Clinical Investigation of Diffuse Large B-cell Lymphoma Exhibiting Initial Symptoms in the Maxilla and Mandible

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Research

**Keywords:** diffuse large B-cell lymphoma, mandibular bone, maxillary bone, imaging finding, clinical feature

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Abstract

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphatic tumor; however, extranodal DLBCLs that exhibit initial symptoms in the maxilla and mandible are rare. Moreover, DLBCL is clinically classified as a moderate to highly malignant lymphatic tumor that can progress rapidly; therefore, early diagnosis is crucial. However, diagnosis is difficult because the disease causes a diverse range of clinical symptoms with no characteristic imaging findings. We conducted a clinical investigation to clarify the clinical characteristics of DLBCL exhibiting initial manifestation in the maxilla and mandible.

Methods

Of the 2748 patients with malignant tumors of the oral and maxillofacial region examined during a period of 11 years between January 2006 and December 2016 at our hospital, 27 primary cases diagnosed with DLBCL based on the chief complaint of symptoms in the gingiva and bone of the maxilla and mandible were enrolled. We evaluate on sex, age, whether treatment was provided by a previous physician, symptoms, disease period until seeking treatment, clinical diagnosis, laboratory findings, and imaging results.

Results

There were 15 cases with maxilla involvement and 12 with mandible involvement. The median disease period until seeking of treatment was 60 d (3–450 d). All cases exhibited a tumor or a mass, and hypoesthesia of the chin was confirmed in 8 cases with mandible involvement. The clinical stage was stage I in 8 cases, stage II in 10 cases, and stage IV in 9 cases. Serum lactate dehydrogenase (LDH) levels were elevated in 13 of 22 patients. The overall survival rate was 63%.

Conclusion

The possibility of Malignant Lymphomas (MLs), such as DLBCL, must be considered while treating lesions of the oral and maxillofacial region.

Background

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma that accounts for 30–40% of such lesions [1]. Nodal lymphomas arise within a lymph node, whereas extranodal lymphomas develop in a non-lymph node tissue. Extranodal DLBCLs in the maxilla and mandible are rare, and differential diagnosis is difficult because they often exhibit clinical findings similar to that in tumors and/or inflammation at other sites. Some reports have described the clinical characteristics of extranodal DLBCLs of the maxilla and the mandible [2, 3]. Therefore, we investigated the clinical characteristics of 27 primary cases of DLBCL definitively diagnosed after they presented at our facility with the chief complaint of symptoms of the maxilla and mandible. Here we report on these characteristics and present on a review of the literature.

Methods

Of the 2748 cases of malignant tumors of the mouth and jaws examined during the 11 years from January 2006 through December 2016 at our hospital, 27 primary cases definitively diagnosed with DLBCL based on the chief complaint of symptoms in the gingiva and bone of the maxilla and mandible were enrolled. There were 19 male patients and 8 female patients. The median age at the initial examination was 72 years (37–95 years). The site of onset was the maxilla in 12 cases, maxillary gingiva in 3, mandible in 10, and mandibular gingiva in 2 (Table 1).
Table 1
Demographic and clinical features of 27 patients.

| No | Age | Gender | Anatomic location | Prior treatment | Duration of illness (days) | Swelling | Paralysis | Ulceration | Pain | Tooth mobility | PS | First clinical diagnosis |
|----|-----|--------|-------------------|-----------------|---------------------------|----------|-----------|------------|------|------------------|----|--------------------------|
| 1  | 67  | M      | Maxillary gingiva | –               | 14                        | +        | –         | –          | –    | –                | 1  | pericoronitis            |
| 2  | 79  | F      | Maxilla           | –               | 90                        | +        | –         | –          | –    | +                | 3  | gingival carcinoma      |
| 3  | 54  | M      | Maxilla           | RCT             | 30                        | +        | –         | –          | –    | +                | 0  | maxillary sinus carcinoma |
| 4  | 67  | M      | Maxilla           | RCT             | 60                        | +        | –         | –          | +    | +                | 0  | ML                       |
| 5  | 41  | M      | Maxilla           | –               | 150                       | +        | –         | –          | –    | +                | 0  | nonepithelial malignant tumor |
| 6  | 72  | F      | Maxilla           | Incision        | 14                        | +        | –         | –          | –    | +                | 0  | inflammation            |
| 7  | 77  | M      | Maxilla           | –               | 21                        | +        | –         | +          | –    | –                | 0  | maxillary sinus carcinoma |
| 8  | 59  | F      | Maxilla           | Tooth extraction | 60                        | +        | –         | +          | –    | –                | 0  | nonepithelial malignant tumor |
| 9  | 81  | M      | Maxillary gingiva | Incision        | 60                        | +        | –         | +          | –    | +                | 1  | gingival carcinoma      |
| 10 | 84  | M      | Maxilla           | –               | 42                        | +        | –         | +          | –    | –                | 3  | nonepithelial malignant tumor |
| 11 | 74  | M      | Maxilla           | Tooth extraction | 14                        | +        | –         | +          | –    | –                | 1  | gingival carcinoma      |
| 12 | 77  | F      | Maxilla           | –               | 14                        | +        | –         | +          | +    | –                | 0  | ML                       |
| 13 | 81  | M      | Maxillary gingiva | Injury treatment | 120                       | +        | –         | –          | –    | +                | 2  | gingival carcinoma      |
| 14 | 95  | F      | Maxilla           | –               | 60                        | +        | +         | +          | –    | –                | 3  | salivary gland carcinoma |
| 15 | 75  | M      | Maxilla           | Incision        | 60                        | +        | +         | –          | –    | +                | 0  | non-epithelial malignant tumor |
| 16 | 57  | M      | Mandibular        | Operation (another diagnosis) | 450 | +        | +         | +          | –    | –                | 0  | malignant tumor         |
| 17 | 52  | F      | Mandibular        | Operation (another diagnosis) | 360 | +        | +         | –          | –    | +                | 0  | osteomyelitis           |
| 18 | 68  | M      | Mandibular        | Tooth extraction | 330                       | +        | –         | –          | +    | –                | 0  | mandibular tumor        |
| 19 | 71  | F      | Mandibular        | –               | 3                         | +        | +         | –          | +    | –                | 0  | carcinoma (PIOSCC)       |
| 20 | 76  | M      | Mandibular        | Tooth extraction | 210                       | +        | –         | –          | –    | –                | 1  | inflammatory granulation tissue |
| 21 | 81  | M      | Mandibular        | RCT             | 90                        | +        | +         | –          | +    | +                | 1  | osteomyelitis           |
| 22 | 83  | M      | Mandibular gingiva| Tooth extraction | 6                         | +        | –         | –          | –    | +                | 1  | malignant tumor         |
| 23 | 70  | M      | Mandibular        | Tooth extraction | 14                        | +        | +         | –          | +    | +                | 0  | ML                       |
We investigated the parameters, including symptoms, clinical diagnosis, clinical stage, treatment method, and prognosis based on the medical records of these patients.

The $\chi^2$ test or Fisher’s exact probability was used for statistical analysis. The values were expressed as mean ± standard deviation. The Kaplan–Meier limit method was employed to determine overall survival (OS). Follow-up intervals were calculated in months from the date of the first visit to our hospital to the date of the last follow-up or death. Statistical significance was determined using log-rank (Mantel–Cox) tests. P-values < .05 were considered statistically significant. The analyses were performed using SPSS Statistics version 25 (IBM, Chicago, IL, USA).

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Tokyo Medical and Dental University, Faculty of Dentistry (No. D2015-600-03).

Results

Table 1 summarizes the clinical findings at the initial examination.

### History of treatment before the initial examination

Sixteen patients (59.3%) had previously undergone diagnosis and treatment of the site at a previous dental clinic or another Department of Oral Surgery before the initial examination performed at our department. Tooth extraction had been performed for six cases, resection for four cases, root canal treatment for three cases, and surgical treatment based on another diagnosis for two cases.

### Disease period until seeking treatment

The median disease period from the time of symptom onset to the time of treatment seeking was 60 d (3–450 d). A significant difference was observed between the median disease period until seeking treatment for maxilla cases (60 d) and mandible cases (120 d).

### Symptoms

Tumors were detected in almost all patients (26 cases; 96.3%). Tooth instability was noted in 11 cases (47.8%; excluding 4 edentulous cases) and desensitization of the chin or buccal region was present in 10 cases (2/15 maxilla cases; 13.3%, 8/12 mandible cases; 66.7%). Pain was reported by 10 patients (37.0%) and ulceration in 9 cases (33.3%). The Eastern Cooperative Oncology Group (ECOG) Performance Status was $\geq 2$ in 5 cases (18.5%).

### Clinical diagnosis at the initial examination

Based on these clinical symptoms and findings, the diagnosis made at the initial examination was suspected ML in 6 cases (22.2%), suspected malignant tumor in 14 (51.9%), suspected benign tumor in 2 (7.4%), and suspected inflammation in 5 (18.5%).

Table 2 summarizes the imaging findings, hematological findings, staging and clinical course.
In contrast to those with other tumors, some cases with marked progression into the bone of the maxilla or the mandible or progression into the maxillary sinus with permeable bone resorption, a return to almost normal anatomical structure was confirmed after treatment. The anatomical structure did not recover completely in cases involving progression into the alveolar bone due to teeth movement. Resorption of the alveolar bone

Table 2

| CT     | MRI     | PET-CT | LDH | EBV | Stage | NCCN-IPI risk group | Treatment | RT |
|--------|---------|--------|-----|-----|-------|---------------------|-----------|----|
| No     |         |        |     |     |       |                     |           |    |
| 1      | –       | –      | 20  | 73.8| 319.6 | 2B                  | L-I       |    |
| 2      | –       | –      | 39.3| 956.3| 6378.5| 2B                  | L-I       |    |
| 3      | –       | –      | 31.7| 1114.2| 7621.1| 2B                  | L-I       |    |
| 4      | 0.681   | –      | 6.8 | 24  | 98.4  | 2B                  | L-I       |    |
| 5      | –       | –      | 204 | –   | 2B    | 2B                  | L-I       |    |
| 6      | –       | –      | 14.6| 1075.6| 5378  | 2B                  | L-I       |    |
| 7      | –       | –      | 33.2| 40.5| 421.2 | 2B                  | L-I       |    |
| 8      | –       | –      | 15.6| 45.5| 200.2 | 2B                  | L-I       |    |
| 9      | –       | –      | 4.5 | 51.6| 180.6 | 2B                  | L-I       |    |
| 10     | 0.45    | –      | 16.7| 1022.1| 5008.3| 2B                  | L-I       |    |
| 11     | 0.58    | –      | 32.4| 121.9| 889.9 | 2B                  | L-I       |    |
| 12     | 0.5     | –      | 47.6| 750.4| 4052.2| 2B                  | L-I       |    |
| 13     | 0.952   | –      | 13.9| 51.6| 180.6 | 2B                  | L-I       |    |
| 14     | –       | –      | 38.5| 1343.2| 9402.4| 2B                  | L-I       |    |
| 15     | 0.486–0.566| –   | 68.6| 269.5| 5470.9| 2B                  | L-I       |    |
| 16     | –       | –      | 29.1| 564.1| 5979.5| 2B                  | L-I       |    |
| 17     | –       | –      | 6.7 | 5.9 | 9.3   | 2B                  | L-I       |    |
| 18     | –       | –      | 20.8| 60.5| 423.5 | 2B                  | L-I       |    |
| 19     | –       | –      | 17  | 24.3| 145.8 | 2B                  | L-I       |    |
| 20     | –       | –      | 16.2| 37.4| 235.6 | 2B                  | L-I       |    |
| 21     | –       | –      | 0.735| 8.7 | 16.2 | 2B                  | L-I       |    |
| 22     | –       | –      | 23  | 5.8 | 2.9   | 2B                  | L-I       |    |
| 23     | –       | –      | 24  | 0.581| 15.1 | 2B                  | L-I       |    |
| 24     | –       | –      | 0.648| 7.2 | 76.6 | 2B                  | L-I       |    |
| 25     | –       | –      | 0.73| 7.2 | 40.8 | 2B                  | L-I       |    |
| 26     | –       | –      | 155 | –   | 155  | 2B                  | L-I       |    |
| 27     | –       | –      | 155 | –   | 155  | 2B                  | L-I       |    |

N.E.D: no evidence of disease, D.O.C: died from other cause, D.O.D: died of disease

Imaging findings

Characteristic imaging findings indicating malignant lymphoma in the maxilla or the mandible include permeable bone resorption on computed tomography (CT) images, low apparent diffusion coefficient (ADC) for the mass on magnetic resonance imaging (MRI) [4], and strong fluorodeoxyglucose (FDG) uptake on positron emission tomography–computed tomography (PET-CT) [5]. Permeable bone resorption on CT was noted in 12/15 patients (80%) who underwent imaging of the maxilla and 5/12 patients (41.7%) who underwent imaging of the mandible. Permeable bone changes were observed when the base of the tumor was in the mandibular body or ramus.

In contrast to those with other tumors, some cases with marked progression into the bone of the maxilla or the mandible or progression into the maxillary sinus with permeable bone resorption, a return to almost normal anatomical structure was confirmed after treatment. The anatomical structure did not recover completely in cases involving progression into the alveolar bone due to teeth movement. Resorption of the alveolar bone
was common on the buccal side of the mandible, in particular, in cases with inflammation. Many patients with lesions in the alveolar bone exhibited compression-type bone resorption.

The median ADC was $0.62 \times 10^{-3}$ mm$^2$/s for the 10 cases where confirmation could not be performed using MRI. FDG uptake on PET-CT was observed in all patients who underwent such testing, and the median SUV\textsubscript{max} value was 16.7. The FDG uptake was stronger in patients with maxilla involvement than in those with mandible involvement. The mean maximum standardized uptake value (SUV\textsubscript{max}) was 29.1 for the cases with maxilla involvement and 13.4 for those with mandible involvement. The SUV\textsubscript{max}, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) increased with larger target lesions, and the values were higher for the patients with maxilla involvement than for those with mandible involvement.

### Hematological findings

Serum lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R) are biomarkers of malignant lymphoma. Serum LDH was higher than the normal upper limit in 13 patients. The measurement of sIL-2R was performed only for three patients, and one patient exhibited an abnormally high value for sIL-2R.

### Clinical stage, National Comprehensive Cancer Network –International Prognostic Index (NCCN-IPI), treatment method, and prognosis

Clinical stage, as per the Ann–Arbor staging, was stage I for 8 patients, stage II for 10 patients, and stage IV for 9 patients. B symptoms (fever, night sweat, and weight loss) were observed in one stage II case and one stage IV case.

NCCN-IPI result based on age ($\geq 60$ y), serum LDH, performance status (PS) (ECOG PS2–4), clinical staging (III, IV), and at least two extranodal lesions was low-intermediate for 9 patients, high-intermediate for 14 patients, and high for 4 patients. The treatment method was 6–8 courses of chemotherapy based on R-CHOP for 19 patients, 3–4 courses of R-CHOP and radiotherapy at 30–40 Gy applied to the head and neck region for 4 patients, and best supportive care (BSC) for 4 patients. Reasons for BSC included difficulty in the treatment procedure, patient refusal to undergo treatment, or dementia. The 5-year survival rate was 63% (Fig. 1a) for the overall study population ($n = 27$), 75% for stage I patients, 70% for stage II patients, and 44% for stage IV patients (Fig. 1b). All the patients in the group classified as high as per the NCCN-IPI were elderly; only one patient could undergo chemotherapy, and all patients had a poor prognosis. All the patients in the low-intermediate group demonstrated disease-free survival. The sample size was relatively small; therefore, no significant differences were noted among the groups.

### Discussion

Malignant lymphoma is the third most common malignant lesion of the oral cavity and the maxillofacial region after squamous cell carcinoma and salivary gland cancer [5, 6]. Malignant lymphomas can be broadly classified based on the histopathological findings as either Hodgkin’s lymphoma or non-Hodgkin’s lymphoma [7]. Majority of the lymphomas that develop in the oral cavity region are non-Hodgkin’s lymphomas.

Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) as defined in the 2017 World Health Organization (WHO) classification, accounts for $>30\%$ of all non-Hodgkin lymphomas in Japan, making it the most prevalent form of NHL [8]. Approximately 40% of DLBCLs involve extranodal lesions [9]. Oral cavity DLBCLs mainly arise in the gingival and palate mucosa, and few studies have reported such lesions arising in the jaw bone [10]. Our data indicated that most of these cases arose in the jawbone, whereas few developed in the gingiva.

Lesions were more common in men than in women (2.4:1), with a higher proportion of male cases being reported than in previous trials [1, 11, 12]. The mean age in our study (69 y) was equivalent to that in earlier studies [1, 11, 12].

As DLBCLs arising in the jawbone often also involve dental infections, many patients undergo treatments such as root canal therapy and periodontal treatment [10]. We found that 59.3% of our patients had undergone some type of dental treatment before the initial examination performed at our department.

Clinical symptoms are diverse, including painless tumors, tooth instability, desensitization of the buccal or chin region, and ulceration. Most patients are asymptomatic in the initial stages, with various symptoms appearing with increase in lesion size. This could be the reason for the high proportion of clinical misdiagnosis and delayed diagnosis [13].

With respect to the imaging findings, bone destruction was not clearly observable on panoramic radiography images; however, careful observation revealed diffuse bone destruction as well as disappearance of the maxillary sinus border in the maxilla and unclear cortical bone in the mandible, with increased X-ray permeability. On CT images, relatively little cortical bone destruction is observable and masses wherein a permissive pattern of bone destruction prevail with no clear periosteal reaction are noted [14]. In our study, 80% of the cases with maxilla involvement exhibited permeable bone resorption on CT images; this percentage was higher than that in those with mandible involvement. We believe that this reflects the fact that the tumor diameter in the cases with maxilla involvement was larger than that for those with mandible involvement. Hypointense signals on T1-weighted MRI and moderate enhancing effects on fat-suppressed contrast-enhanced T1-weighted MRI are common observations. In jawbone DLBCL, ADC is low on diffusion-weighted images and, in contrast to many other squamous cell carcinomas in the oral cavity, strong diffusion is observed [15]. On FDG-PET, the FDG uptake localized to the tumor region was observed. Similar to that in other tumors, SUV\textsubscript{max} is unrelated to malignancy or
prognosis, being dependent on the tumor size. The SUVmax was smaller for patients with maxilla involvement and a large tumor diameter (median: 42 mm) than for those with mandible involvement and a small tumor diameter (median: 33 mm).

The serum LDH activity and sIL-2R levels are measured as biomarkers for lymphoma patients [16]. However, these are rarely measured in patients who are not initially diagnosed with malignant lymphoma in the clinical setting. The LDH levels were elevated in approximately 50% of our patients who underwent hematological testing in the early stages. The serum LDH levels often rise non-specifically; therefore, we believe that it should be used as an auxiliary aid for diagnosis.

Many DLBCLs of the oral cavity and the maxillofacial region are believed to be stage I or II at the onset [12]; however, about one-third of our patients were classified into stage IV. This ratio was higher than that reported in previous studies. B symptoms are generally uncommon and were noted in only 7.4% of our patients. While the OS of 63% could not be described as highly favorable, it was consistent with previous reports. NCCN-IPI result closely reflected the prognosis. In the future, treatment methods for patients with poor prognosis need to be developed.

**Conclusions**

The possibility of MLs, such as DLBCL, must be considered while treating lesions of the oral and maxillofacial region.

**Abbreviations**

DLBCL  
diffuse large B-cell lymphoma  
ML  
malignant lymphoma  
ECOG  
Eastern Cooperative Oncology Group  
CT  
computed tomography  
ADC  
an apparent diffusion coefficient  
MRI  
magnetic resonance imaging  
FDG  
fluorodeoxyglucose  
PET-CT  
positron emission tomography–computed tomography  
SUVmax  
maximum standardized uptake value  
MTV  
metabolic tumor volume  
TLG  
total lesion glycolysis  
LDH  
lactate dehydrogenase  
sIL-2R  
soluble interleukin-2 receptor  
NCCN-IPI  
National Comprehensive Cancer Network-International Prognostic Index  
PS  
performance status  
BSC  
best supportive care  
DLBCL, NOS  
Diffuse large B-cell lymphoma, not otherwise specified  
WHO  
World Health Organization  
NHL  
non-Hodgkin lymphomas
Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Tokyo Medical and Dental University, Faculty of Dentistry (No. D2015-600-03). Informed consent for participation was obtained from the patients.

Consent for publication

Informed consent for publication of this article and its contents was obtained from the patients.

Availability of data and materials

The data is available through e-mail from the corresponding author.

Competing interests

The authors report no financial or other conflict of interest relevant to this article, which is the intellectual property of the authors.

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Authors’ contributions

YM conceived this report, drafted the article and revising it critically for important intellectual content. HH and TY helped to draft the manuscript. YO, KO, TK, TK, HH, YM, HS, HT and HK helped to collect of patient information. KK drafted the pathological part of the article and revising it. JS drafted the image-finding part of the article and revising it. All authors read and approved the final manuscript.

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**Figures**

![Figure 1](image)

**Figure 1**

Kaplan–Meier survival analysis in patients with mucoepidermoid carcinoma. (a), representation of total 5-year overall survival (OS) in patients with DLBCL. OS in patients with DLBCL according to (b), Ann–Arbor classification.