Primary gingival diffuse large B-cell lymphoma with muscle invasion: A case report

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Abstract. Primary gingival diffuse large B-cell lymphoma (DLBCL) with muscle invasion is rare and accounts for ~0.5% of all reported cases of extranodal lymphoma. The present study describes the case of a 49-year-old man that initially presented at Yingshan County People's Hospital (Nanchong, China) in August 2017 with a chief complaint of tenderness and swelling of the jaw. Computed tomography revealed a mass in the gingiva, and enlarged lymph nodes in the cervical, mediastinal and gastro-hepatic ligaments. Histological examination indicated the gingival mass was a DLBCL, which was positive for CD20, BCL-6, BCL-2, C-MYC and MUM1. The patient received three lines of anti-neoplastic therapy (R-CHOP, R-CHOEP and SYHX1903) and achieved stable disease for 6 years. Subsequently, the patient experienced trauma in the left forearm due to a car accident and the subsequent color Doppler imaging led to a diagnosis of muscular hematoma; however, magnetic resonance imaging and biopsy of the forearm muscle confirmed DLBCL invasion. Due to the patient suffering from heart failure after the third line of the previous chemotherapy, palliative radiotherapy was administered to the left forearm, and the patient achieved a partial response. In conclusion, primary gingival DLBCL with muscle invasion is rare and easily misdiagnosed, and individualized treatment should be considered for these complex cases.

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Introduction

Non-Hodgkin lymphoma (NHL) is the most prevalent form of malignant lymphoma and 40% of patients with NHL have diffuse large B-cell lymphoma (DLBCL) (1). DLBCL is an aggressive malignancy characterized by rapid progression and diverse clinical manifestations, depending on the site of origin and extent of disease dissemination (2). Gingival DLBCL is rare and occurs in ~1% of patients with primary extranodal lymphoma. Its rarity poses significant diagnostic and therapeutic challenges, as the initial clinical features often mimic benign conditions (3). Gingival DLBCL commonly manifests as a localized mass or ulcerative lesion in the oral mucosa, frequently accompanied by painless and progressive lymphadenopathy. These non-specific symptoms can lead to delayed diagnosis and disease progression. Most studies of gingival DLBCL have described histopathological and imaging features of this type of blood cancer; however, to the best of our knowledge, therapeutic strategies for gingival DLBCL with muscle invasion have not been described (4,5). The present study describes the clinical presentation, diagnostic approach, and therapeutic management of a patient with gingival DLBCL involving local muscle tissue. This case highlights the importance of a multidisciplinary approach, integrating oncology, maxillofacial surgery, and radiation therapy to achieve optimal outcomes. We aim to provide insights into the complexities of managing this rare but clinically significant presentation.

Case report

The physical examination of a 49-year-old man who initially presented at Yingshan County People's Hospital (Nanchong, China) in August 2017 revealed a firm mass in the lower left gingiva that measured ~3 cm, with tenderness and swelling. The Eastern Cooperative Oncology Group Performance Status score of the patient was 2 (3); and their blood test results were

negative for the hepatitis B and C viruses, the human immunodeficiency virus (HIV) and the Epstein-Barr virus (EBV), although their lactate dehydrogenase (LDH) level was elevated (577 U/l; normal range: 120-250 U/l). The patient received a positron emission tomography computed tomography (PET-CT) scan, but these images became unavailable after an upgrade of the hospital's imaging system in 2019. The contrast-enhanced CT scans revealed the same findings as the PET-CT scans. Contrast-enhanced CT scans demonstrated a mass in the gingiva, and enlarged lymph nodes in the cervical, mediastinal and gastro-hepatic ligaments (Fig. 1). Bone marrow aspiration was performed and the specimens were subsequently analyzed using immunohistochemistry and a bone marrow smear, all of which demonstrated normal findings. The patient underwent gingival excision biopsy in August 2017, the diagnosis was established through immunohistochemical staining of the gingival biopsy specimen. The following markers were evaluated: CD20 (+), BCL-6 (+), BCL-2 (+), C-MYC (+), MUM1(+), NF-κB (+) and Ki-67 (+, 50-60%; data not shown). However, the patient declined next-generation sequencing (NGS) and fluorescence *in situ* hybridization (FISH) testing due to financial constraints, preventing determination of double-hit lymphoma (DHL) or triple-hit lymphoma (THL). These findings led to a diagnosis of DLBCL stage III (Ann Arbor staging system) (2) and an International Prognostic Index score of 4 (high risk) (3).

A total of six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP, rituximab 600 mg + cyclophosphamide 800 mg + doxorubicin 110 mg + vincristine 2 mg + prednisone 500 mg) was administered as first-line chemotherapy. PET-CT showed no evidence of disease for 40 months (Fig. 2). A follow-up contrast-enhanced CT scan in December 2020 showed tumor progression with invasion of the left orbital region (data not shown). According to the National Comprehensive Cancer Network guidelines (2023, version 6) for relapsed/refractory (R/R) DLBCL, a regimen that is not cross-resistant to R-CHOP should be used, and autologous stem cell transplantation (ASCT) or CAR-T therapy should also be considered (6). However, due to the financial burden of ASCT or CAR-T, the patient did not undergo these treatments; therefore, the patient received four cycles of etoposide (400 mg), prednisone 500 mg, vincristine 2 mg, cyclophosphamide 1200 mg and doxorubicin 110 mg with rituximab 600 mg as second-line chemotherapy. The patient again achieved complete response until December 2021, when another contrast-enhanced CT scan detected retroperitoneal lymph node metastases (data not shown).

The patient then enrolled in a clinical trial at Sichuan Cancer Hospital (Chengdu, China): 'A multicenter, single-arm, open phase I/II clinical trial to evaluate the safety and tolerability of SYHX1903 (a cyclin-dependent kinase-9 inhibitor) in patients with relapsed/refractory malignant lymphoma' (trial no. CTR20212017). The patient achieved partial response after 1 month, but developed shortness of breath, tiredness and palpitations at 15 months after enrollment. Echocardiography at that time showed a massive pericardial effusion, and there was a large increase in the serum level of troponin (7.8 ng/ml; normal range, 0-0.1 ng/ml; data not shown). The patient was diagnosed with heart failure (New York Heart Association Class III) (6), and the cardiologist considered the high doses of doxorubicin and the study drug (SYHX1903) as potential causes. Thus, the patient withdrew from the clinical trial and regular follow-up was conducted.

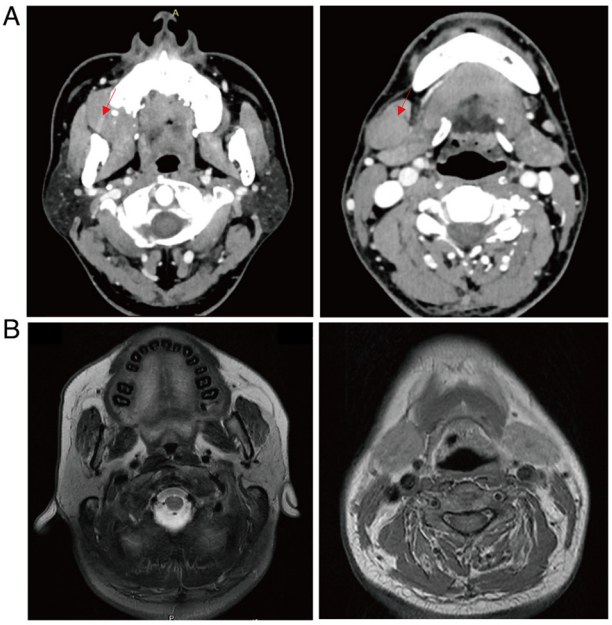

Figure 1. Preoperative gingival excision biopsy CT and postoperative MRI images (August 2017). (A) Preoperative CT shows a mass in the right upper gingiva and right lower mandible (red arrow). (B) Postoperative MRI shows no distinct lesion. CT, computed tomography; MRI, magnetic resonance imaging.

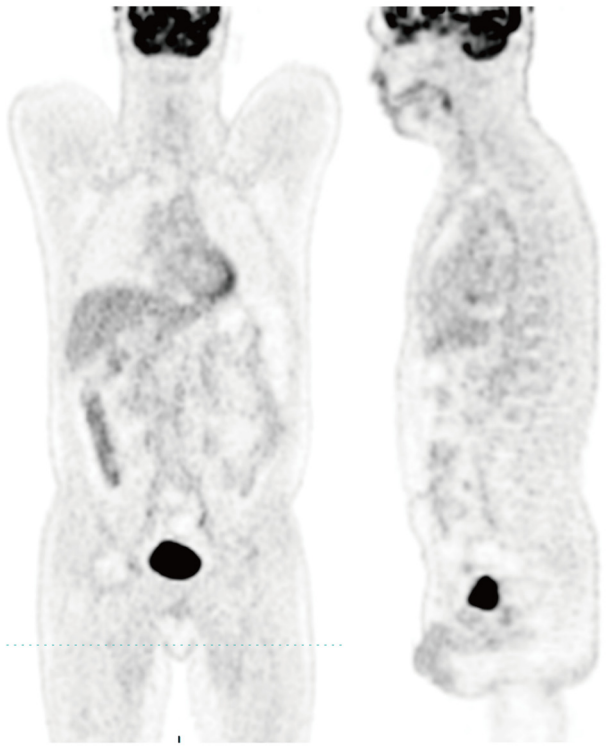

Figure 2. PET-CT showing complete response of the tumor (May 2018). PET-CT scans reveal the absence of detectable disease (no evidence of disease) following treatment, with no evidence of abnormal metabolic activity or residual tumor mass. PET-CT, emission tomography computed tomography.

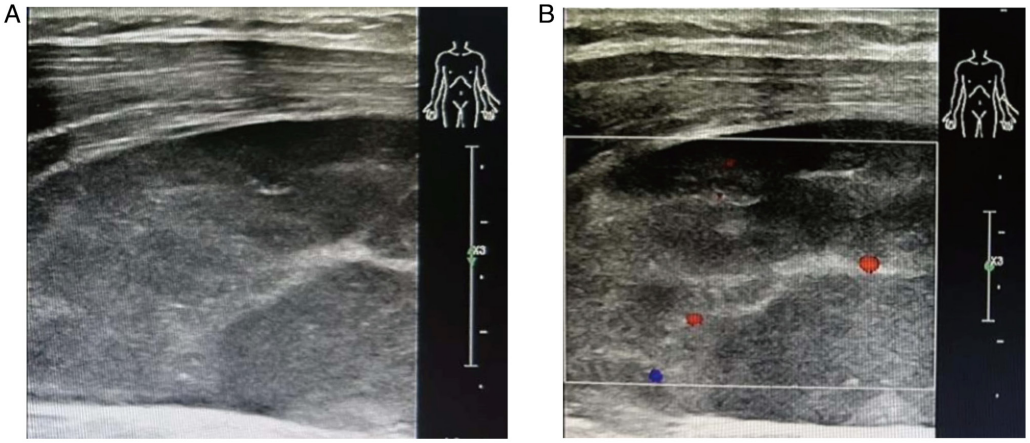

Figure 3. Ultrasound imaging after trauma to the forearm (January 2024). (A) Color Doppler imaging shows a spindled hypoechoic mass with a regular shape and a clear boundary in the left brachioradialis and supinator muscles, and (B) color Doppler flow imaging shows a spot blood flow signal around the mass.

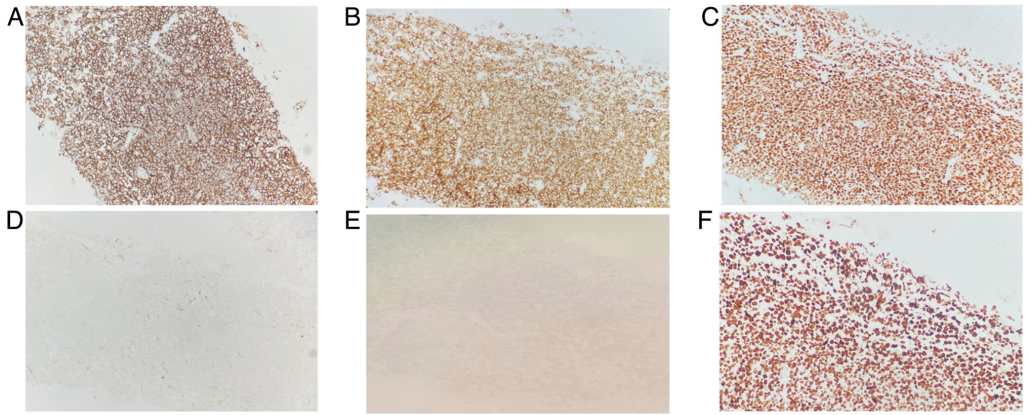

Figure 4. Histopathological findings from biopsy of the forearm (magnification, x200; January 2024). Tumor cells were positive for (A) CD20, (B) CD79a and (C) MUM1; negative for (D) CD10 and (E) BCL-6; and the (F) Ki-67 proliferation index was 90%.

In January 2024, the patient injured their left forearm in a car accident and presented with limb swelling. Examination by color Doppler imaging (CDI) revealed a hypoechoic mass with a clear boundary and regular shape that was ~8.0x3.0 cm. Color Doppler flow imaging showed a spot blood flow signal around the mass and the suggested diagnosis was 'hematoma considered' (Fig. 3). The results from subsequent magnetic resonance imaging (MRI) demonstrated a signal with intermediate intensity on the T1-weighted images and a signal with slightly higher intensity than the normal surrounding muscle on T2-weighted images. These results demonstrated a spindle-shaped mass in the brachioradialis and supinator that was ~4.5x9.6 cm. Contrast-enhanced CT of the chest and abdomen indicated no evidence of abnormality (data not shown). These results led to prompt administration of a CT-guided biopsy of the forearm muscle. The results of immunohistochemical staining were CD20 (+), CD79a (+), BCL-2 (-), C-MYC (-), CD10 (-), BCL-6 (-), MUM1 (+) and Ki-67 (+, 90%) (Fig. 4). These results confirmed a diagnosis of muscle invasion by gingival DLBCL. After a multidisciplinary consultation, local radiotherapy (RT) was administered, due to the patient suffering from heart failure during the third line of the previous chemotherapy. The RT dose was 40 Gy in 20 fractions and led to partial response after 4 weeks (Fig. 5). The

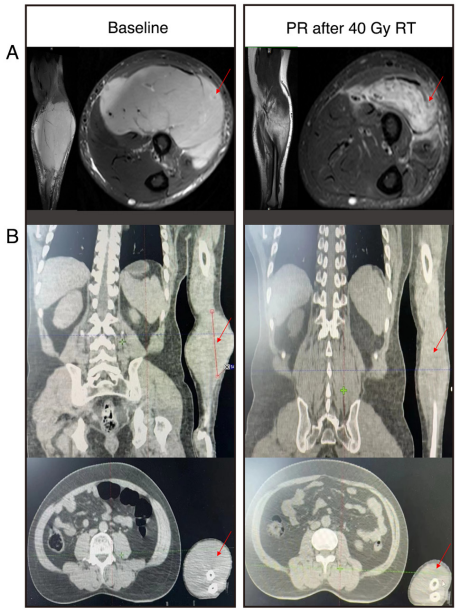

Figure 5. Radiological assessment of tumor response to radiotherapy. (A) Magnetic resonance imaging with contrast and (B) computed tomography of the forearm. The results clearly show a larger tumor mass (red arrow) at baseline (left, March 2024) than after RT (right, April 2024), and indicate PR. PR, partial response; RT, radiotherapy.

Table I. Clinical characteristics of patients with primary DLBCL in the gingiva.

First author, year	Case no.	Sex/Age, years	Elevated serum LDH	Tumor size (maximum diameter), cm	AA stage	Treatment	Survival time, months	(Refs.)
Sato *et al*, 2009	1	F/57	-	2.5	IE	RT	79	(26)
Sato *et al*, 2009	2	F/65	+	3.5	IE	R-CHOP + RT	13	(26)
Sato *et al*, 2009	3	F/68	-	3.5	IE	CHOP + RT	22	(26)
Sato *et al*, 2009	4	M/60	-	2	IE	R-CHOP + RT	16	(26)
Sato *et al*, 2009	5	F/68	+	>5	IE	NA	NA	(26)
Sato *et al*, 2009	6	M/62	-	2.0	IE	R-CHOP	19	(26)
Sato *et al*, 2009	7	M/76	-	4	IE	R-THP-COP + RT	33	(26)
Sato *et al*, 2009	8	F/72	-	3	IE	NA	NA	(26)
Sato *et al*, 2009	9	F/62	+	1.5	IE	CHOP + RT	177	(26)
Sato *et al*, 2009	10	F/77	-	3.5	IE	PR + CHOP	31	(26)
Sato *et al*, 2009	11	M/57	-	3	IIE	R-CHOP	52	(26)
Sugimoto *et al*, 2014	12	M/73	NA	1.5	IE	R-THP-COP	36	(3)
Ürün *et al*, 2012	13	M/53	-	NA	IE	R-CHOP	18	(27)
Angiero *et al*, 2006	14	M/56	-	2	NA	CHOP	59	(28)
Sepúlveda *et al*, 2016	15	F/40	NA	3	NA	CHOP + RT	60	(29)
Li *et al*, 2024	16	M/79	NA	NA	IIE	None	12	(30)
Li *et al*, 2024	17	F/83	NA	NA	NA	None	1	(30)
Kaibuchi *et al*, 2015	18	M/87	NA	3.5	NA	None	30	(31)
Aoki *et al*, 2022	19	M/84	-	0.4	IE	None	24	(32)
Flatow-Trujillo *et al*, 2019	20	F/61	-	NA	NA	None	22	(33)
Wong *et al*, 2014	21	M/50	-	2.9	IE	R-CHOP	15	(34)
Wong *et al*, 2014	22	F/31	-	1.6	IE	R-CHOP	4	(34)
Deng *et al*, 2024	23	M/49	+	3.0	III	R-CHOP + RT	84	The present study

AA, Ann Arbor; CHOP, cyclophosphamide, adriamycin, vincristine and prednisolone; F, female; LDH, lactate dehydrogenase; M, male; NA, not available; PR, partial resection; R, rituximab; RT, radiotherapy; THP-COP, pirarubicin, cyclophosphamide, vincristine and prednisolone.

irradiated field was then decreased and an additional dose of 10 Gy was administered in 5 fractions. The last RT dose was in April 2024, and at the most recent follow-up (August 2024) the patient had a good quality-of-life and a survival time beyond 84 months.

Discussion

In most patients with extranodal NHL the digestive system is affected, and this type of cancer is rare in the gingiva (7). Notably, there is a paucity of data regarding primary gingival DLBCL in patients who are HIV-negative (3), although most patients who present with gingival DLBCL have tumors in the maxilla (8,9). A review of the literature identified 22 other cases of primary gingival DLBCL in HIV-negative patients between 2008 and 2024 (Table I). The median age of the patients was 63.2 years (range, 31-87 years), and most of these patients had normal LDH levels, stage I-II cancer, received R-CHOP or RT, and had a favorable prognosis. Notably, it is possible that immune dysregulation may be involved in primary gingival DLBCL. For example, Shapiro (10) reported on the case of an 81-year-old patient with gingival DLBCL who was EBV-positive and was taking methotrexate for 50 years as treatment for psoriasis; this patient experienced tumor remission after discontinuing methotrexate. By contrast, in the present case report, the patient was EBV-negative, they did not use any immunosuppressive agent, and the initial R-CHOP regimen had a long-term and stable curative effect.

DHL and THL are highly aggressive variants of B-cell lymphoma that are characterized by simultaneous rearrangements of *MYC* and one or more additional oncogenes, such as *BCL2* or *BCL6* (11). Relative to other lymphoma subtypes, these genetic abnormalities contribute to a more unfavorable prognosis due to increased tumor cell proliferation, greater resistance to treatment and a higher likelihood of relapse (12). These more aggressive types of lymphoma often necessitate more intensive therapeutic approaches and are associated with significantly lower survival rates (13). Identifying these genetic mutations is critical for achieving precise prognostication and tailoring individualized treatment regimens, because DHL and THL tend to be more treatment-resistant and associated with less favorable responses to standard therapies (14). However, in the present case, the patient was unable to bear the financial burden and thus refused further NGS and FISH testing. However, based on the aggressive disease progression, this patient may have had DHL or THL.

A rare feature of the present patient was invasion of the gingival DLBCL to muscle in the forearm. Notably, two possible mechanisms could be suggested for this: i) Disease dissemination via a hematogenous or lymphatic pathway, or ii) disease extension from adjacent organs, such as the bones or lymph nodes (15). The most frequently encountered clinical symptoms in patients with gingival DLBCL are painful swelling and local edema. Muscle lymphoma has certain distinctive characteristics on MRI that allow it to be distinguished from other soft-tissue tumors (16). In particular, the signal intensity of a T1-weighted image has a similar or slightly increased signal intensity compared with normal muscle, and the T2-weighted signal has a high intensity relative to normal fat tissue (17,18). The MRI of the present patient clearly demonstrated these features. The identification of tumor recurrence in the forearm was fortuitous and only occurred because the patient required imaging following a car accident. The CDI results of lymphoma in skeletal muscle are nonspecific and often make it difficult to distinguish lymphoma from hematoma, sarcoma, metastases or myositis (19). This emphasizes the need for a biopsy and pathological evaluation for the diagnosis of skeletal lymphoma. The immunohistochemical staining results of the forearm muscle: CD10 (-), BCL-6 (-) and MUM1 (+), led to the diagnosis of non-germinal center B-cell (non-GCB) type DLBCL, and suggested a poor prognosis (20).

Previous studies have reported that R-CHOP can significantly decrease disease relapse and progression in patients with non-GCB type DLBCL (21,22). For example, Nyman *et al* (23) reported that the R-CHOP regimen eliminated differences in prognosis for patients with immunohistochemically defined GCB and non-GCB phenotypes of DLCBL. However, in the present case, the patient suffered from severe cardiac problems following a previous chemotherapy regimen and was therefore administered palliative RT to relieve symptoms and delay local disease progression. The guidelines of the International Lymphoma Radiation Oncology Group suggest the use of RT for R/R aggressive DLBCL, with salvage doses up to 55 Gy (24). Wong *et al* (25) described 217 patients with R/R DLBCL who altogether received 370 courses of palliative RT. The median equivalent dose was 19 Gy (range, 2-42 Gy) and the rate of local control at 6 months was 66.7%. In the present case, 40 Gy in 20 fractions was initially administered, and the patient achieved a partial response. To minimize radiation damage, the irradiated field was then reduced and an additional dose of 10 Gy in 5 fractions was administered.

In conclusion, invasion of gingival DLBCL to the muscle is rare, and the diagnosis requires consideration of medical history and a combination of procedures, including imaging and histological examination. Individualized treatment of these patients is necessary, although determination of the most appropriate treatment regimen can be challenging.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

WX, XD and YL conceived and designed the study. WP and JZ collected the data. QY and BC analyzed and interpretated the results. WX and XD wrote the manuscript. WG and YL confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethical approval and consent to participate

The patient provided written informed consent for the publication of this case report.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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