Diffuse large B cell lymphoma originating from the maxillary sinus with skin metastases: A case report and review of literature

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Abstract

BACKGROUND
Diffuse large B-cell lymphoma (DLBCL) is the most common type of malignant lymphoma (ML), accounting for 30%-40% of cases of non-Hodgkin's lymphoma (NHL) in adults. Primary paranasal sinus lymphoma is a rare presentation of extranodal NHL that accounts for only 0.17% of all lymphomas. ML from the maxillary sinus (MS) is a particularly rare presentation, and is thus often difficult to diagnose. We have reported the first known case of DLBCL originating from the MS with rapidly occurring multiple skin metastasis.

CASE SUMMARY
An 81-year-old Japanese man visited our hospital due to continuous pain for 12 d in the left maxillary nerve area. His medical history included splenectomy due to a traffic injury, an old right cerebral infarction from when he was 74-years-old, hypertension, and type 2 diabetes mellitus. A plain head computed tomography (CT) scan revealed a 3 cm × 3.1 cm × 3 cm sized left MS. On day 25, left diplopia and ptosis occurred, and a follow-up CT on day 31 revealed the growth of the left MS mass. Based on an MS biopsy on day 50, we established a definitive diagnosis...
INTRODUCTION
Non-Hodgkin’s lymphoma (NHL) refers to a category of neoplasms originating in lymphoreticular system cells; these malignancies are extremely diverse, and frequently tend to affect organs and tissues that would ordinarily contain no lymphoid cells[1,2]. Some 40% of NHL cases develop in extranodal sites, and the stomach, liver, soft tissue, dura, bone, intestine, and bone marrow are among the most common primary extranodal lymphoma sites[1]. However, primary NHL has been found to rarely affect the nasal cavities or the paranasal sinuses[1].

The most common variety of malignant lymphoma (ML) originating from the germlinal center is diffuse large B-cell lymphoma (DLBCL), which accounts for some 30%-40% of adult NHL cases worldwide. This group of diseases is heterogeneous, with variable outcomes that are differentially characterized through clinical features, cell of origin (COO), molecular features, and, of late, frequently recurring mutations[3-8]. One particular type of NHL, primary paranasal sinus lymphoma (PPSL), is a rare presentation of extranodal NHL: It accounts for just 0.17% of all lymphomas, and has a distinct natural history unlike other lymphomas, and can frequently be difficult to diagnose[3,9]. This rare presentation of lymphoma is typified by bulky local tumors; ML of the maxillary sinus (MS) is likewise very rare, but it is also the most common site of origin for PPSL[3,10-16]. In one study of DLBCL originating from the sinonasal tract, a significant difference (P < 0.01) was found in the age at time of diagnosis between men (65.3-years-old) and women (71.1-years-old)[17]. In addition, the most common DLBCL primary sites were the MS (36.1%) and the nasal cavity (34.5%), with the nasal cavity being more common as a primary site in Asian/Pacific Islander
patients (43.4%), and the MS being more common in patients of Caucasian (36.3%) and African (42.1%) descent[17]. Primary immunodeficiency diseases, a group of uncommon gene defects with various manifestations, demonstrate a high risk of malignancy[13]. It is extremely rare for DLBCL metastasize to the skin: there have been only known two case reports, with one originating from the lungs and the other from the testis[4,18]. To date, there have not been any reports of DLBCL originating from the MS with skin metastasis; therefore, we have reported the first such case, together with a brief review of the literature.

**CASE PRESENTATION**

**Chief complaints**
An 81-year-old Japanese man visited our hospital due to pain in the left maxillary nerve area (We defined the day of this visit as day 1).

**History of present illness**
The symptom had first occurred 12 d prior, and it was continuous, prickly, and persistent. He tried to keep the affected part cooled, but the symptom did not improve. On the other hand, he had no recent loss of appetite or body weight, nor night sweats.

**History of past illness**
The patient’s medical history included a splenectomy due to traffic injury, an old right cerebral infarction from when he was 74-years-old, hypertension, type 2 diabetes mellitus, and constipation. He was given 15 mg of mosapride, 75 mg of clopidogrel, 20 mg of esomeprazole magnesium, 4 mg of benidipine, 5 mg of linagliptin, 1500 mg of metformin, and 24 µg of lubiprostone on a regular basis.

**Personal and family history**
The patient had no history of smoking or drinking alcohol. He did not undergo regular medical exams. The patient had previously been a carpenter, but was no longer employed. He had no food or drug allergies. He did not need any assistance for everyday life activities. He had a family of six, and presented no family history of malignant disease.

**Physical examination**
The patient was 165 cm tall and weighed 60 kg. His vital signs were normal, with blood pressure of 137/82 mmHg, heart rate of 75 regular beats/min, body temperature of 36.1 °C, oxygen saturation of 98% in ambient air, and respiratory rate of 16/min; his Glasgow Coma Scale score was 15 points (E4V5M6). Nothing else abnormal was detected upon physical examination, including skin or neurological findings.

**Laboratory examinations**
A routine laboratory examination revealed increased values for white blood cells, proportions of monocyte and basophil, calcium, lactate dehydrogenase, plasma glucose, glycated hemoglobin, C-reactive protein, erythropoietin, immunoglobulin G, immunoglobulin A, fibrinogen, d-dimer and decreased values of red blood cells, hemoglobin, hematocrit, proportion of neutrophil, lymphocyte, eosinophil, platelets, sodium, albumin, high-density lipoprotein cholesterol, zinc, thyroid stimulating hormone, free triiodothyronine, and free thyroxine. On the other hand, other tests had normal results, including biochemistry, urine qualitative and sediment, and two fecal occult blood tests (Table 1).

**Imaging examinations**
A plain head computed tomography (CT) scan revealed a 3 cm × 3.1 cm × 3 cm sized left MS in the patient, completely filled with mass, with a partially high-density area confirmed inside (Figure 1).

**Further diagnostic work-up**
The patient was referred to an otolaryngologist. At this point, the otolaryngologist suspected a diagnosis of malignant melanoma. On the other hand, she also considered a biopsy under general anesthesia to be very risky due to the patient’s advanced age. Therefore, she made an appointment for a follow-up CT 2 mo later. Following this, left
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Table 1 Routine laboratory examination, urinalysis, and fecal occult blood test from the patient’s first visit

| Parameter (Units)                                      | Measured value | Normal value |
|-------------------------------------------------------|----------------|--------------|
| White blood cell (10^3/µL)                            | 13.2           | 3.8-8.5      |
| Neu (%)                                               | 30             | 48-61        |
| Lym (%)                                               | 13             | 25-45        |
| Mon (%)                                               | 54             | 4-7          |
| Eos (%)                                               | 0              | 1-5          |
| Bas (%)                                               | 3              | 0-1          |
| Blast (%)                                             | (-)            | (-)          |
| Red blood cell (10^6/µL)                              | 2.67           | 3.78-4.97    |
| Hemoglobin                                            | 8.7            | 13.7-17.4    |
| Hematocrit                                            | 26.4           | 40.2-51.5    |
| Platelet (10^3/µL)                                    | 113            | 131-365      |
| Aspartate transaminase (IU/L)                         | 28             | 12-31        |
| Alanine aminotransferase (IU/L)                       | 13             | 8-40         |
| Lactic acid dehydrogenase (IU/L)                      | 311            | 110-210      |
| Alkaline phosphatase (IU/L)                           | 294            | 100-330      |
| Gamma-glutamyl transpeptidase (IU/L)                  | 34             | 9-49         |
| Total bilirubin (mg/dL)                               | 0.38           | 0.3-1.2      |
| Total protein (g/dL)                                  | 6.8            | 6.7-8.3      |
| Albumin (g/dL)                                        | 3.3            | 3.9-4.9      |
| Creatine phosphokinase (IU/L)                         | 61             | 65-275       |
| Blood urea nitrogen (mg/dL)                           | 13.1           | 8-22         |
| Creatinine (mg/dL)                                    | 0.77           | 0.4-0.8      |
| Amylase (IU/L)                                         | 84             | 39-134       |
| Sodium (mEq/L)                                        | 137            | 138-146      |
| Potassium (mEq/L)                                     | 4.1            | 3.6-4.9      |
| Chloride (mEq/L)                                      | 101            | 99-109       |
| Calcium (mg/dL)                                       | 11.9           | 7.1-10.1     |
| C-reactive protein (mg/dL)                            | 1.35           | 0-0.4        |
| Plasma glucose (mg/dL)                                | 156            | 70-109       |
| Glycated Hemoglobin (NGSP) (%)                        | 7.8            | 4.6-6.2      |
| Low-density lipoprotein cholesterol (mg/dL)           | 78             | 66-141       |
| High-density lipoprotein cholesterol (mg/dL)          | 26             | 41-95        |
| Triglyceride (mg/dL)                                  | 109            | 30-150       |
| Serum iron (µg/dL)                                    | 74             | 60-200       |
| Total iron-binding capacity (µg/dL)                   | 337            | 250-355      |
| Unsaturated iron binding capacity (µg/dL)             | 263            | 130-320      |
| Ferritin (ng/mL)                                      | 137.7          | 21-282       |
| Copper (MCG/DL)                                       | 143            | 66-130       |
| Erythropoietin (mIU/mL)                               | 35.7           | 4.2-23.7     |
| Haptoglobin (mg/dL)                                   | 104            | 19-170       |
| Zinc (µg/dL)                                          | 71             | 80-130       |
A plain computed tomography scan on day 1. The 3 cm × 3.1 cm × 3 cm sized left maxillary sinus of the patient was completely filled with mass, and a partially high-density area was confirmed inside.

diplopia and ptosis occurred on day 25, and they persisted, so the patient visited our hospital on day 31. A physical examination confirmed left ptosis (Figure 2A). Additionally, when we opened his eyes passively, hyperexophoria of the left eye was confirmed (Figure 2B). A follow-up CT performed on the same day revealed the growth of the left MS mass, together with oppression and involvement of the orbital base, and the destruction of the anterior, internal, and external walls. An MS biopsy was performed on day 50, after a 7-d washout period. The hematoxylin and eosin stain pathological findings revealed the following: (1) Aggregates of large, atypical lymphocytes with irregular nuclei with uneven chromatin, and small to large nucleoli evident in a necrotic background; (2) Some cells showed multilobulated nuclei; and (3) Mitosis and apoptotic bodies were conspicuous (Figure 3A). Immunohistochemical staining revealed positive results for cluster of differentiation (CD) 20-positive cells, bcl-6-positive cells, and MUM1-positive cells (Figures 3B-D, respectively). It also
revealed negative results for the T cell markers CD3, CD7, and CD45RO. A genetic test was not performed. Here, we excluded the possibility for T cell origin, as well as for the sinus/nasal origin, and established a definitive diagnosis of DLBCL, non-germinal center B-cell-like (GCB) originating from the left MS.

We prepared systemic chemotherapy with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), but the patient was admitted on day 62 due to rapid deterioration of his condition. During the physical examination, he could not open his left eye due to the circumocular swelling (Figure 2C). In addition, multiple skin tumors were confirmed on the chest and abdomen of the patient (Figure 2D and E, respectively). A plain CT scan revealed the following: Growth of the left MS mass, together with oppression and involvement of the orbital base, destruction of the anterior, internal, and external walls, and protuberance outside (Figure 4A); multiple tumors (0.5-1.5 cm in size) in both lungs (Figure 4B); multiple subcutaneous tumors and chest wall tumors (Figure 4C); abdominal paraaortic lymph node swelling (3 cm in size) and left kidney nodule (1-2 cm in size) (Figure 4D). He was referred to a dermatologist on the same day, and a skin biopsy was later performed on day 70. The histopathological images of the biopsy specimen from the skin mass were found to be the same as those of the left MS mass (Figures 5A-C). The measured value of the soluble interleukin-2 receptor on day 77 was 8063 U/mL, and BRAFV600E mutation was negative.

**FINAL DIAGNOSIS**

We established a definitive diagnosis of DLBCL, non-GCB, originating from the left MS, with rapidly occurring multiple skin, left kidney, and abdominal paraaortic lymph.
Figure 3 Histopathological images of the biopsy specimen from the left maxillary sinus mass taken on day 50. A: Aggregates of large atypical lymphocytes with irregular nuclei having uneven chromatin and small to large nucleoli are evident in a necrotic background. Some cells show multilobulated nuclei. Mitosis and apoptotic bodies are conspicuous. Hematoxylin and eosin staining (× 200 magnification); B: Cluster of differentiation 20-positive cells were confirmed through immunohistochemical staining (× 400 magnification); C: Bcl-6-positive cells were confirmed through immunohistochemical staining (× 400 magnification); and D: MUM1-positive cells were confirmed through immunohistochemical staining (× 400 magnification).

node metastasis.

TREATMENT
We notified the patient and his family of the disease, and they opted for palliative care, considering his condition and age.

OUTCOME AND FOLLOW-UP
The patient died on day 80. An autopsy CT was performed to confirm the cause of death, and it revealed the same findings as on day 62. However, the tumors on the skin had decreased in size. The clinical course of the patient is shown in Figure 6.

DISCUSSION
We have presented the first known case of DLBCL originating from the MS with rapidly occurring multiple skin metases. Another interesting finding was that the tumor progressed very rapidly, disseminating to the patient’s entire body, including the skin, and the patient died only 3 mo after the first appearance of symptoms. This type of rapidly progressive DLBCL case is very rare, and there is value in reporting this event.
DLBCL is remarkably heterogeneous at the clinical, genetic, and molecular levels, and the heterogeneous subtypes it contains have a variety of molecular dysregulations at the genetic, protein, and microRNA levels\[6,19\]. The clinical presentation of the patient is a particularly important feature, as it can help to differentiate inflammatory processes or other etiologies from neoplastic processes in the bones\[20\]. For DLBCL originating from the MS, the most common presenting symptoms are a mildly painful swelling of the unilateral maxilla, nasal obstruction, stuffiness, pain, mucopurulent rhinorrhea, recurrent epistaxis, diplopia, and rapidly enlarging masses, often with both local and systemic symptoms (such as fever, recurrent night sweats, or weight loss)\[1,11,13,21,22\]. Other, less commonly reported symptoms include palatal ulcer, chronic periodontal abscess, and persistent toothache\[23,24\]. Additionally, according to a radiographic imaging study of DLBCL originating from the MS, common findings included a discrete mass (59%), sinus opacification (53%), and/or bony erosion (35%)\[11\]. Regarding symptoms and CT findings, our case is comparable to DLBCL originating from the MS. On the other hand, we should have included soluble interleukin-2 receptor as a routine laboratory examination on first visit, and repeated that examination. Had we done so, we might have reached the DLBCL diagnosis and started treatment without delay.

DLBCL can be divided into GCB and non-GCB phenotypes, based on CD10, bcl-6, and MUM1 gene expression\[19,25,26\]. Because the Hans algorithm is highly concordant with the results of gene expression profiling, DLBCL is divided into GCB and non-GCB groups, based on the Hans algorithm\[8\]. The non-GCB/activated B cell-like subtype demonstrates frequent progression compared to the GCB subtype, despite standard immunochemotherapy\[5,6\].

Accurate COO-based staging should be incorporated into bone marrow (BM) examinations for DLBCL\[27\]. In addition, any organ may potentially be involved;
Figure 5 Histopathological images of the biopsy specimen from skin mass taken on day 70. A: Aggregates of large atypical lymphocytes with irregular nuclei having uneven chromatin and small to large nucleoli are evident in a necrotic background. Some cells show multilobulated nuclei. Mitosis and apoptotic bodies are conspicuous. Hematoxylin and eosin staining (× 40 magnification); B: Aggregates of large atypical lymphocytes with irregular nuclei having uneven chromatin and small to large nucleoli are evident in a necrotic background. Some cells show multilobulated nuclei. Mitosis and apoptotic bodies are conspicuous. Hematoxylin and eosin staining (× 200 magnification); and C: CD20-positive cells were confirmed through immunohistochemical staining (× 400 magnification).

Ideally, DLBCL is diagnosed through an excisional biopsy of a suspicious lymph node, which will show sheets of large cells disrupting the integrity of the underlying follicle center structure, and will stain positive for CD20, CD79a, and other pan-B-cell antigens [4,5]. COO is found through histopathology and immunohistochemical stains, while molecular features such as double- or triple-hit diseases are found using fluorescent in situ hybridization analysis[5]. DLBCL’s immunophenotype classification has a close relationship to local lymph node metastasis, and has been found to possess prognostic significance. Immunophenotype classification has also proven useful for chemotherapy protocol selection[4,26]. On the other hand, commercial tests for frequently recurring mutations are still not in routine use as a way to inform treatment[5]. Additionally, imprint cytology may potentially help in detecting DLBCL’s characteristic morphological features[28].

Though timely diagnosis is critical, misdiagnoses of this disease as being more common reactive or inflammatory lesions, such as infections, are not unusual, with the majority of patients (68%) having an advanced tumor at the time of diagnosis (stage IV of the Ann Arbor classification)[20-23,29]. Likewise, in this case, by the time of the definitive diagnosis, the patient was already at stage IV of the Ann Arbor classification-a reminder of the vital importance of timely diagnoses.

DLBCL is an aggressive lymphoma that should receive prompt immunochemotherapy; spontaneous tumor regression in patients is seen only rarely before treatment is initiated[30]. The mainstay of DLBCL treatment should continue to be combination chemoradiation, though other situational treatment options include monotherapy using chemotherapy or radiotherapy[11,17]. The overwhelming majority of localized disease patients can be cured using combined modality therapy or combination
chemotherapy on its own[1]. Approximately 50% of patients can be cured using doxorubicin-based combination chemotherapy and rituximab[1]. Rituximab has been found to significantly improve patient survival of DLBCL, especially for non-GCB subtype patients[31,32]. Regarding this last point, in this case, it might have been worth trying systemic chemotherapy, including rituximab, as a treatment to improve the patient’s condition, as well as his prognosis.

According to a recent study, a new potential treatment option for non-GCB DLBCL, with the synergistic antitumor effect of oridonin and the PI3K/mammalian target of rapamycin (mTOR) inhibitor NVP-BEZ235 was found to show promise, though the underlying mechanism may be multifunctional, involving apoptosis, threonine kinase/mTOR and NF-kB inactivation, and reactive oxygen species-mediated deoxyribonucleic acid damage response[33]. In addition, the Hans algorithm could be regarded as a theragnostic biomarker for the section of young DLBCL patients who could benefit from an immunochemotherapy regimen of intensified dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (also known as “R-ACVBP”)[34]. On the other hand a regimen of rituximab, cyclophosphamide, doxorubicin, and prednisone with bortezomib (also known as “VR-CAP”) was not seen to demonstrate improved efficacy compared to R-CHOP in non-GCB DLBCL[35].

The prognosis is variable[13]. It is crucial to pay early attention to the patient’s manifestation, select suitable treatment, and monitor manifestations[13]. Despite large advances in DLBCL treatment, approximately one patient in three has been found to progress or die, suggesting that there may also be other oncogenic events[36]. One study found a 5-year survival rate of 80%, suggesting a relatively positive prognosis for primary lymphoma of the MS[16]. The use of chemotherapy and radiotherapy have been found to significantly improve patient survival, whereas there is a significant association between Ann Arbor staging and comparatively poor outcomes[3,17]. On the other hand, one case report of DLBCL that developed in the left MS states that it relapsed as a left frontal brain mass after the disease was in remission for 4 years; this indicates the need to carefully perform long-term follow-up, even in the event of a complete remission[14].
Clinical DLBCL prognostic systems, such as the rituximab international prognostic index (IPI), age-adjusted IPI, and National Comprehensive Cancer Network IPI, use clinical factors to stratify patient risk; however, treatment approach is not affected by this[5]. IPI serves as an independent prognosticator for patients with DLBCL, and significant survival improvements were seen with the addition of rituximab[36]. In general, prognoses are relatively poor for non-GCB DLBCL, and it has been reported that there is a difference between the prognostic significances for GCB and non-GCB DLBCL[25,27]. In one study, the non-GCB type served as an independent predictor of both progression-free survival ($P < 0.004$) and overall survival ($P = 0.042$), whereas the GCB type was not found to serve as a prognostic factor independent of IPI score[27].

Using the COO of BM involvement for further prognostication can be a useful progression-free survival indicator, independent of IPI score[27]. Patients with c-myc-altered disease on its own, as well as in combination with bcl2 and/or bcl6 translocations (particularly when immunoglobulin serves as the myc translocation partner), have been found to demonstrate a poor response to up-front chemoimmunotherapy and salvage autologous stem cell transplant in the event of a relapse[7].

One novel finding regarded programmed cell death-ligand 1 (PD-L1), a member of the B7 family (also known as B7-H1) that serves as an inhibitory ligand, which is expressed on the surfaces of macrophages, dendritic cells, fibroblasts, and T cells[7]. It has been found to be more commonly expressed in the non-GCB subtype than in the GCB subtype, and there is a negative correlation between its expression in a tumor microenvironment and c-myc. Additionally, PD-L1 positivity predicts short DLBCL patient survival[7]. Therefore, strategies such as anti-PD-L1 antibody treatment should be recommended more often for patients found to have PD-L1 expression[7]. Another novel finding was that NF-κB/p65 expression has prognostic value for cases of high-risk non-GCB DLBCL, and it is considered a target suited to new therapy development[37]. Cases of non-GCB DLBCL that have negative FOXP3 are associated with favorable DLBCL prognostic parameters[8]. Serum neuron-specific enolase level may serve as an independent prognostic factor for non-GCB subtype patients; it may additionally serve as a novel disease aggressiveness marker and as a prognostic factor for non-GCB DLBCL in the era of rituximab[38]. A high Ki-67 Labeling index is considered a poor OS risk factor in the late-elderly age group and in non-GCB DLBCL patients treated with R-CHOP[32,39].

Finally, this case led to the interesting autopsy CT finding that the skin tumors had decreased in size. Related to this phenomenon, there is a report of a case of spontaneous regression of DLBCL of the MS in the setting of concurrent pneumonia and Clostridioides difficile colitis[30]. Furthermore, another case report of DLBCL encountered as a choroidal mass indicated ocular lesion resolution after fine-needle aspiration biopsy, possibly due to a mechanism of immune response[40]. While it has been proposed that the location of the tumor may be a major factor, and likewise proposed that an antitumor immune response may be a likely cause of spontaneous remission, the specific mechanisms underlying DLBCL tumor regression remain unknown[30]. Based on these reports, the tumor location and/or antitumor immune response might be important factors and/or the proposed cause of spontaneous tumor remission, but the detailed mechanism is unknown. Further basic and clinical research is warranted to elucidate this mechanism. Additionally, several of these cases occurred in concurrent infection settings[30]. Data and knowledge from carefully investigating this phenomenon could potentially lead to a more thorough understanding of the biology of DLBCL, as well as more effective immune-mediated therapies[30].

This case study has several limitations: this article only reviews a single case report and case series of DLBCL originating from the MS. Therefore, the actual situation and nature of the disease may differ from the results of our literature review, as a result of reporting bias. In addition, it was a primary lymphoma in the nasal sinus, and this patient had prior splenectomy secondary malignancies. In a previous report, splenectomized patients had an increased risk of being hospitalized for hematologic malignancies including of NHL, Hodgkin lymphoma, multiple myeloma, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, and any leukemia (rate ratios = 1.8-6.0). They also had an increased risk of death due to any cancer including of NHL, Hodgkin lymphoma, and any leukemia (rate ratios = 1.3-4.7). These observed risks were increased more than 10 years after splenectomy. On the other hand, we could not get information of histology about the removed spleen.
CONCLUSION

We have presented the first case of DCBCL originating from the MS with multiple rapidly occurring skin metastases. This case suggests the need for careful, detailed examinations when encountering patients presenting with a mass: When a neoplastic lesion is confirmed through image inspection, we should investigate thoroughly, including further image investigations and pathologic examination. Careful follow-up is also necessary.

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