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BRIEF REPORT

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Mental foramen in panoramic radiography can be a reference for discrimination of punched-out lesions in the mandible in patients with symptomatic multiple myeloma: A cross-sectional study

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Abstract: Multiple myeloma (MM) is a hematopoietic malignancy characterized by monoclonal proliferation of plasma cells. MM features bony radiolucencies called punched-out lesions (POLs), which require appropriate diagnosis due to increased risk of surgically-related adverse events. Although dental surgeons can identify dental focal infections (DFIs) in MM patients, the prevalence and characteristics of POLs in the jawbone of MM patients have not been investigated. We examined the prevalence of POLs in the mandible of MM patients, evaluated its relationship with MM International Staging System progression, and examined panoramic radiographs as a diagnostic reference for POLs in a single center in Japan. We identified 98 patients (55 men, 43 women) with a median age of 63 (range, 34 to 91) years. Of these, 18 patients (18.4%) had POLs in the mandible, including two patients in stage I (2/37; 5.4%), six in stage II (6/43; 14.0%), and ten in stage III (10/18; 55.6%). The prevalence of POLs significantly increased with MM stage progression ($p < 0.0001$). POLs confirmed on computed tomography (CT) were also detected on panoramic radiographs. The Hounsfield unit value at the site of POLs was nearly the same or lower than that of the mental foramen. Although the prevalence of POLs in the mandible is low, dental surgeons need to differentiate POLs as radiological findings when examining DFIs in MM patients. Confirmation of POLs in the mandible is possible by CT and panoramic radiography, and the mental foramen is likely to be a reference for discrimination.

***Keywords*:** hematologic malignancy, bone disease, mandible, dental focal infection, panoramic radiography, computed tomography

Introduction

Multiple myeloma (MM), also known as plasma cell myeloma, accounts for 1% of all malignancies and 10-15% of all hematopoietic neoplasms. It is characterized by the monoclonal proliferation of plasma cells that originate from the post-germinal lymphoid B-cell lineage and develop in the bone marrow of progenitor cells following lineage commitment (*1,2*). MM is classified as asymptomatic or symptomatic, depending on the absence or presence of myeloma-related organ or tissue dysfunction such as hypercalcemia, renal insufficiency, anemia, and bone disease (*1,2*). The osteoclast-activating factor, which is released from myeloma cells, enhances bone resorption, thereby precipitating osteolytic bone disease in more than 80% of MM patients (*2*). Osteolytic bone diseases can result in skeletal and surgically-related adverse events such as severe bone pain, pathological fractures, surgical site infection (SSI), and septicemia (*2-6*). These complications have a negative impact on the patient's quality of life and overall survival. In fact, patients with MM have an increased incidence of bone fractures (43%) and risk of death compared to all patients with malignant bone disease (*7*). In addition, approximately 21% of bone diseases in MM patients are associated with postoperative complications such as abnormal bleeding and SSI (*5*). Therefore, it is important to thoroughly assess bone condition preoperatively in MM patients who plan to receive surgical intervention.

Osteolytic lesions in MM patients show a characteristic radiological feature called punched-out lesions (POLs) (*8*), which are multiple radiolucent lesions of various sizes with well-defined non-sclerotic margins (*8,9*). Dental surgeons have the opportunity to evaluate dental focal infections (DFIs) in the

stomatognathic region, which includes the jawbones, before chemotherapy in patients with hematopoietic malignancies, including MM (*10*), and panoramic radiography is often used in the screening of jawbones (*11*). In addition, tooth extraction may be performed to radically remove DFIs (*10*). Although radiodiagnostic proficiency and experience distinguishing between various diseases are crucial for DFI scrutiny in the jawbones, the prevalence and characteristics of POLs and the diagnostic value of panoramic radiography in MM patients have not yet been thoroughly investigated.

In this context, we conducted a study in a single center in Japan to evaluate the prevalence of POLs in the mandible of symptomatic MM patients to analyze the relationship of POL incidence with MM progression and examine the efficacy of panoramic radiographs as a diagnostic reference for POLs.

Materials and Methods

Study design

We conducted a cross-sectional study using medical records of patients with symptomatic MM who visited the National Center for Global Health and Medicine (NCGM), Tokyo, Japan. The time period of this study spanned from January 2011, when the electronic medical record system was introduced at our hospital, to December 2016, the end date of the study when it was approved by the Ethics Review Committee in July 2017. Patients were considered for inclusion in this study when they were referred from the Division of Hematology to the Department of Oral and Maxillofacial Surgery before undergoing chemotherapy. The prevalence of POLs in the enrolled patients' mandible and skull was investigated by computed tomography (CT). The expression rate of the POLs was then compared. We then evaluated whether panoramic radiographs can be used to confirm the presence or absence of POLs.

We analyzed the relationship between POLs and MM stages. The staging was in accordance with the MM International Staging System (ISS), which reflects the progression of MM. In addition, the bone mineral density of CT-confirmed POLs in the mandible, measured in Hounsfield units (HUs), was further evaluated and compared with that of healthy sites such as the mental foramen and cortical bone. Quality was referred to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (*12*).

The study was conducted according to the tenets of the Declaration of Helsinki (2013 revision) and all investigations were performed according to the protocols that were reviewed and approved by the ethical committee of the NCGM (NCGM-G-002190-01). The requirement for informed consent was waived because of the cross-sectional study design.

Eligibility criteria

Subjects were enrolled using the inclusion and exclusion criteria described below. The inclusion criteria were as follows: *i*) patients who visited the NCGM between January 2011 and December 2016; *ii*) those who were diagnosed with symptomatic MM with mandible involvement confirmed on CT; and *iii*) those who visited the Department of Oral and Maxillofacial Surgery for radiographic screening of the jawbone.

The exclusion criteria were as follows: *i*) patients diagnosed with asymptomatic MM; *ii*) those who had already received a bisphosphonate or a RANK ligand inhibitor (*e.g.*, denosumab) *via* any route for any duration because of the known relationship between these medications and osteonecrosis of the jaw (*13*); *iii*) those who had already undergone tooth extraction at another dental clinic or hospital as part of their oral evaluation before chemotherapy; and *iv*) those who moved to another hospital before undergoing radiographic screening of the jawbone.

Data collection

We procured data of all participating patients from the medical, dental, and nursing records of the NCGM. We noted the following variables: age, sex, diagnosis, MM stage, intraoral findings, subjective symptoms, and radiological findings in the cranial and oral maxillofacial regions, including oral panoramic radiographs and CT at the time of diagnosis.

Evaluation of MM progress

The ISS is based on beta-2 microglobulin and albumin levels. It was introduced in 2005 (*14*) and has since been considered the standard for the initial staging of patients with MM (*15*). This staging system defines three stages with varied prognoses (Table 1). This staging system was used to evaluate the degree of MM progression at the time of jawbone scrutiny.

Mandibular assessment

The mandible is a single large bone that makes up the lower part of the facial skeleton and can be subdivided into seven sites: the alveolus, symphysis, mandibular

Table 1. International staging system for multiple myeloma

MM Stage	Definition	
	β2MG [mg/L]	Alb [g/dL]
I	< 3.5	≥ 3.5
II	Not stage I or III	
III	≥ 5.5	NS

MM, multiple myeloma; β2MG, beta-2 microglobulin; Alb, albumin; NS, no setting.

Table 2. Percentage of punched-out lesions in the skull and the mandible according to the international staging system

Sites	ISS stage			Total	Cochran-Armitage trend test
	I	II	III		
Skull	8/37 (21.6%)	16/43 (37.2%)	18/18 (100%)	42/98 (42.9%)	$p < 0.0001$
Mandible	2/37 (5.4%)	6/43 (14.0%)	10/18 (55.6%)	18/98 (18.4%)	$p < 0.0001$

ISS, international staging system.

body, mandibular ramus, mandibular angle, coronoid process, and subcondylar process (*16*). Using the mandible's morphological classification as a guide, we collated the POLs in the mandible of our subjects using CT. However, since it was difficult to strictly distinguish alveolus POLs from dental infections, the alveolus site was excluded. In this study, POLs were defined as radiolucent lesions in the absence of dental infection. Histopathological examinations were not used to define POLs. Radiolucent lesions that were suspected of having any possibility of association with dental infections based on clinical symptoms and images were not regarded as POLs. The presence or absence of POLs and the site of onset were also evaluated by panoramic radiographs. In addition, we verified whether the mental foramen, a radio-anatomical structure clearly visible on panoramic radiographs, can be used as a reference when distinguishing POLs by measuring the bone mineral density of the mandible, accomplished by setting an ellipse on the horizontal cross-section of the CT screen and calculating the average value in the range of 5 mm^2. The measurement sites of the HU value were the following: *i*) mandibular cortical bone on the healthy side without POLs, *ii*) mental foramen, and *iii*) bone inside the POL.

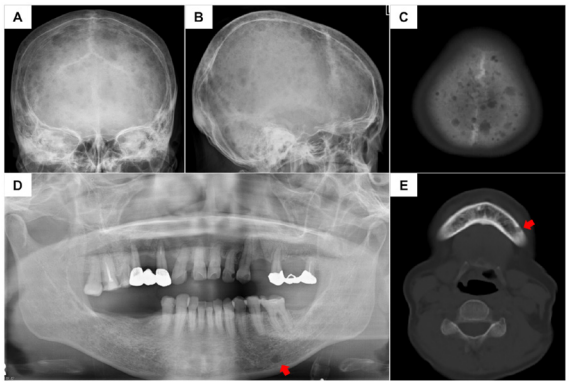

Figure 1. Skull and panoramic radiographs and CT imaging of a 57-year-old woman with MM stage III. (A, B) Skull radiography from the front and side. Various sizes with well-defined multiple POLs in the parietal, frontal, occipital, and temporal bone can be seen. **(C)** Axial CT imaging of the parietal bone showing various sizes with well-defined multiple POLs. **(D)** Panoramic radiograph. A POL with a clear boundary is observed in the mandibular body corresponding to the left second premolar and first molar (arrows). Dental infections were unlikely because they were far from the teeth through healthy bones, and the patient had no deactivated teeth. **(E)** Axial CT imaging of the left mandibular body. A POL with a well-defined, approximately 4-mm × 5-mm internal uniform low-concentration lesion with smooth margins is found in the lateral cortical bone of the left mandibular body (arrows).

Statistical analyses

Data are presented as mean with standard deviation (SD) or median with range for continuous variables and number with percentage for categorical variables. The Cochran-Armitage trend test was used to analyze the incidence of POLs in relation to ISS stage progression. In addition, a one-way analysis of variance for repeated measures followed by Tukey's test for multiple comparisons was used to compare the HU value among the three measurement sites. Statistical analyses were performed using the SAS statistical software package, Version 9.4 (SAS Institute, Cary, NC, USA), and $p < 0.05$ indicated statistical significance.

Results and Discussion

Patient characteristics

Overall, 138 patients with symptomatic MM visited the Department of Oral and Maxillofacial Surgery during the study period. After exclusion, we identified 98 patients (55 men [56.1%], 43 women [43.9%]) with a median age of 63 (range, 34 to 91) years at their first visit to our department. The 98 identified patients were classified according to the ISS; there were 37 patients (37.8%) in stage I, 43 (43.9%) in stage II, and 18 (18.4%) in stage III.

Prevalence of POLs and its correlation with the ISS progress

Of the 98 patients diagnosed with symptomatic MM, 42 (42.9%) and 18 (18.4%) had POLs in the skull and the mandible, respectively (Table 2). Figure 1 shows one of the representative cases of POLs in the skull and the mandible of a patient with MM stage III (Figure 1A-E). All patients with POLs in the mandible also had POLs in the skull. We evaluated the proportion of POLs found in the skull and the mandible based on the ISS. There were 37 patients in ISS stage I. Of them, eight (21.6%) had POLs in the skull, while two (5.4%) had POLs in the mandible. Out of the 43 patients in ISS stage II, 16 (37.2%) had POLs in the skull, while six (14.0%) had

POLs in the mandible. Out of the 18 patients in ISS stage III, 18 (100%) had POLs in the skull, while ten (55.6%) had POLs in the mandible. In POLs in both the skull and mandible, POL prevalence significantly increased as their ISS progressed ($p < 0.0001$).

Table 3 summarizes the proportion of POLs by sites of the mandible confirmed on CT and panoramic radiograph. POLs, confirmed by CT, occurred frequently from the mandibular ramus (n = 16; 88.9%) to the mandibular angle (n = 15; 83.3%) followed by the mandibular body (n = 12; 66.7%), the subcondylar process (n = 8; 44.4%), and the coronoid process (n = 2; 11.1%). There were no POLs confirmed in the symphysis. Four patients did not undergo panoramic radiographic examinations probably due to their low level of activity in daily life. POLs were confirmed in panoramic radiographs as follows: mandibular ramus (n = 12; 85.7%), mandibular angle (n = 11; 78.6%), mandibular body (n = 9; 64.3%), subcondylar process (n = 6; 40.0%), and coronoid process (n = 1; 6.7%), which almost had the same proportions as those confirmed by CT. Various POLs in panoramic radiographs and CT imaging of the mandible are available as supporting information (Supplementary Figure 1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=45*).

Intraoral manifestations associated with POLs

Of the POL cases in the jawbone, only one (5.6%) had painless swelling with a smooth mucosal surface that coincided with the POL site without teeth. In this study, there were no patients with an abnormal perception of the trigeminal innervation area, pathologic fractures, or a poor quality of life due to POLs in the jawbone.

Comparison of bone mineral density between POLs and healthy sites

When comparing the bone mineral density between the affected and the healthy sites in the mandible in HU value, the POLs in the mandibular cortical bone (226-669 HU [503.2 mean ± 140.8 SD]) showed the same value as that in the mental foramen in several cases. However, it was statistically significantly lower than that of the healthy mandibular cortical bone (1236-1983 HU [1473.9 mean ± 167.7 SD]) and that of the mental foramen (289-998 HU [714.3 mean ± 188.6 SD]) ($p < 0.0001$).

This study investigated the prevalence of POLs in the mandible and their correlation with MM progress in patients with symptomatic MM. Our report was the first to show that POLs can occur in the mandible during the early stages of MM, especially in the mandibular ramus and at the mandibular angle. Furthermore, the expression proportion of POLs increased with MM stage progression, and panoramic radiographs proved useful in confirming MM-associated POLs.

The annual number of new MM cases in Japan was approximately six per 100,000 in 2018 (*17*). Although this proportion was nearly the same as those in the United States and Europe (*18,19*), it has remarkably increased year by year in Japan. In fact, the number of patients with MM in 2018 reached about eight times its number from the 1970s (*17*). MM is extremely rare in people under 30 years of age, with a reported frequency of 0.02% to 0.3%. Approximately 90% of cases occur in patients over 50 years (*2*). In our survey, 83 out of 98 (84.7%) were more than 50 years old, consistent with previous studies.

As mentioned earlier, MM can manifest as osteolytic lesions without subjective symptoms. Almost 80% of patients with MM have radiological findings on skeletal surveys most commonly affecting the following sites: vertebrae (65%), ribs (45%), skull (40%), shoulder (40%), pelvis (30%), and long bones (25%) (*20*). However, no studies examined the mandible, a site primarily evaluated by dental surgeons during DFI screening before chemotherapy (*10*). In our survey, the prevalence of POLs in the skull was 42.9%, similar to previous studies. As a new finding, POLs in the mandible were identified in 18.4% of the patients. Although POLs do not commonly occur in the mandible, we suggest that if osteolytic lesions unlikely to be associated with DFIs are found in the mandible of MM patients, the possibility of POLs should be considered.

As mentioned earlier, dental surgeons often evaluate the oral cavity and the jawbone as a pre-chemotherapy screening for DFIs in patients with hematologic malignancies, and if necessary, remove the foci during the extraction of the associated tooth (*10*). However, it should be noted that surgery on MM patients with POLs is prone to postoperative complications, reported to have occurred in as many as 20.8% of cases. These include abnormal bleeding, abnormal bone fractures, and SSI (*5*). In another study, the risk of developing

Table 3. Proportion of punched-out lesions by site of the mandible confirmed on CT and panoramic radiograph

Screening method	Sites of the mandible					
	Symphysis	Body	Angle	Ramus	Coronoid process	Subcondylar process
CT	0/18 (0%)	12/18 (66.7%)	15/18 (83.3%)	16/18 (88.9%)	2/18 (11.1%)	8/18 (44.4%)
Panoramic radiograph[†]	0/14 (0%)	9/14 (64.3%)	11/14 (78.6%)	12/14 (85.7%)	1/14 (6.7%)	6/14 (40.0%)

[†]Four patients did not undergo panoramic radiographic examinations probably due to their low level of activity in daily life.

bacterial infections such as septicemia and osteomyelitis in MM patients was seven-fold compared to the control subjects without previous hematologic malignancies. During the first year following diagnosis, the risk was 11-fold (*21*). In addition, a more progressed stage of ISS leads to easier infection by bloodstream pathogens and a higher mortality rate (*22,23*). Although there is still no valid literature reporting on the postoperative course for the oral maxillofacial region of MM patients with POLs, if surgery is required, we should carefully perform the differential diagnosis and explain to patients the benefits of surgery as well as possible complications.

Panoramic radiographs, a radiologic technique for producing a single image of the facial structures, including the dental arches and jawbones, are particularly good at visualizing the mandible with less three-dimensional bone overlap. On the other hand, panoramic radiographs have a three-dimensional curved zone, called the focal trough, in which anatomical structures are well defined (*24*). Objects outside the focal trough are blurred, magnified, reduced in size, and sometimes distorted to the extent of not being recognizable, which is more likely to occur at a site anterior to the mandible, including the anterior teeth and symphysis. These circumstances indicate that the diagnostic accuracy at sites outside the focal trough is relatively low (*24*). In this study, the number of POL cases in the mandible was as small as 18; thus, it is not definitive. However, the proportion of POLs in the mandibular body, mandibular ramus, and mandibular angle, which were relatively clear in panoramic radiographs, were overwhelmingly high. Furthermore, POLs were not found in the symphysis. Therefore, panoramic radiographs can be used for assessing the mandible of MM patients. In addition, the HU value in CT correlates with the degree of radiolucency in two-dimensional plain radiographs (*25*). Considering the results of our study, which showed that POLs had a similar or slightly lower bone mineral density than the mental foramen, comparison with the mental foramen can be a diagnostic reference when evaluating the mandible with panoramic radiography.

According to Cardoso *et al.*, the initial oral symptoms of MM that triggered consultation varied. Among these were painless gingival swelling, difficult swallowing, and paresthesia in the trigeminal distribution of division III (*26*). However, in this study, only one patient had oral symptoms consistent with the POL site presenting as painless swelling with a smooth mucosal surface.

This study has several limitations. First, this is a cross-sectional study; thus, the clinical course of POLs in the oral cavity has not been sufficiently examined. Second, oral symptoms associated with MM may appear over time. Therefore, further studies are required to investigate the clinical course of POLs in the mandible and the effects of dental and oral surgery on MM patients with concomitant POLs in the mandible. In addition, although the ISS is used for the staging of symptomatic MM in this study, Palumbo *et al.* proposed the Revised-International Staging System (R-ISS) in 2015, which combines the ISS with chromosomal abnormalities detected by interphase fluorescent in situ hybridization and serum lactate dehydrogenase level (*27*). R-ISS is expected to be a staging classification that better reflects the improved prognosis of patients after the approval of new drugs such as proteasome inhibitors (*e.g.*, carfilzomib) in 2016 and monoclonal antibodies (*e.g.*, daratumumab) in 2017 (*28,29*); further, it has also been applied to radiological diagnostic studies related to osteolytic bone lesions in recent years (*30*). In this study, this classification of MM may provide new insights into the impact of POLs in the jawbone on patient quality of life and of the hematologic treatment on POLs over time.

In conclusion, although the prevalence of POLs in the mandible is low, POLs in the mandible were confirmed in patients with symptomatic MM, and their prevalence increased as the MM stage progressed. Confirmation of POLs in the mandible is possible not only by CT but also by panoramic radiography, and the mental foramen is likely to be a reference for discrimination. Considering the reports that surgery on MM patients with POLs is prone to postoperative complications, dental surgeons need to differentiate POLs when examining DFIs in multiple myeloma patients before surgery.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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