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ORIGINAL ARTICLE

Differences between osteoradionecrosis and medication-related osteonecrosis of the jaw

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Abstract

Purpose The appearance of osteoradionecrosis (ORN) and medication-related osteonecrosis of the jaw (MRONJ) is similar, but clinically important differences between ORN and MRONJ exist. The aim of this study was to compare the clinical data between ORN and MRONJ and to reveal the critical differences between these diseases.

Methods We retrospectively reviewed the epidemiological data, clinical findings, and treatment in 27 ORN and 61 MRONJ patients. Radiographic signs before the initiation of treatment were also assessed.

Results The median age ($P = 0.0474$) and the ratio of female to male patients ($P < 0.0001$) were significantly higher in MRONJ patients. There were significantly more MRONJ patients who reported a history of pain when compared with ORN patients ($P = 0.0263$). As an aetiological factor, tooth extraction was significantly more relevant to MRONJ than ORN ($P = 0.0352$). When assessing the radiographic signs on computed tomographic images, periosteal reaction was found only in MRONJ patients ($P = 0.0158$). Minimal debridement was performed significantly more frequently for MRONJ ($P = 0.0093$), and by contrast, surgical resection was performed more frequently for ORN ($P = 0.0002$).

Conclusions Understanding the clinical and underlying pathological differences between ORN and MRONJ probably contributes to the selection of appropriate treatment for each patient.

Keywords Osteoradionecrosis of the jaw · Medication-related osteonecrosis of the jaw · Computed tomography · Surgery

Introduction

Both osteoradionecrosis (ORN) and medication-related osteonecrosis of the jaw (MRONJ) are problematic complications associated with the treatment of primary malignant tumours, metastatic lesions, and osteoporosis. The incidence of both diseases is low [1–3], but the number of patients with MRONJ continues to increase because of the implementation of new drugs [4]. The advancement of radiation therapy (RT) techniques (e.g. intensity-modulated radiation therapy [IMRT]) decreases the number of patients with ORN, but it has not eliminated this complication. The incidence of MRONJ in osteoporosis and oncology patients is 0.001–0.1 and 1–15%, respectively [1]. The most recent large-scale studies reported incidences of ORN following IMRT of 4.3% [2] and 6.2% [3].

The appearance of ORN and MRONJ is similar (briefly, exposure of necrotic bone and infection of the surrounding soft tissue), but differences in patient factors, imaging findings, aetiology and pathogenesis have been identified [4–7]. In general, conservative treatment such as antibiotic administration and local irrigation is recommended for early stage ORN and MRONJ. However, when both diseases deteriorate and become refractory, surgical intervention is required [8–10]. To select the appropriate treatment for each disease, oral and maxillofacial surgeons must understand the different factors underlying ORN and MRONJ. The aim of this study was to compare the clinical characteristics and treatment of ORN and MRONJ and to reveal the clinically important differences between these diseases.

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Material and methods

Participants

All patients were diagnosed with ORN or MRONJ at the Department of Oral and Maxillofacial Surgery, Kobe University Hospital, between June 2015 and February 2017. Epidemiological data were retrospectively gathered from electronic medical records including information about age, sex, disease location, comorbidity and steroid use. Panoramic radiographs and computed tomography (CT) scans were taken before the initiation of treatment in all patients included in this study. The first group consisted of 27 patients with ORN. ORN was defined according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (http://ctep.canchttp://ctep.cancer.gov/forms/CTCAEv3.pdf. http://ctep.cancer.gov/forms/CTCAEv3.pdf). This study included patients who had grade ≥ 2 ORN according to CTCAE v3.0. Grade 2 ORN was defined as the loss of mucosal coverage and bone exposure lasting 3–6 months [11]. The second group consisted of 61 patients who had developed MRONJ. The acceptance criteria of the American Association of Oral and Maxillofacial Surgeons (AAOMS) were used to establish the diagnosis of MRONJ [9].

In the MRONJ group, the following data were collected: primary disease information, administration route of antiresorptive agents (i.e. oral or intravenous), and staging at the first visit according to AAOMS criteria [9]. Briefly, the MRONJ staging was as follows: stage 0, radiographic changes only; stage 1, exposed bone without symptoms; stage 2, exposed bone with infection; and stage 3, exposed bone with pathological fracture, extraoral fistula or osteolysis extending to the inferior border of the mandible or sinus floor [9]. For staging of ORN at the first visit, the classification proposed by Lyons et al. was applied in this study [12]. In brief, stage 1, affected bone < 2.5 cm; stage 2, asymptomatic affected bone > 2.5 cm; stage 3, symptomatic affected bone > 2.5 cm; and stage 4, affected bone with pathological fracture, orocutaneous fistula or involvement of the inferior alveolar nerve [12]. As mentioned above, the clinical features of stage 3 MRONJ in the AAOMS criteria and stage 4 ORN in the Lyons classification were similar. In both groups, the following information about the clinical symptoms was gathered from the electronic medical records: history of pain, history of recurrent infections (i.e. repeated administration of antibiotics to reduce acute inflammation caused by local infection), chronic pus discharge, pathological fracture, orocutaneous fistula, dietary change (e.g. change from normal diet to puree) and trismus. Aetiology was divided into the following groups: tooth extraction, implant, denture and unknown. In both groups, the following radiographic signs in CT images were assessed by one radiologist and one experienced oral and maxillofacial surgeon in a blind manner: osteolysis, osteosclerosis, periosteal reaction and sequestration. In patients who had multiple lesions in the maxilla and mandible, the most severe and symptomatic lesions were evaluated. Treatment was divided into conservative, minimal debridement (i.e. sequestrectomy under local or general anaesthesia) and surgical resection with or without reconstruction. In all ORN patients and 47 of 61 MRONJ patients (77%), blood tests were conducted to assess their general health before surgery or antibiotic administration. The following blood test values were compared between the ORN and MRONJ groups: red cell count, haemoglobin, platelet count, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR), alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase and albumin. All patient data, including CT images and blood tests, were evaluated after obtaining written informed consent from each patient. Ethical approval was exempted because of the retrospective nature of this study.

Statistical analysis

Statistical analyses were performed using R (R Development Core Team, 2011). The groups were compared by Mann–Whitney *U* test for continuous variables and by Fisher's exact tests for categorical variables. A *P* value less than 0.05 was considered statistically significant.

Results

All ORN patients received RT (conventional RT in 25 patients and IMRT 2) for treatment of head and neck malignancy. Twenty-eight of 61 MRONJ patients (45.9%) received antiresorptive therapy for metastatic carcinoma or multiple myelomas. Out of 61 MRONJ patients, 25 (41%) had a history of oral bisphosphonates (BP), 16 (26.2%) had a history of intravenous BP, 10 (16.4%) had used denosumab and 10 (16.4%) had undergone multiple antiresorptive agent therapies (e.g. the administration of intravenous BP and subsequently denosumab).

Comparison of the clinical features between ORN and MRONJ is shown in Table 1. The median age was significantly higher in the MRONJ group ($P = 0.0474$). There were a significantly higher number of females in the MRONJ group ($P < 0.0001$). There was no significant difference in comorbidity (hypertension, diabetes mellitus and chronic kidney disease) between the groups. The number of patients with daily steroid administration was significantly higher in the MRONJ group ($P = 0.0078$). Both ORN and MRONJ frequently occurred in mandible. The Lyons staging of ORN at the first visit to our department was stage 4 in 44.4% of cases and stage 1 in 40.8% of cases. The most predominant MRONJ staging according to AAOMS criteria was stage 2 (45.9%). The number of patients who had a history of pain was significantly higher in the MRONJ group ($P = 0.0263$). In contrast, the number of patients who complained about dietary changes ($P = 0.0013$) and trismus ($P = 0.0033$) was significantly higher in the ORN group. All pathological fractures in this

Table 1 Comparison of the clinical characteristics of MRONJ and ORN

	ORN ($n = 27$)	MRONJ ($n = 61$)	P value
Median age (range)	68 (58–90)	74 (48–96)	0.0474[a]
Sex			< 0.0001[b]
Male	23 (85.2)	12 (19.7)	
Female	4 (14.8)	49 (80.3)	
Comorbidity			
Hypertension	8 (29.6)	21 (34.4)	0.8068[b]
Diabetes mellitus	1 (3.7)	6 (9.8)	0.4306[b]
Chronic kidney disease	1 (3.7)	4 (6.6)	1[b]
Steroid use	0 (0)	13 (21.3)	0.0078[b]
Location			0.903[b]
Mandible	22 (81.5)	47 (77.1)	
Maxilla	4 (14.8)	11 (18.0)	
Both	1 (3.7)	3 (4.9)	
Staging at first visit[c]			
0	–	1 (1.6)	
1	11 (40.8)	17 (27.9)	
2	2 (7.4)	28 (45.9)	
3	2 (7.4)	15 (24.6)	
4	12 (44.4)	–	
Symptoms			
History of pain	22 (81.5)	59 (96.7)	0.0263[b]
History of recurrent infection	19 (70.4)	45 (73.8)	0.7977[b]
Chronic pus discharge	18 (66.7)	42 (68.9)	1[b]
Pathological fracture	6 (22.2)	4 (6.6)	0.622[b]
Orocutaneous fistula	7 (33.3)	15 (24.6)	1[b]
Dietary change	12 (44.4)	7 (11.5)	0.0013[b]
Trismus	13 (35.1)	10 (16.4)	0.0033[b]
Aetiology			0.0697[b]
Extraction	7 (25.9)	32 (52.5)	0.0352[b]
Implant	2 (7.4)	2 (3.3)	0.5833[b]
Denture	1 (3.7)	3 (4.9)	1[b]
Unknown radiographic signs	17 (63.0)	24 (39.3)	0.0063[b]
Osteolysis	24 (88.9)	50 (82.0)	0.5363[b]
Osteosclerosis	15 (55.6)	28 (45.9)	0.49[b]
Periosteal reaction	0 (0)	11 (18.0)	0.0158[b]
Sequestration	16 (59.3)	39 (63.9)	0.8118[b]
Treatment			< 0.0001[b]
Conservative	14 (51.9)	39 (63.9)	0.3473[b]
Minimal debridement	1 (3.7)	17 (27.9)	0.0093[b]
Surgical resection	12 (44.4)	5 (8.2)	0.0002[b]
Blood tests	(n = 27)	($n = 47$)	
Red cell count ($10^4/\mu L$)	355 (251–584)	381 (259–499)	0.8026[a]
Haemoglobin (g/dL)	11.2 (9–15.5)	11.25 (8.2–14.1)	0.234[a]
Platelet count ($10^4/\mu L$)	23.2 (5–46.6)	23.6 (4.2–51)	0.6312[a]
Blood urea nitrogen (mg/dL)	16.2 (10.2–40.4)	16.6 (7.1–80.5)	0.4354[a]
Creatinine (mg/dL)	0.9 (0.66–2.41)	0.78 (0.41–2.65)	0.4839[a]
Estimated glomerular filtration rate (mL/min/1.73 m^2)	64.1 (20.6–91.8)	56 (16.9–139.6)	0.0628[a]
Alkaline phosphatase (U/L)	216 (146–559)	254 (83–864)	0.3953[a]
Aspartate aminotransferase (U/L)	20 (12–227)	22 (10–67)	1[a]
Alanine aminotransferase (U/L)	15 (7–65)	14 (5–69)	0.6818[a]
Albumin (g/dL)	3.6 (2.7–4.6)	3.8 (2.1–4.4)	0.992[a]

Unless otherwise noted, data are reported as number (percentage) of study patients

ORN osteoradionecrosis, *MRONJ* medication-related osteonecrosis of the jaw

[a] Mann–Whitney *U* test

[b] Fisher's exact test

[c] ORN staging (1–4) according to the classification proposed by Lyons et al. [12]; MRONJ staging (1–3) according to AAOMS classification [9]

study occurred in the mandible. For the aetiological factors, tooth extraction was significantly more relevant to MRONJ ($P = 0.0352$). In contrast, the aetiology was unknown in a significantly higher number of ORN patients ($P = 0.0063$). When assessing the radiographic signs in CT images, periosteal reaction was found in a significantly higher number of MRONJ patients ($P = 0.0158$). In terms of treatment selection, minimal debridement was performed significantly more

frequently in the MRONJ group ($P = 0.0093$). In contrast, surgical resection with or without reconstruction was performed significantly more frequently in the ORN group ($P = 0.0002$). In evaluating the patients' blood test results, there was no significant difference between the both groups.

Discussion

Although ORN and MRONJ may appear similar, clinically important differences between these diseases have been previously identified [4–6]. In the reports by Grisar et al. [4] and Began et al. [6], the age and ratio of female to male patients were significantly higher in MRONJ cases, which are similar to the results found in our study. Regarding the clinical symptoms, significantly more pathological fractures and skin fistulae occurred in ORN patients in their reports [4, 6]. In our study, dietary change and trismus occurred significantly more frequently in ORN patients. In the report by Began et al. [6], dental extraction was more relevant to MRONJ, which is similar to our findings. When evaluating the imaging features of ORN and MRONJ, Obinata et al. [5] reported that osteolysis and spreading of soft tissue inflammation were predominant in ORN, and osteosclerosis was predominant in MRONJ. They also noted that periosteal reaction in CT imaging was found only in MRONJ, which is in accordance with our results [5]. Grisar et al. [4] reported that the treatment was more often conservative in MRONJ patients than in ORN patients (61.3 vs. 36.2%). Similarly, in our study, minimal debridement was performed more frequently in MRONJ patients, and by contrast, surgical resection was performed more frequently in ORN patients. Additionally, the current study compared the blood test results between ORN and MRONJ patients and showed that the eGFR value tended to be lower in MRONJ patients, whereas the difference did not achieve statistical significance.

There are a number of previous studies investigating the pathological differences between ORN and MRONJ. The histopathological study by Mitsimponas et al. [13] found that MRONJ is a disorder characterised by disruption of the normal bone architecture and organisation, and ORN is a condition characterised by increased fibrosis. ORN lesions are more homogenous and the necrosis is more extensive, and by contrast, MRONJ has a patchy appearance where multiple and partially confluent areas of necrotic bone are mingled with vital bone residues [7, 13]. They hypothesised that the structural alteration of MRONJ is attributed to partial avascularity [13]. The study by Hoefert et al. [14] focusing on functional immune defence found that one of the important pathological aspects of MRONJ is local immunosuppression by BP on monocytes and macrophages. Additionally, a notable absence of inflammatory cells, normal marrow elements or fat cells was observed in the study by Marx and Tursun [15]. The main problem with a locally compromised immune system is the decrease in vascularity, which normally enables the effective migration of macrophages into the affected bone [14, 15]. We found that one of the important differences between ORN and MRONJ was periosteal viability, represented as a periosteal reaction observed in CT images. The periosteal blood supply is predominant in the caudal part of the mandibular body [16], which is a site predisposed to osteonecrosis. Irradiation for head and neck malignancy damages periosteal blood supply in the mandibular body, although periosteal reaction was not observed in all ORN patients in this study. In contrast, periosteal vascularity is mostly intact in MRONJ patients. The difference in periosteal vascularity probably influences the treatment outcome (i.e. the outcome of conservative surgical management is better in MRONJ, whereas minimal debridement for ORN often fails) [10, 17]. An important and well-known patient factor is age. MRONJ patients are often elderly with a history of bone metastasis or rheumatic disease. When a patient's kidney function decreases, the repeated administration of antibiotics and antiinflammatory analgesics should be avoided. This study showed that almost all of the MRONJ patients had a history of pain. Conservative surgical management, which aims to control local infection and results in pain relief, is an important treatment option that can be an alternative to repeated analgesic administration, especially in elderly patients. It should be emphasised that ORN patients included in this study were also elderly and experienced severe pain even though there were significant differences compared with MRONJ patients. In conclusion, oral and maxillofacial surgeons should understand the clinical and pathological differences between ORN and MRONJ indicated in this study to treat patients with osteonecrosis of the jaw appropriately.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Not required.

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