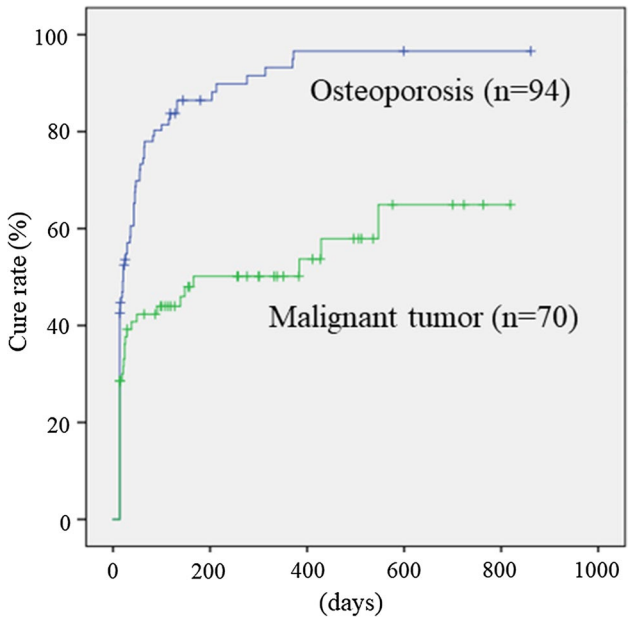

Fig. 3 Relationship between primary disease and treatment outcome

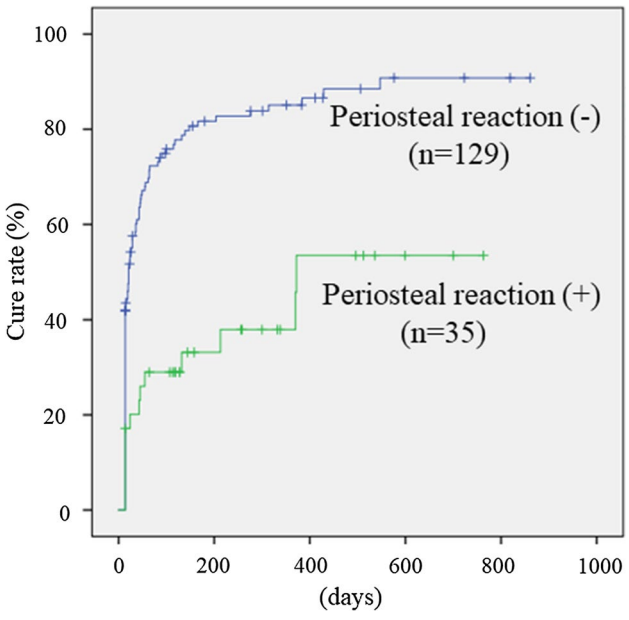

Fig. 4 Relationship between periosteal reaction and treatment outcome

Discussion

Recently, it has been reported that surgical therapy significantly increases the cure rate for patients with MRONJ, compared with the conservative therapy [4–6]. We have performed extensive surgery for MRONJ, as reported previously [7]. However, some patients did not achieve full recovery, despite extensive surgery; many patients with periosteal reactions were among those who did not achieve full recovery. In this study, CT findings, such as periosteal reaction, separation of sequester, and osteosclerosis, were also included among independent variables;

Table 3 Factors related to periosteal reaction

Variable	Periosteal reaction (−)	Periosteal reaction (+)	Univariate analysis	Multivariate analysis*		
			p value	*p* value	Odds Ratio	95% CI
Gender						
Male	37	9	0.834	0.042*	2.797	1.040–8.484
Female	92	26				
Age	77 (67–82)	75 (65–82)	0.850	0.594		
Site						
Upper jaw	42	5	0.036*	0.043*	3.206	1.038–9.896
Lower jaw	87	30				
Stages						
Stage 1	9	4	0.214	0.611		
Stage 2	86	18				
Stage 3	34	13				
Type of antiresorptive agent						
Dmab	29	12	0.187	0.271		
BP	100	23				
Separation of sequester						
Absent	90	29	0.140	0.236		
Present	39	6				
Osteosclerosis						
Mild	65	5	< 0.001*	0.001*	6.196	2.102–18.259
Severe	64	30				
Trigger						
Others	56	17	0.702	0.499		
Tooth extraction	73	18				
Primary disease						
Osteoporosis	82	12	0.003*	0.001*	5.477	2.070–14.488
Malignant tumor	47	23				
Administration period						
< 4 years	66	25	0.054	0.260		
≥ 4 years	62	10				
Corticosteroid						
Absent	94	29	0.276	0.721		
Present	35	6				
Diabetes						
Absent	111	29	0.599	0.495		
Present	18	6				
Leukocytes (/μL)	5800 (5050–7500)	6300 (5200–7500)	0.138	0.737		
Albumin (g/dL)	3.9 (3.6–4.2)	3.7 (3.4–4.1)	0.469	0.422		
Creatinine (mg/dL)	0.78 (0.64–1.04)	0.83 (0.64–1.12)	0.672	0.910		
Drug holiday before surgery for more than 90 days						
Absent	67	18	1.000	0.771		
Present	62	17				
Wound (suture/open)						
Primary sutured	116	31	0.761	0.602		
Opened	13	4				

Values are expressed as median (25–75% tile)

the relationships between various factors and the cure rate were examined. The results showed that the presence of a periosteal reaction, as well as primary disease of malignant tumor, were independent risk factors related to cure rate. In contrast, there was no significant difference in treatment outcome between BP and Dmab. Since all patients with malignant tumors were administered high dose antiresorptive agent and all patients with osteoporosis were administered low-dose antiresorptive agent, it is unknown which is more important as a risk factor related to poor outcome, primary disease, or dosage of antiresorptive agent. However, we think that the dosage of antiresorptive agent may influence the treatment outcome strongly.

Ida et al. [12] examined the CT images of the jawbone of 1142 patients, and revealed that a periosteal reaction was observed in 40% of patients with osteomyelitis; in 91% of those patients, periosteal responses were recognized in one or more layers parallel to the cortical bone. Fatterpekar et al. [8] reported 5 typical radiographic findings of MRONJ: (1) structural alteration of the trabecular bone, (2) cortical erosion, (3) sclerosis, (4) sequestrum, and (5) periosteal new bone. Indeed, the reported rates of periosteal reactions in MRONJ are relatively high: 11/75 (14.7%) [10], 15/34 (44.1%) [11], 3/6 (50%) [8], and 19/28 (67.9%) [9]. Conversely, a periosteal reaction was not found among patients with osteoradionecrosis (ORN) of the jaw, a condition that is partially similar to MRONJ [11, 13]. It may be that the antiresorptive agent mainly acts on osteoclasts and exerts a minimal effect on soft tissue; however, radiation therapy greatly influences both bone and the surrounding soft tissues, including the periosteum, reducing blood flow and promoting scar formation.

In this study, 35 of 164 MRONJ patients (21.3%) exhibited a periosteal reaction. Furthermore, we examined factors related to the occurrence of periosteal reactions and found that 4 variables were significantly correlated with periosteal reaction by multivariate analysis: gender (female), site (lower jaw), primary disease (malignant tumor), and osteosclerosis (severe). In contrast, there was no significant difference in frequency of periosteal reaction between BP and Dmab. It is unclear why females showed a higher percentage of periosteal reactions. In another clinical study, we found that female patients receiving a high dose of antiresorptive agent developed MRONJ significantly more frequently than males, as determined by the multivariate Cox regression analysis (unpublished data). We suspect that differences in male and female jaw structure may be related to the development of periosteal reactions or MRONJ. Cancer patients who were administrated a high dose of antiresorptive agent, or those with more severe osteosclerosis, were more susceptible to periosteal reactions. These findings indicate that a periosteal reaction is not a reactive phenomenon (e.g., similar to osteomyelitis); instead, this reaction represents a more destructive lesion formed because of obstacles to bone remodeling, associated with the apoptosis of osteoclasts. Further research is needed on periosteal reactions in MRONJ patients.

To the best of our knowledge, this is the first study to show that periosteal reactions in MRONJ are associated with a lower cure rate, despite extensive surgery. In the future, it may be necessary to reconsider the surgical method for patients exhibiting periosteal reactions. This study is limited, because it is a retrospective investigation with a small number of patients; therefore, generalization of the results may be difficult. Hence, a more detailed study with a larger number of patients is necessary. In summary, our results indicate that MRONJ with a periosteal reaction is associated with poor treatment outcome despite surgical treatment; thus, surgical methods for such patients should be reconsidered.

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Author contributions Study design: YK and MU. Data collection: YK, YK, SS, SH, KO, HY, AK, SI, and SS. Data analysis: SY, SS, and MU. Data interpretation: SY, SS, and MU. Drafting manuscript: YK. Revising manuscript: YK, YK, SS, SH, KO, HY, AK, SI, SS, SY, MU, and HI. YK and HI accept responsibility for the integrity of the data analysis. All the authors agree to be accountable for all the 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.

Compliance with ethical standards

Conflict of interest All authors state that they have no conflicts of interest.

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