# Oral manifestations and clinical progression of a rare double-hit B-cell lymphoma: a case report and review of the literature

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Double-hit (DH) lymphoma is a rare subtype of B-cell lymphoma characterized by the chromosomal rearrangement of *c-Myc* and *Bcl-2*, and/or *Bcl-6*. *c-Myc* is an oncogene that keeps cells proliferative. *Bcl-2* and *Bcl-6* grant cells antiapoptotic features. The concurrent expression of these genes and their synergistic effect make DH lymphoma refractory to traditional chemotherapy, with an extremely poor prognosis. Here, we present a case of DH lymphoma in the oral cavity, including its rapid clinical course, extensive involvement of multiple sites and organs, and response to aggressive chemotherapy. It is important for dental providers to be familiar with lymphoma's oral manifestations and consider the disease in the differential diagnosis for expansile palatal lesions. The early detection and accurate diagnosis of lymphoma by dental practitioners can help expedite proper multidisciplinary care and lead to significant reductions in patient morbidity and mortality. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e38–e43)

## BACKGROUND

Lymphoma is the second most common malignancy of the oral cavity, accounting for 2.2% to 2.5% of all malignancies of the head and neck region.[1,2] Typically, the initial presentation of lymphoma in the head and neck region includes a quick and painless swelling, nonhealing ulcer, paresthesia, anesthesia, or increased tooth mobility.[3] Painless lymph node enlargement or a submucosal lesion in the junction between the hard and soft palates is highly suspicious. Systemic signs and symptoms include fever of unknown origin, night sweats, and inexplicable weight loss, which are known as "B symptoms." Other nonspecific constitutional symptoms include itchy skin, fatigue, and loss of appetite.

Lymphomas are classified as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL), according to their histologic and behavioral patterns. NHL commonly appears in extranodal locations. In the oral cavity, it affects the palate, gingiva, tongue, cheek, floor of the mouth, lips, salivary glands, and maxillary sinuses.[4] NHL is predominantly derived from the cells of the B-lymphocyte series. Diffuse large B-cell lymphoma (DLBCL) is the most common histologic subtype, accounting for 70% to 80% of NHL cases. It is characterized by the diffuse proliferation of large transformed B-cells[5,6] and is the most frequently diagnosed lymphoma in the Western world.[7] It usually affects men between the seventh and eighth decades of life.[8]

DLBCLs are genetically heterogeneous, with various clinical behaviors, genetic features, and transcriptional signatures. Most DLBCLs do not show the specific clinical or pathologic features that were included in *DLBCL, not otherwise specified*, or DLBCL, NOS. Gene expression profiling identified other DLBCL subtypes, including germinal center and activated B-cell (ABC) forms.[7] Although DLBCL is considered to be clinically aggressive, it is treatable, with approximately two-thirds of the cases responding sufficiently well to standard chemoimmunotherapy. However, some DLBCL cases were found to be "extra aggressive" and required therapy different from the previously identified DLBCL subtypes. In the 2008 World Health Organization (WHO) classification, these cases were categorized as "B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BCLU)."[9] Case-series studies have been conducted to identify the clinical prognostic markers for this subtype. Scores using clinical factors, such as patient age, disease stage, serum lactate dehydrogenase (LDH) level, and number of extranodal sites have been developed to stratify prognosis, but none has demonstrated promising predictive value for clinical outcome.[6] Thus, gene expression analysis has been explored as an alternative approach to uncovering DLBCL heterogeneity.

Several protein overexpressions were found to be prevalent in DLBCLs and may serve as molecular markers for clinical prognosis and management. c-Myc protein expression was found to be increased in up to one-third of the DLBCL cases.[7] In addition, Bcl-2 and c-Myc coexpression was found in 20% of the DLBCLs.[5] Increased c-Myc expression has been shown to predict poor outcome if increased Bcl-2 is also present.[10] Lymphomas with simultaneous Myc and Bcl-2 expression were described as the "double expressor" phenotype and raised great interest because of their prediction of clinical outcomes. Similar to what was observed with protein expression, the concurrent c-Myc, Bcl-2, and/or Bcl-6 chromosomal translocation appeared to be associated

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Received for publication Aug 6, 2019; returned for revision Oct 28, 2019; accepted for publication Dec 8, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.12.004

with extremely poor clinical outcomes in several retrospective studies.[10-14] Existence of Bcl-2 and/or Bcl-6 rearrangement significantly impacted the survival rate of c-Myc–positive lymphomas after chemotherapy treatment.[10,15] These cases have been referred to as double-hit lymphoma (DH, when c-Myc translocation is present with Bcl-2 or Bcl-6 translocation) or triple-hit lymphoma (TH, when c-Myc, Bcl-2, and Bcl-6 translocation are all present). In recognition of the above data, the updated 2016 WHO classification separated DH or TH lymphoma from DLBCL and created a new category for them. They are referred to as "high-grade B-cell lymphoma with translocations involving Myc and Bcl-2 or Bcl-6."[16] However, the "double expressers" without gene rearrangements remain in the subset of DLBCL-NOS.

To date, only 1 DH lymphoma case with Myc/Bcl-6 rearrangement in the head and neck region, at the base of the tongue, has been recognized and reported in the literature.[17] The author presented detailed cytogenic and immunophenotypic information but only limited clinical features of this entity. More clinical information will be necessary and beneficial for dental providers to recognize this entity. Here, we report an additional rare DH lymphoma case with translocation of c-Myc and Bcl-6, including its rapid progression, clinical presentation, and its response to chemotherapy treatment.

## CASE SUMMARY

A 77-year-old Chinese man initially presented to his dentist with a toothache and swelling of 2 weeks' duration. The dentist considered the clinical signs and symptoms to indicate an odontogenic infection and prescribed antibiotics, but the patient did not respond to treatment. He was then referred to our hospital's oral and maxillofacial outpatient clinic for evaluation. Clinical examination showed a large expansile lesion of the left maxillary alveolus, ranging from tooth #11 to the tuberosity anteroposteriorly and from the midpalate to the vestibule buccolingually. The surface mucosa was purplish-red and, grossly, intact without obvious ulceration (Figures 1A and 1A'). The mass was soft, nonfluctuant, and slightly tender upon palpation. The involved teeth were class III mobile, but vital. Multiple palpable and enlarged lymph nodes were appreciated in the left submandibular region. Lymph nodes were 10 × 10 mm in size, nontender, fixed to the surroundings, and rubbery in texture. The patient denied having a significant medical history, except that he had smoked for greater than 20 years and had quit 20 years ago, or having any constitutional symptoms, such as fever, night sweats, loss of appetite, or unintentional weight loss. Maxillofacial computed tomography (CT) with contrast revealed multiple soft tissue masses in the head and neck region with extensive involvement, including the left maxillary alveolus extending into the left maxillary sinus, right maxillary sinus, right posterior orbital apex, and left frontal sinus. Erosive destruction of alveolar bone in the left maxilla was observed (Figure 2A). Extensive abnormal adenopathy involving the left submandibular and cervical regions was

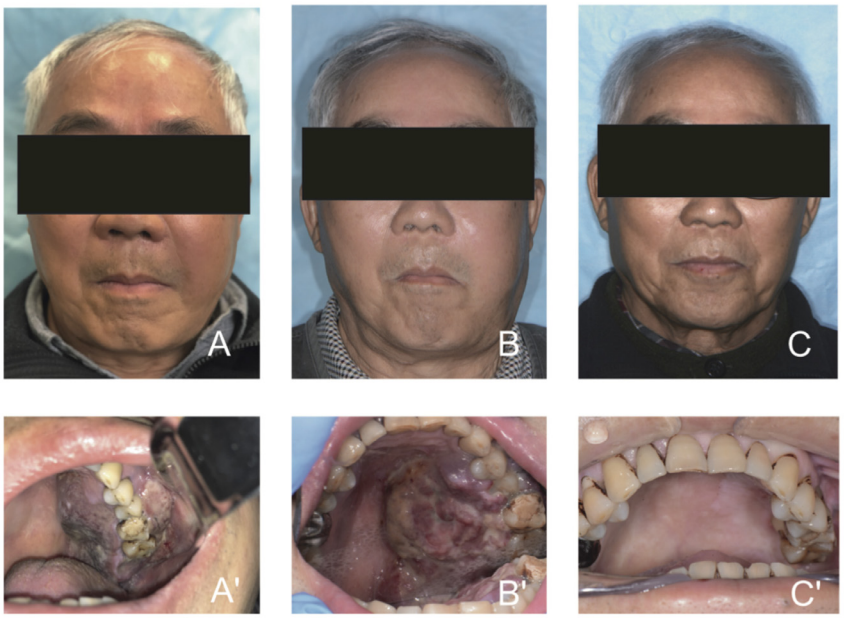


Fig. 1. **A,** Frontal view at initial presentation. **A',** Intraoral lesion at initial presentation. **B,** Frontal view 10 days after initial presentation and biopsy. **B',** Intraoral lesion 10 days after initial presentation and biopsy. **C,** Frontal view after 3 cycles of chemotherapy. **C',** Intraoral manifestation after 3 cycles of chemotherapy.

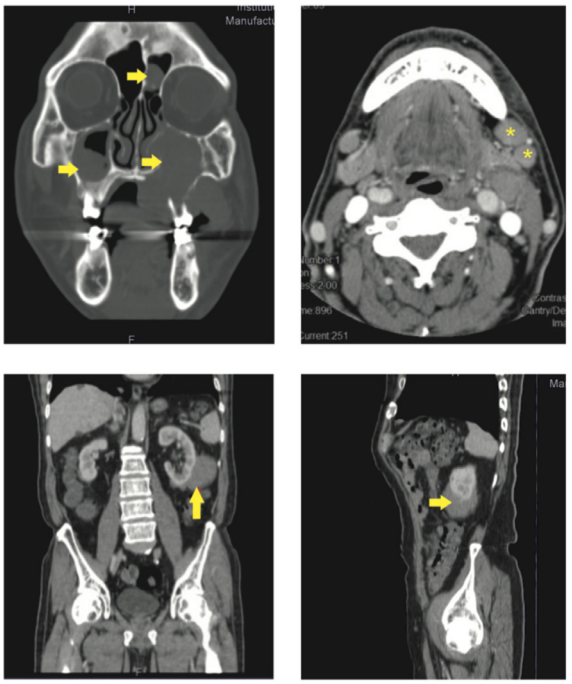

Fig. 2. **A,** Coronal view of computed tomography (CT) maxface. Yellow arrows indicate multiple loci involvement of tumor, including frontal sinus, bilateral maxillary sinus. **B,** Axial view of CT maxface. Yellow asterisks indicated left submandibular lymphadenopathy. **C,** Anteroposterior (AP) view of pelvic CT scan. **D,** Saggital view of pelvic CT scan. Yellow arrows indicate perirenal soft tissue lesion.

present, with the largest measuring 30 × 24 mm in the jugulodigastric chain (Figure 2B). CT scans with contrast of the chest, abdomen, and pelvis were also obtained, revealing a large 40 × 60 mm soft tissue mass at the inferior pole of the left kidney, extending into the retroperitoneal space (Figures 2C and 2D). A provisional clinical diagnosis of multiple malignant soft tissue neoplasms versus metastatic lesions was made. The differential diagnosis included antral carcinoma, malignant neoplasm of the salivary glands, lymphoma, and sarcoma. Incisional biopsy under local anesthesia was immediately performed, with multiple samples taken at different sites from the left maxillary alveolar soft tissue mass. The patient's laboratory values were significant with 46.1 × $10^3$/μL white blood cell count, 85% segmented neutrophils, and 28 mg/dL blood urea nitrogen.

The patient returned to our clinic 10 days after the initial examination and biopsy complaining of enlargement of the lesion as well as aggravated pain on the left side of the face. The clinical examination revealed obvious enlargement of the left midface. Intraorally, the left maxillary soft tissue lesion had increased in size by 20%, crossing the midline of the palate. The surface of the mass appeared to be nodular. Ulcerations had developed directly adjacent to the biopsy sites (Figures 1B and 1B').

Initial biopsy results showed large cells with multiple nucleoli and increased mitotic activity. CD10, BCL6, and MUM1 staining results were consistent with nongerminal center B cells. Ki67 staining showed a highly proliferative profile, with greater than 90% of cells testing positive. A subsequent fluorescence in situ hybridization (FISH) study was performed and the results interpreted at Hematologics, Inc. Results were positive for *c-Myc/IGH t (8;14)* gene rearrangement and *Bcl-6* gene rearrangement (Figure 3). A final diagnosis of high-grade B-cell lymphoma with *c-Myc* and *Bcl-6* rearrangements (DH lymphoma) was made.

Given the rapid progression of the tumor, the patient was immediately referred and admitted to Hematology/Oncology for chemotherapy. Lumbar puncture was negative for cerebrospinal fluid cytology, ruling out central nervous system (CNS) involvement. The patient was treated with modified R-CHOP (rituximab 375 mg/$m^2$, cyclophosphamide 375 mg/$m^2$, doxorubicin 30 mg/$m^2$, vincristine 1.4 mg/$m^2$, and prednisone), intrathecal methotrexate 12 mg, and cytarabine (ara-C) 100 mg.

Currently, the patient has completed 3 cycles of chemotherapy. Facial swelling and the intraoral maxillary lesion size have reduced significantly (Figures 1C and 1C'), and the renal mass was not discernible radiographically. However, a small tumor mass in the maxillary sinus remains unresolved, as seen on the CT scan, requiring further chemotherapy or local radiotherapy treatment (image not available).

## LITERATURE REVIEW

DH lymphoma is an intriguing subset of B-cell lymphoma, which is defined by a chromosomal breakpoint

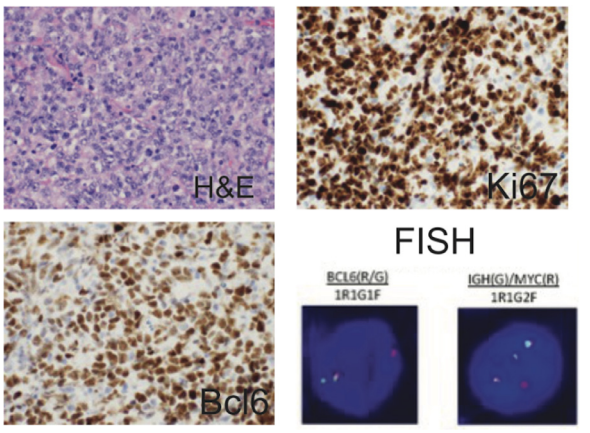


Fig. 3. Stains. Hematoxylin and eosin (H&E): staining of double-hit lymphoma; Ki67: immunohistochemistry of Ki67 staining for proliferation; Bcl-6 immunohistochemistry staining of Bcl-6 protein expression; fluorescent in situ hybridization (FISH) of *c-Myc* and *Bcl-6* rearrangement.

affecting the MYC/8q24 locus with other recurrent breakpoints, such as BCL-2/18q21 or BCL-6/3q27.[4] Patients with such gene translocations have demonstrated worse responses to treatment in several retrospective studies. The reported 2-year survival rate was 35% in patients with *c-Myc* rearrangement versus 61% in patients without rearrangement.[14] Akin to the impact of protein coexpression, the concomitant *Bcl-2* rearrangement adversely affected the therapeutic outcome of cases with positive *c-Myc* rearrangement.[18] Bcl-6 protein expression or gene translocation also appeared to confer a poor prognosis in patients with c-Myc expression and/or translocation.[19] Of all DH or TH lymphomas, approximately 62% involved c-Myc and Bcl-2 translocation, 8% were c-Myc$^{+}$/Bcl-6$^{+}$, and 16% were TH lymphomas[5] (Figure 4). Other genes found to be involved in DH/TH status include *CCND1* and *BCL3*.

Clinically, DH/TH lymphomas are much more common in older patients, with the reported median age ranging from 51 years to 65 years, and extremely rare in children younger than 18 years of age.[20] Most patients presented with de novo disease and were rarely found to be human immunodeficiency virus (HIV) positive.[21] The majority of cases had extranodal involvement and showed elevated LDH levels. Patients with DH/TH lymphoma have a significantly increased risk of bone marrow and CNS involvement.[22] Therefore, these patients should undergo routine staging procedures, including imaging with positron emission tomography/computed tomography (PET/CT), bone marrow aspiration and biopsy, serum LDH level, and liver and kidney function tests.[23] However, no clinical parameters were found to predict the prognosis. Patient age at diagnosis appeared to be marginally correlated with the prognosis; age 60 years or less may suggest a slightly better clinical outcome.[24]

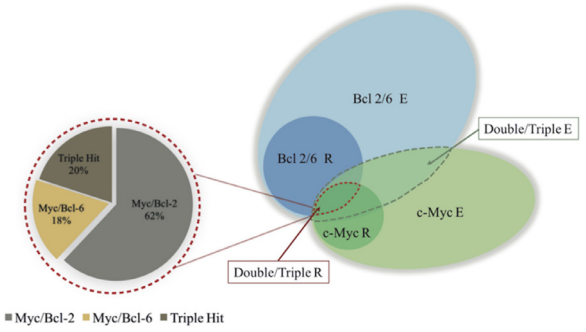


Fig. 4. Area within green dotted line represents *c-Myc* and *Bcl-2/-6* double- or triple-expressor lymphomas with high *c-Myc* and Bcl-2/-6 protein expression. Area within red dotted line represents double- or triple-hit lymphoma with both *c-Myc* and *Bcl-2/-6* rearrangement. Pie chart within the red dotted line represents percentage of double-hit/triple-hit lymphomas with *Myc/Bcl-2, Myc/Bcl-6*, and *Myc/Bcl-2/Bcl-6* rearrangement.

In the literature, greater than 40% of cases of lymphoma in the head and neck region were initially underrated or misdiagnosed as a different pathology and were treated as such.[2] Most treatments included extractions, periodontal cleaning, and abscess treatments, which delayed proper treatment and allowed progression of lymphoma. The learning point of this case is that in the head and neck region, lymphoma must be considered in the differential diagnosis when there is an inexplicable toothache, tooth mobility, soft tissue mass, ulceration, unhealed extraction socket, or lytic bone change. For oral lesions, when an abnormal infiltrate is identified, it is not only important to distinguish lymphoma from other neoplasms but also crucial to characterize the infiltrate to identify prognostically important subtypes.[17] Applying immunohistochemical staining with markers can assist with identifying the infiltrating cells, especially in the presence of crushing or cauterization artifacts.

However, the diagnostic workup of DH and TH lymphomas remains controversial.[25] Some authors have advocated extensive cytogenetic testing in all patients with DLBCL; however, this is costly and prohibitive in some centers. FISH is essential for determination of the DH/TH status; however, not all B-cell lymphomas have to be evaluated on FISH. Given the high cost and increased burden on laboratories, there currently is no consensus on which of the large B-cell lymphomas should undergo this testing as recommended by the WHO.[26] Interestingly, according to a study from the University of Pennsylvania, a multiple-hit status could not be inferred from any baseline clinical characteristics, such as age, gender, LDH level, or CNS involvement.[24] Therefore, there is an increased risk of misdiagnosis in patients with a DH/TH status. Currently, the testing is usually restricted to highly proliferative lymphomas, as indicated by immunohistochemistry for Ki-67 and c-Myc protein expression. An extremely high Ki67 index of greater than 75% is usually detected in DH/TH lymphomas, suggesting that a proliferative boost to the tumor cells is a strong driving force. FISH has been recommended to determine the DH or TH status in cases that are of the germinal center B-cell lymphoma subtype; are highly proliferative, with a Ki67 index greater than 90%; or are c-Myc protein positive.[25] And dental care providers should raise questions regarding such biopsy results and request for FISH, if indicated.

Treatment of DH/TH lymphomas remains clinically challenging. It has been reported that patients with DH/TH lymphoma have a median overall survival (OS) of only 4.5 months and that 70% of patients die within 8 months of diagnosis.[21] DLBCL is curable in 60% of patients receiving standard R-CHOP (rituximab plus

cyclophosphamide, doxorubicin, vincristine, and prednisone) treatment. However, *c-Myc* translocations with *Bcl-2* and/or *Bcl-6* translocations have been associated with poor survival rates among patients with DLBCL treated with R-CHOP. *c-Myc* is generally considered a proto-oncogene and is expressed in low levels. It is a transcription factor controlling cell cycle, metabolism, DNA repair, stress response, and protein synthesis. *Bcl-2* has potent antiapoptotic functions and is widely expressed in immature B cells and memory B cells.[27] *Bcl-6* is a zinc finger transcription repressor that is a commonly involved oncogene and highly associated with the pathogenesis of DLBCL.[15] *Bcl-6* expression represses many target genes involved in apoptosis. With *c-Myc* and *Bcl-2/6* translocation and overexpression, cells are more proliferative and resistant to apoptosis. The synergistic action of *c-Myc* and *Bcl-2* and/or *Bcl-6* has been hypothesized to be responsible for the dismal outcome in patients with DH/TH lymphoma. Interestingly, a retrospective analysis revealed that Bcl-6$^-$/Myc$^+$ expression had poorer progression-free survival compared with those with Bcl-6$^+$/Myc$^+$ expression in DLBCL.[28] The Bcl-6 protein and translocations did not appear to be associated with resistance to R-CHOP treatment in a previous study.[29] This may explain why our patient experienced significant clinical improvement of the oral lesion after 4 cycles of chemotherapy treatment. However, in a meta-analysis of cohort studies, *Bcl-6* rearrangement was shown to be negatively associated with OS but not with progression-free survival in DLBCL.[30] The prognostic significance of *Bcl-6* expression still remains controversial.

Multiple therapeutic regimens have been proposed for the treatment of DH lymphoma. Usually, an aggressive induction approach is recommended because of the poor response to conventional R-CHOP chemotherapy.[7] Several studies have advocated for a more aggressive "Burkitt-like" approach. However, for cases of limited-staged DH lymphoma with normal LDH and no other clinical risk factors, the treatment approach can be started with R-CHOP for 3 cycles, followed by involved-field radiation therapy consolidation because of the reported favorable outcomes.[31] Most of the therapeutic strategies for DH/TH lymphoma have been based on retrospective studies of c-Myc$^+$/Bcl-2$^+$. Little information is available for c-Myc$^+$/Bcl-6$^+$.

Non−DH/TH lymphomas respond very well to chemotherapy; oral manifestations start regressing as early as the seventh day of treatment.[2] In the case of DH/TH lymphoma presented here, the clinical dissolution of tumor was obvious after 1 cycle of chemotherapy, as reported by the patient. The patient was symptom-free after 3 cycles of chemotherapy, although remnants of the tumor were seen on imaging. Therefore, the correct diagnosis is crucial for timely treatment, relief of symptoms, and avoidance of worsening prognosis in patients with DH/TH lymphoma. In addition, these patients may need localized radiotherapy in combination with chemotherapy. In such cases, the oral surgeon needs to collaborate with the oncologist to plan for extraction or treatment before initiation of radiotherapy to avoid osteoradionecrosis, although the phenomenon is rare in the maxilla.

## CONCLUSIONS

DH or TH lymphoma is a newly categorized subset of B-cell lymphoma and remains a therapeutic challenge, with low survival rates and a poor prognosis. A detailed medical history and clinical and radiologic evaluations are crucial for timely biopsy and accurate diagnosis, thus facilitating treatment. Understanding lymphoma's classification will help determine the prognosis and direct clinical treatment planning.

## ACKNOWLEDGMENTS

We express our sincere thanks to Dr. Nancy Li at the Pathology Department of Highland Hospital for her guidance and discussion of the case.

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