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Uncommon presentation of diffuse large B-cell lymphoma: oral and pulmonary involvements in a young patient: a case report

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Abstract

Background Diffuse large B-cell lymphoma is the most common subtype of non-Hodgkin lymphomas that remains a major diagnostic challenge due to the variety of its clinical presentations. This case highlights the importance of early biopsy of oral lesions without tendency to heal to attain the diagnosis more quickly. To the best of our knowledge, this study is the first to focus on both oral and pulmonary involvements in a patient with diffuse large B-cell lymphoma.

Case presentation The presented case describes an Iranian 18-year-old girl with chronic cough and dyspnea referred for evaluation of the upper jaw due to bone exposure, bone loss, and soft tissue ulceration. Her medical history revealed mediastinal mass, cavitary lesion, and mediastinal lymphadenopathy. However, cytologic and immunohistochemical analysis did not show any evidence of malignancy. In this case a lymphoproliferative disease was suspected but ultimately the oral biopsy diagnosed diffuse large B-cell lymphoma and chemotherapy could be started.

Conclusions Systemic conditions should be considered as a possible cause of oral lesions and a biopsy should also be performed immediately if there is any doubt concerning the nature of the lesion. Moreover, some conditions necessitate multiple biopsies to attain an accurate diagnosis.

Keywords Lymphoma, DLBCL, Oral manifestations, Jaw disease, Lung diseases

Background

Lymphomas are a heterogeneous group of malignant neoplasms of lymphocytes and their precursor cells, accounting for 3.37% of all cancer cases worldwide and 5% of all malignant diseases in the head and neck region [1–3]. They are traditionally classified into two major categories, including Hodgkin's lymphomas (HL) and non-Hodgkin lymphomas (NHL) [1].

In 30% of lymphomas, extranodal involvement occurs in tissues outside the lymph nodes, and head and neck region is the second most common site after the gastrointestinal tract [4, 5]. NHL has more propensity to disseminate to extra-nodal tissues than HL [5].

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL worldwide, characterized histologically by a diffuse proliferation of large transformed B cells and commonly affects old men between the seventh and eighth decades of life [6]. Its nodal or extranodal involved sites can be gastrointestinal tract, thyroid, breast, bone, skin, testes, and brain. However, pulmonary involvement is an uncommon finding and represents 4% of patients with NHL [7]. Although 40% of patients

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with DLBCL are affected by extranodal involvement, oral involvement of extranodal NHL is rare (about 2%), sometimes presenting as ulceration with bone destruction [8, 9]. Particularly, maxillary bone involvement is very rare and occurs in less than 1% of patients with NHLs and 8% of all tumors in the skeletal system [10].

Given the fact that patients with intraoral lymphoma often present with nonspecific clinical signs and symptoms such as painless swelling, non-healing ulcer, increased tooth mobility, paresthesia and anesthesia, and radiological signs such as obstruction of paranasal sinuses, it is not surprising that a lesion may be misinterpreted as a far more common diagnosis or be diagnosed as lymphoma in a late stage with a higher mortality rate [1, 6].

DLBCL is an aggressive but curable disease in most patients who received systemic chemoimmunotherapy and is usually diagnosed by a biopsy of suspicious lymph nodes or an extranodal tumor followed by morphological and immunophenotypic investigations consisting of immunohistochemical (IHC) analysis or flow cytometry analysis or a combination of both techniques with positive pan-B-cell antigens such as CD_{20} and CD_{79a} [8, 11, 12]. In more details, a panel of immunostains including CD_{20}, CD_3, CD_5, CD_{45}, BCL_2, BCL_6, Ki_{67}, IRF_4/MUM_1, and MYC was recommended for IHC analysis to determine the types of lymphoma. Patients with MYC expression and BCL_2 and/or BCL $_6$ should test MYC rearrangement by fluorescence in situ hybridization (FISH). In some cases, additional markers such as CD_{30}, CD_{138}, EBV, HHV_8, and ALK_1 can help determine subtypes [8]. Bone marrow biopsy may also be considered where a suspected coexisting hematological condition would influence clinical management [12].

Here, we presented a case of DLBCL in which diagnostic challenges were encountered. To the best of our knowledge, this study is the first to focus on both oral and pulmonary involvements in a patient with DLBCL. This case highlights the importance of appropriate history taking, detailed clinical, radiological, and pathological assessments, and also considering systemic conditions as a possible cause of oral lesions. We hope that this study helps physicians who encounter the similar manifestations to attain a diagnosis more quickly and prevents a situation in which the patient undergoes nondiagnostic interventions.

Case presentation

In January 2023, an Iranian 18-year-old girl referred to the Oral Medicine Department of Shiraz University of Medical Sciences for evaluation of oral lesions progressively worsening over the last 15 weeks. Initially, the patient noted attachment loss as an indicator of a destructive disease that resulted in the gingiva to migrate toward the buccal surface of maxillary right first molar roots and the alveolar bone no longer supported the tooth, but later, other lesions developed. Although the oral biopsy was performed 8 weeks prior to the initial visit, that evaluation was nondiagnostic due to nonspecific mixed inflammatory cells infiltration and no evidence of malignancy at the subsequent IHC analysis. Therefore, the patient was transferred to our department.

Her medical history revealed chronic cough and dyspnea from 18 months ago, which was initially diagnosed as asthma in August 2022, followed by asthma therapy. However, the cough and dyspnea had worsened and she was overcome by nausea during the next days. Thereafter, the patient was admitted to the hospital and diagnosed with mediastinal mass, cavitary lesion, and mediastinal lymphadenopathy. However, cytologic and IHC analysis did not show any evidence of malignancy. In addition, she complained of inexplicable weight loss and nausea. The rest of her history including familial and social history was unremarkable and none of her family members reported malignancy.

At this point of time, the intraoral examination revealed painless lesions as shown in Fig. 1. In more detail, an exposed bone of the maxilla was on the posterior region of the right-sided hard palate. Its surrounding non-necrotic palatal mucosa was pink or normally colored with irregular border (Fig. 1A). In addition, clinical examination showed bone loss involving the buccal surface of the maxillary right first molar (Fig. 1B) and a

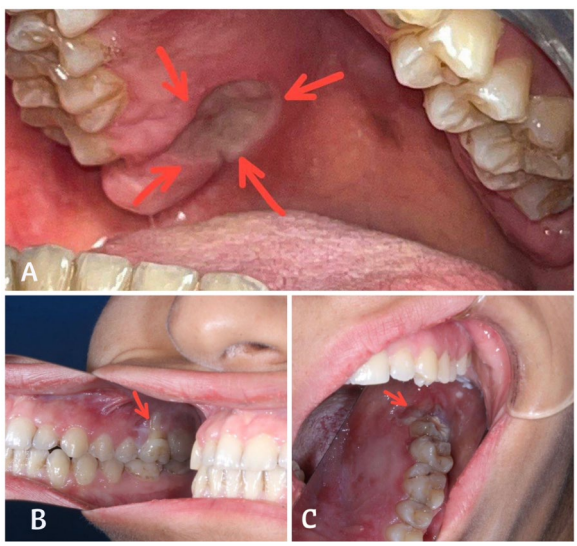

Fig. 1 Clinical photographs of a 18-year-old patient with DLBCL. **A** Exposed bone area. **B** Mirror view of the bone loss involving the maxillary right first molar. **C** Mirror view of ulceration on the left tuberosity area (red arrows point at the oral involvements)

small ulcer on the left tuberosity area (Fig. 1C). On further examination, the involved teeth were vital, and there was no mobility.

In the extraoral examination, the patient was afebrile and had no palpable lymphadenopathy in the head and neck region. Moreover, recent laboratory tests revealed anemia and elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), as shown in Table 1. Serological tests also reported that the patient was nonreactive for viral markers including human immunodeficiency virus (HIV) antibody, hepatitis B surface antigens (HBs Ag), and hepatitis C virus antibody (anti-HCV).

Table 1 Summary of recent laboratory tests

Laboratory tests	Result	Unit	Reference range
WBC	6.7 Neutrophils: 70.1% Lymphocytes: 25.8% Mixed cells: 4.1%	$\times 10^3$/UL	4–10
RBC	4.7	$\times 10^6$/UL	3.9–5.8
Hemoglobin	10	g/dl	12–17
Hematocrit	34.9	%	36–53
MCV	74.3	FL	80–100
MCH	21.3	Pg	26–33
MCHC	28.7	g/dl	30–36
Platelet	270	$\times 10^3$/UL	150–450
C-ANCA	0.5	U/ml	Negative: < 12
P-ANCA	0.8	U/ml	Negative: < 12
ESR 1 h	65	mm/h	Female: Up to 15
CRP	24	–	Negative: < 6
LDH	401	U/L	235–470

WBC, white blood cells; RBC, red blood cells; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase; C-ANCA, antineutrophil cytoplasmic autoantibody: cytoplasmic; P-ANCA, perinuclear antineutrophil cytoplasmic autoantibody

Cone beam computed tomography (CBCT) was performed to detect potential destruction of the maxillary bone and destruction of the buccal and palatal cortices in both sides of the maxilla was noted from the upper molar alveolar bone to the maxillary tuberosity area (Fig. 2). The other radiographic features detected in CBCT were the appearance of floating teeth in the air (Fig. 3), abnormal trabecular pattern (Fig. 4), and mucosal thickening of both maxillary sinuses (Fig. 5).

Due to nondiagnostic results of the initial biopsy, a second biopsy for a definitive diagnosis was performed, and soft tissue specimens were obtained from the right palatal mucosa and tuberosity area. Due to the nonpathognomonic clinical and radiographic features of the presented case, the differential diagnosis is broad, ranging from inflammatory conditions to malignant neoplasms. Although the oral manifestations mimicked more common conditions such as advanced periodontal disease or osteonecrosis, our assessments did not confirm either of the above-mentioned conditions, and the microscopic examination revealed only ulceration of the oral mucosa and severe chronic inflammatory infiltration of the connective tissue by mostly lymphocytes, a few eosinophils, and histiocytes (Fig. 6). Therefore, a panel of immunostains was performed for IHC analysis. The analysis demonstrated positivity for CD_5 in T lymphocytes, and scattered positivity for CD_{20} and high Ki_{67} proliferative index in the large cell population. $BCL_{6,}$ CD_{30}, MUM_1, and PAX_5 were also positive in the large cells examined, while CD_{10} and CD_{68} were negative. In addition, tumor cells showed positivity for OCT_2, scattered

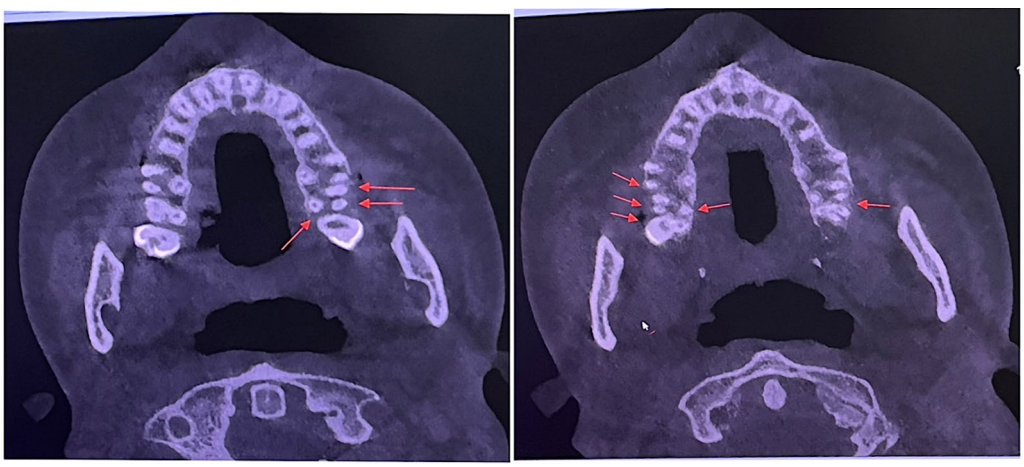

Fig. 2 Red arrows point at the alveolar bone destruction in the axial view of maxillary molar regions of the patient with DLBCL

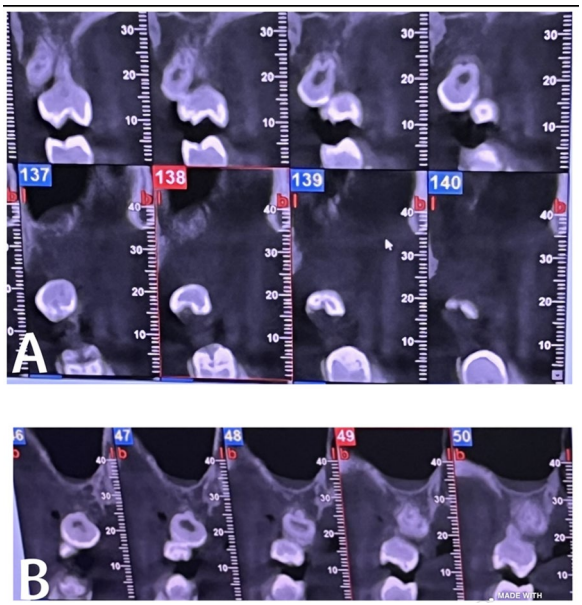

Fig. 3 The appearance of floating teeth in the air in both sides of maxillary molar regions of the patient with DLBCL. **A** Coronal view of the maxillary left second and third molar. **B** Coronal view of the maxillary right second molar

positivity for CD_{23} and BOB_1, and inconclusive staining for LMP. The results of the IHC analysis of the repeat biopsies of those areas were consistent with DLBCL. Then, the patient was immediately referred to an oncologist, and clinical and paraclinical examinations were performed following admittance to the hospital for subsequent management as follows.

Molecular testing including FISH analysis for MYC, BCL_2, and BCL_6 showed no evidence of gene rearrangement. Moreover, the bone marrow biopsy revealed a mild hypocellular marrow with no evidence of lymphomatous involvement.

The staging was performed according to the Ann–Arbor classification and our patient was at stage II. Then, the patient received six cycles of chemotherapy with the R-EPOCH regimen which included rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin. After completion of the sixth cycle of chemotherapy, significant remission of intraoral maxillary lesions was revealed as shown in Fig. 7 and improvement of her symptoms. Moreover, fluorodeoxyglucose (FDG) positron emission tomography (PET) combined with computed tomography (CT) was performed 4 weeks after completion of the 6th cycle of chemotherapy and found no evidence of metabolically active tumoral lesions throughout the whole body, showing regression of the disease. Three weeks later, biopsy of the right lung mass was also taken and found only necrotic tissue with inflammation, confirming complete response with regression of the disease.

Regarding the prognostic factors, there is some evidence that patients over the age of 60 with higher stage and/or poor health have a higher mortality rate. Furthermore, extranodal NHLs are more aggressive when they occur in the oral cavity [9]. Overall, the patient presented here has low risk based on international prognostic index.

Discussion

In the oral cavity, lymphomas are the second most common malignancy after squamous cell carcinoma [6, 13]. Despite the fact that oropharyngeal lymphomas generally occur in the Waldeyer's tonsillar ring and extranodal involvement is rare, accounting for 2–5% of cases [1, 14]; both soft tissues and jaw bones can be affected and encountered by a dentist in a clinical practice [15]. The intraoral lymphomas are often mistaken for inflammatory or reactive processes [1], thus leading to delay in the correct diagnosis and initiation of the treatment. Therefore, the role of the dentist is essential in early diagnosis to allow the patients to immediately start treatment.

In the present case, the oral lesions appeared clinically as exposed bone of the maxilla, bone loss, and soft tissue ulceration along with imaging features of destruction of bone walls in both sides of the maxilla, the appearance of floating teeth in the air, and abnormal trabecular pattern. Based on the nonpathognomonic clinical and radiographic features of the presented case, its differential diagnosis is broad, ranging from inflammatory conditions to malignant neoplasms. In more detail, the clinical appearance of the exposed bone on the hard palate of our patient simulated osteonecrosis of the maxilla. However, the patient denied any antiresorptive or antiangiogenic medication use, previous head and neck radiotherapy, and history of diabetes mellitus (DM), excluding the possibilities of medication-related osteonecrosis of the jaws (MRONJ), osteoradionecrosis, and DM-related osteomyelitis or osteonecrosis [15]. In 2018, a study by Luz *et al.* showed that Langerhans cell histiocytosis should be considered as a differential diagnosis in case of unclear osteolytic changes of the jaw bone, especially in the absence of MRONJ [16]. Although exposed bone in the jaw is poorly documented in the literatures, Lončar *et al.* in 2019, also reported other possible etiologic factors including trauma, odontogenic infections, herpes zoster infection associated osteonecrosis, HIV-associated necrotizing ulcerative periodontitis, long-term corticosteroid usage, ischemia, occlusion, and coagulopathies that should be considered as differential diagnosis [17]. However, our assessments did not confirm any of the above-mentioned conditions. Finally, a second oral

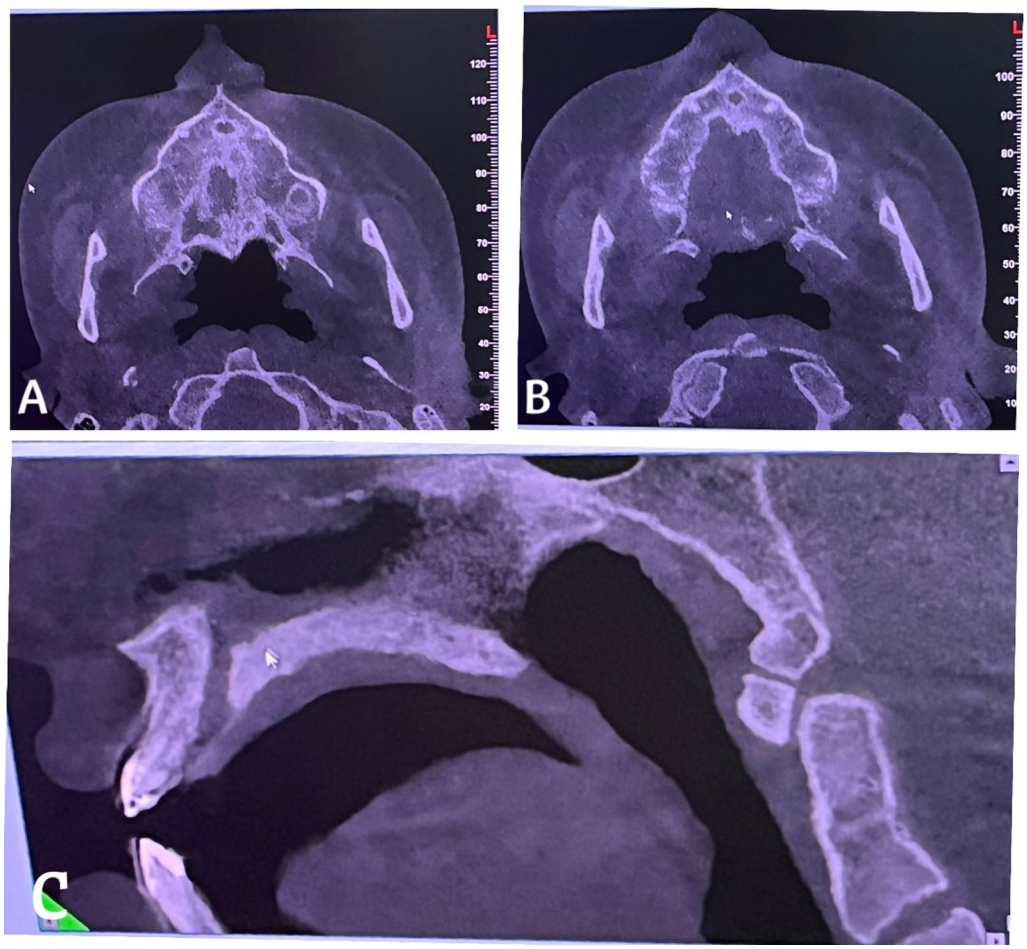

Fig. 4 The abnormal trabecular pattern of the patient with DLBCL in the axial (**A**, **B**) and sagittal (**C**) views

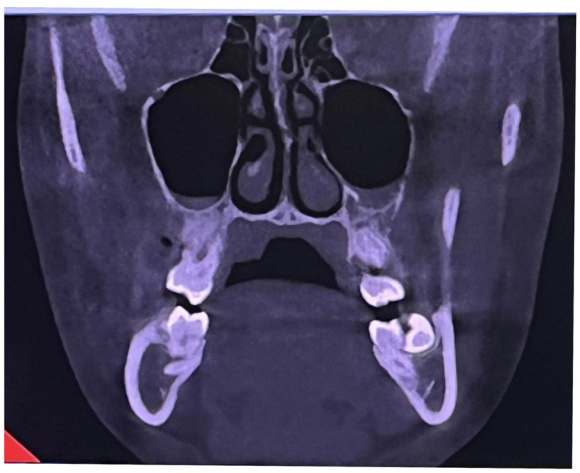

Fig. 5 The mucosal thickening of both maxillary sinuses in the coronal view of the patient with DLBCL

biopsy for a definitive diagnosis was performed and led to a diagnosis of DLBCL. Therefore, the findings of the current study reconfirmed a previous study by Tseng *et al.* in 2021, stated that oral manifestations of lymphomas are nonspecific mimicking other more common conditions such as advanced periodontal disease, osteomyelitis, or other malignancies, making it challenging to attain an early diagnosis [18].

To the best of our knowledge, there is little information available in the literature on DLBCL characteristics in the oral cavity. A recent literature review in 2022 focused on oral manifestations of extranodal lymphomas and stated that their clinical and subjective symptoms are varied on the basis of the location and there is usually a diagnostic challenge in lymphomas involving gingiva/alveolar crest or maxilla/mandible. Although they reported that swelling or an ulceration is the most common finding noted by the patient, a number of lymphoma cases showed clinical and radiographic appearance initially resembled horizontal bone loss compatible with marginal periodontitis but

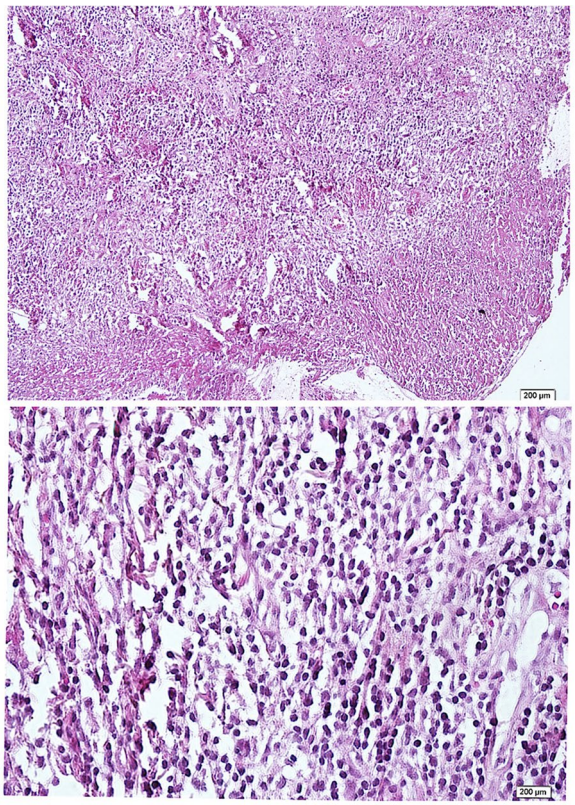

Fig. 6 Microscopic photograph of the oral specimen in the patient with DLBCL

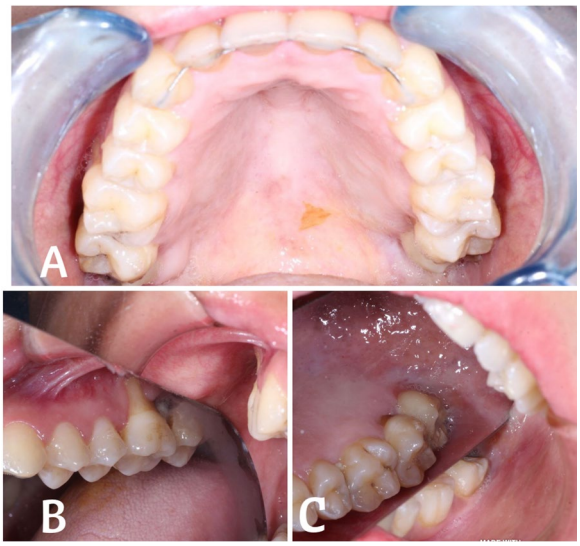

Fig. 7 Clinical photographs of a 18-year-old patient with DLBCL after six cycles of chemotherapy with R-EPOCH regimen, showing regression of the disease. **A** Palatal mucosal healing. **B** Mirror view of the bone loss involving the maxillary right first molar. **C** Mirror view of the left tuberosity area

later developed bulging or ulcerated lesions. They also reported that lymphomas involving gingiva or alveolar crest may present radiographic findings such as destruction of bone walls, soft tissue lesion with bone destruction, floating teeth, and abnormal trabecular pattern. Therefore, the findings of this case report mirror those of the above-mentioned study [2].

In our case, multiple biopsies were necessary to attain an accurate diagnosis of the patient's condition, highlighting the diagnostic challenge. Biopsy must be considered in lesions without a tendency to heal to exclude malignancy and confirm the diagnosis [19]. Although inflammation is a common finding in oral biopsies, lymphoma should be considered from other neoplasms when the original biopsy shows abnormal inflammatory infiltration [20]. Accurate diagnosis is the most effective approach to manage lymphoma [10]. Therefore, a clinicopathologic correlation is essential to achieve a correct diagnosis in suspicious clinical cases. Ideally, it is necessary to perform an excisional or incisional biopsy to obtain a sufficient specimen for analysis [10]. Rebiopsy should also be considered when the specimen amount is insufficient, the original biopsy shows nonspecific inflammatory changes, or an artifact interferes with the diagnosis of a neoplastic process [21]. For example, in a similar case reported by Vardas *et al*. in 2022, the initial biopsy of the exposed bone of the maxilla and surrounding soft tissue ulcer presented nondiagnostic results and a rebiopsy ultimately revealed the final diagnosis of DLBCL [15].

From an overall perspective, the clinical presentations of lymphomas include B symptoms (fever of unknown origin, night sweating, and inexplicable weight loss), loss of appetite, fatigue, and itchy skin [6]. Particularly, systemic B symptoms are markers of advanced disease that present in about 30% of patients with DLBCL [8]. On the other hand, several factors are known to be associated with increased risk of NHLs, including genetics (such as a family history of hematologic malignancies and chromosomal translocation), immune conditions (such as Sjögren's syndrome and rheumatoid arthritis), infections, toxins and drugs, modifiable risk factors (such as alcohol consumption and smoking), and employment (such as agricultural or health workers). Particularly, patients with congenital or induced immunodeficiency have a higher risk of developing extranodal NHLs than the general population [9].

Our assessments did not confirm either of abovementioned conditions except for inexplicable weight loss. In addition, she complained of a chronic cough and dyspnea for 18 months prior, which was diagnosed as mediastinal mass, cavitary lesion, and mediastinal lymphadenopathy. However, there was no evidence of malignancy based on cytology and IHC analysis.

Subsequently, the oral biopsy diagnosed DLBCL. The findings observed in this case report are in line with a previous study conducted by Tseng *et al*. on 607 cases of oral lymphoma, where extranodal oral involvement may be part of a disseminated disease [18]. Therefore, systemic conditions should be considered as a possible cause of oral lesions and a biopsy can most likely enable a correct diagnosis and should be performed if there is any doubt concerning the nature of the lesion [2].

In regard to pulmonary involvement, Yamane *et al*. reported another case of DLBCL in a 68-year-old woman presenting with cough, bloody sputum, and pulmonary cavitation; again, transbronchial biopsy initially found no evidence of malignancy and a surgical biopsy subsequently revealed the final diagnosis of DLBCL [22]. Although the mechanism of cavitation is unknown, DLBCL with high malignancy, leading to a tendency to necrosis, may be associated with cavity formation. DLBCL with pulmonary cavitation is very rare and is extremely difficult to differentiate from infection, primary lung cancer, or granulomatosis with polyangitis according to the findings of imaging alone [7]. Moreover, the diagnostic yield of biopsy in DLBCL can be low, even if an open-lung biopsy is performed to obtain large specimens and lymph nodes. Therefore, a biopsy of extrapulmonary disease may be needed to attain the diagnosis [23]. In the present case, the lymphoproliferative disease was suspect, but ultimately, the oral biopsy diagnosed DLBCL and chemotherapy could be started. Therefore, the present case report reconfirmed a previous study by Storck *et al*. suggesting that a biopsy in the head and neck region should immediately be performed following suspicious findings due to the fact that tumors in this region are easily accessible [24].

Although DLBCL is a clinically aggressive disease, it is considered to be treatable and about two-thirds of the cases respond sufficiently well to standard chemoimmunotherapy [6]. R-CHOP regimen including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone has been the standard treatment for DLBCL for nearly two decades. However, it is frequently combined with consolidative radiation [25]. Therefore, interest in developing new and more efficient treatments with lesser side effects has been advanced. In particular, R-EPOCH without consolidative radiation has emerged as a potential new treatment, which included dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin [25]. In the young case of DLBCL presented here, secondary breast cancer due to mediastinal radiation was of concern. Therefore, R-EPOCH was a superior treatment for her, and significant remission and improvement of her symptoms were evident after six cycles of chemotherapy with R-EPOCH regimen.

Conclusions

DLBCL is an aggressive but curable disease that belongs to NHL. Misdiagnosis or delay in diagnosis may result in not only unnecessary interventions, but also prevents patients from receiving the necessary treatment at the appropriate time. Pulmonary involvement is an uncommon finding in patients with DLBCL. However, a biopsy of extrapulmonary disease may be needed to attain the diagnosis due to the low diagnostic yield of biopsy in DLBCL with pulmonary involvement. On the other hand, oral involvement of extranodal lymphomas may be part of a disseminated disease. However, it is rare and remains a major diagnostic challenge due to nonspecific clinical signs and symptoms mimicking other more common conditions such as advanced periodontal disease, osteomyelitis, or other malignancies. The presented case also described a 18-year-old girl with chronic cough and dyspnea referred for evaluation of oral lesions in the upper jaw. In this case, a lymphoproliferative disease was suspect, but ultimately, the oral biopsy diagnosed DLBCL and chemotherapy could be started.

Although there is a need in the scientific community for early diagnosis methods, we reconfirm that systemic conditions should be considered as a possible cause of oral lesions, and a biopsy should also be performed immediately if there is any doubt concerning the nature of the lesion. Moreover, some conditions necessitate multiple biopsies to attain an accurate diagnosis.

Abbreviations

HL	Hodgkin's lymphomas
NHL	Non-Hodgkin lymphomas
DLBCL	Diffuse large B-cell lymphoma
IHC	Immunohistochemical
FISH	Fluorescence in situ hybridization
WBC	White blood cells
RBC	Red blood cells
MCV	Mean corpuscular volume
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
ESR	Erythrocyte sedimentation rate
CRP	C-reactive protein
LDH	Lactate dehydrogenase
C-ANCA	Antineutrophil cytoplasmic autoantibody, cytoplasmic
P-ANCA	Perineuclear antineutrophil cytoplasmic autoantibody
CBCT	Cone beam computed tomography
FDG	Fluorodeoxyglucose
PET	Positron emission tomography
CT	Computed tomography
DM	Diabetes mellitus
MRONJ	Medication related osteonecrosis of the jaws

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Author contributions
FR was supervisor and project administrator. AS was mainly involved in investigation and writing original draft. FR, ZM, and VM reviewed and edited the original draft and all the authors have read and approved the submitted version.

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Availability of data and materials
The data supporting the findings of this study are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests.

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