Case Report

Physical torment: A predisposition for diffuse B-cell lymphoma

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Abstract

Lymphomas of the oral cavity are rare and represent only 3%–5% of all lymphomas. Diffuse large B-cell lymphomas (DLBCLs) are a heterogeneous group of tumor and the most common type of all non-Hodgkin's lymphomas (NHLs). They mostly arise from soft tissue as asymptomatic swelling and involvement of jaw bones is infrequent. We present a case of a 23-year-old patient who developed DLBCL in oral cavity region 4 months after blunt trauma. The patient lacked other physical symptoms at the time of presentation. Histopathology, bone marrow and immunohistochemistry revealed DLBCL. After chemotherapy of eight cycles, swelling was totally reduced and no relapse observed in 10 months' follow-up period. Thus, the present report represents an example of possible rapport between trauma and unresolved soft-tissue swelling which may be caused by NHLs.

Keywords: Diffuse large B-cell lymphoma, non-Hodgkin's lymphoma, trauma

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INTRODUCTION

Lymphomas constitute a group of neoplastic proliferation process of the lymphocytes and their precursor cells, mainly affecting lymph nodes, spleen and other nonhematopoietic tissues. Lymphoma, a cancer of lymphoid tissue is the second-most common neoplasm after squamous cell carcinoma in head and neck region.[1,2] They are classified as Hodgkin's and non-Hodgkin's lymphoma (NHL). Extranodal NHL in the oral cavity is considered to be pretty uncommon.[3] Diffuse large B-cell lymphoma (DLBCL) is the most common variant of non-Hodgkin's intermediate-grade lymphomas, and affect mainly lymph nodes and the lymphatic organs, but they also frequently involve extranodal sites.[4] In the area of head and neck, they are located mainly in salivary glands, eyeballs, nasopharynx, maxillary sinus, vestibule, palate and lips.[5] PUBMED search revealed about seven cases of malignant lymphoma reported after a history of previous trauma, among those five were reported in head and neck region.[2,6-9] These lymphomas manifested 1–2 months after blunt trauma to the occipital region, cheek, forehead, periorbital and eye.

This article reports a case of trauma-induced primary DLBCL in the left maxillary vestibule in a 23-year-old male patient.

CASE REPORT

A male patient aged 23-year-old reported to the oral surgery department with a chief complaint of swelling in the left

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middle third of face since 4 months. History revealed a traumatic incident at the site of swelling 4 months back where he was hit by a hard object. Extraoral examination revealed asymmetrical face with dome-shaped swelling on the left side [Figure 1a] extending superior-inferiorly 0.5 cm below inferior-orbital ridge to 0.5 cm above the corner of mouth and anterior-posteriorly from left lateral wall of nose to 1 cm anterior to tragus. The skin over the swelling appeared normal with no secondary changes. On palpation, the lesion was tender; firm in consistency with local rise in temperature, left submandibular lymph nodes were enlarged, tender and unfixed. Intraoral examination revealed vestibular obliteration extending from 13 to 16 [Figure 1b].

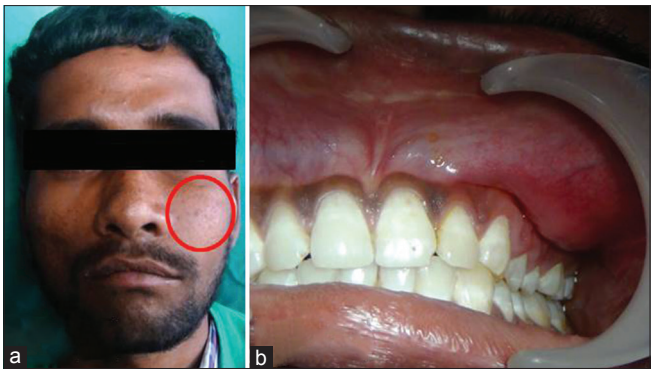

Figure 1: (a) Clinical image showing dome shaped swelling on the left side of the face. (b) Intraoral image showing left vestibular obliteration

Orthopantomogram and occlusal radiographs were unremarkable, whereas magnetic resonance imaging showed altered signal intensity collection in left buccal space between left temporalis and buccinator muscle with inferior tracking to submandibular space and spiral computed tomography (CT) showed soft-tissue swelling in the left anterior maxillary region [Figure 2].

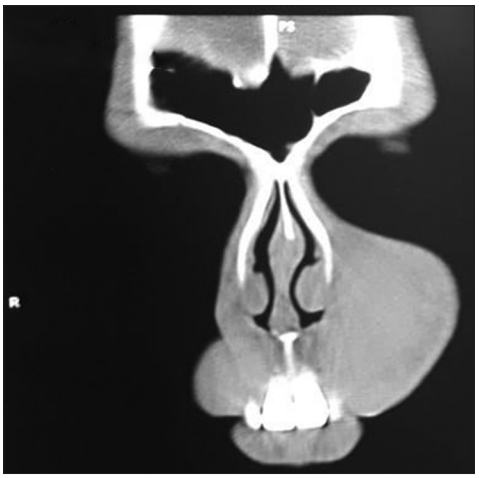

Figure 2: Computed tomography scan of paranasal sinuses showing soft-tissue swelling in left maxillary region

An incisional biopsy was advised under local anesthesia. On histopathological examination, the hematoxylin and eosin (H&E) stained tissue section showed diffuse proliferation of atypical round cells in loose connective tissue stroma. These large populations of anaplastic round cell showed cleaved and multilobulated cells resembled centrocytes, cells with peripheral margination of chromatin and prominent 2–3 nuclei resembled centroblasts, and few cells resembled immunoblast. The tumor cells are seen infiltrating the striated muscle [Figures 3 and 4]. Even the fine-needle aspiration cytology of submandibular lymph node showed similar cytological features [Figure 5a and b]. Based on these features of large cell lymphoma was suspected and further investigation was carried out. Immunohistochemistry showed pancytokeratin negative ruling out epithelial origin, CD20 showed positivity [Figure 6a], BCL-2 positivity [Figure 6b] and proliferation index with Ki-67 <70% [Figure 6c]. Correlating the clinical, histopathological and immunohistological features, a final diagnosis of diffuse large B-cell lymphoma (BCL) was given.

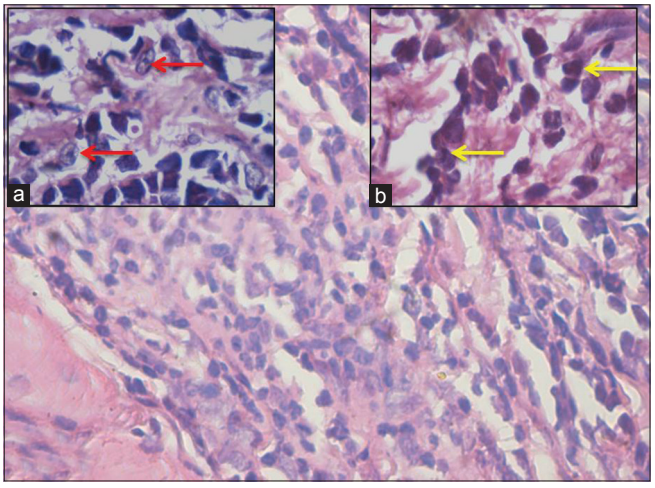

Figure 3: Histopathological image shows diffuse proliferation of round cells in the form of sheet in the background of loose fibrillar stroma (H&E, ×100) (inset image: [a] Showing centrocytes [red arrow], [b] showing centroblasts [yellow arrow] H&E, ×1000)

The patient was referred to cancer institute where chest X-ray, ultrasound of abdomen, bone scan and bone marrow biopsy did not reveal any abnormality and confirmed the lesion to be localized. The patient was sent to medical oncologist for chemotherapy. He was given rituximab 500 mg (MABTAS 500 mg), cyclophosphamide 1200 mg (Cycloxan), doxorubicin 50 mg (Zubidox 50 mg) and onvinc-1 twice weekly for a total of eight cycles. Following the chemotherapy, the swelling was completely

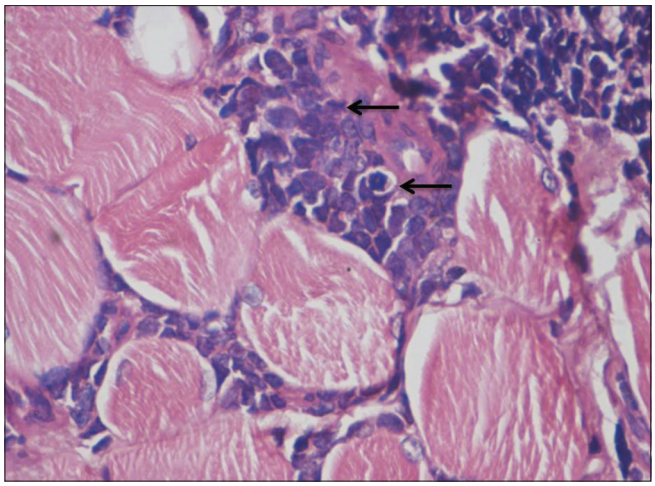

Figure 4: Histopathological image showing tumor cells infiltrating muscle (abnormal mitotic figure-black arrow) (H&E, ×200)

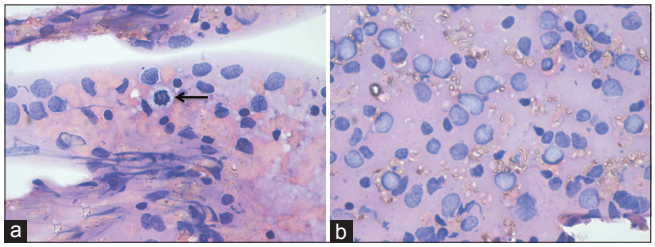

Figure 5: (a and b) Histopathological image of fine-needle aspiration cytology showing centrocytes and centroblasts (H&E, ×400) (abnormal mitotic figure-black arrow)

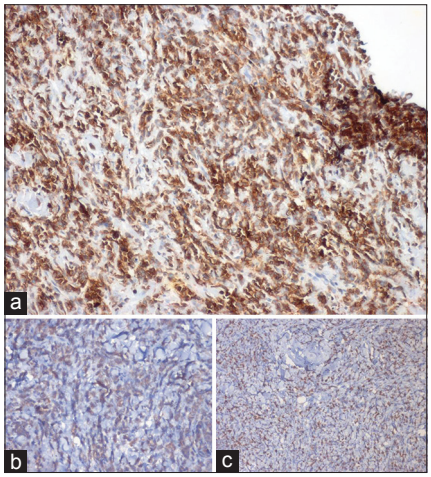

Figure 6: (a) Immunohistochemical image shows strong positivity for CD20 indicating B-cell origin of lymphocytes (×100). (b and c) Immunohistochemical image shows strong membranous B-cell lymphoma-2 positivity ([b] × 200) and nuclear positivity of Ki-67 showing <70% ([c] ×100)

resolved. Postoperative CT scan of the neck and brain showed normal impression.

DISCUSSION

Lymphoma classification is controversial, many changes have been proposed from decades. However, the new classification is based on morphological and immunological features, and the current premise is focused on genetic and molecular studies.[10] Lymphomas are of two major categories: Hodgkin's lymphoma (HL) and NHL, disparity between these two can only be recognized under the microscope. Reed–Sternberg cells, multinucleated giant cells characteristic of HL histopathologically and other neoplasms of lymphoid system are referred to as NHL which are derived from B-lymphocyte predominantly.[11]

NHLS of the oral cavity exist as primary or secondary to extension from Waldeyer's ring. These are rare and accounting for 3%–5% of the lymphomas. The most common type of NHL of oral cavity is DLBCL. Outside the Waldeyer's ring, the hard palate and maxillary vestibule appears to be involved frequently. These lesions are symptomatic and presents as rapidly enlarging mass.[12]

Etiology of primary DLBCLs of oral cavity is unknown apart from being diagnosed in HIV patients. Epstein–Barr virus, HIV virus, radioactive contaminations and hybrid genes resulting from translocation are some of the etiological factors for NHL. Trauma as a predisposing has always been a subject of debate.[6,8] Prolonged or repeated inflammation caused by trauma may induce cellular atypia leading to carcinogenesis,[12] similar to that of the present case.

In the 19th century, German pathologist Virchow suggested the causal link between cancer and inflammation. Many molecular players are involved in cancer-related inflammation, which includes nuclear factor kappa-B (NF-κβ), signal transducer activator of transcription-3 and primary inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, 23 and tumor necrosis factor-alpha.[12] NF-κβ is a key orchestrator on innate immunity and inflammation, and few studies have demonstrated that NF-κβ may act as a mechanistic link between inflammation and cancer, but the individual role of NF-κβ activity in the development of malignancy in inflammation still remains unclear. In multiple types of hematologic malignancies, NF-κβ is rendered constitutively active through chromosomal rearrangements and overexpression of NF-κβ subunits, mutations in upstream regulators or through enhanced proteasomal activity.[12,13] Another explanation for the development of a lymphoma is that circulating lymphoma cells may lodge and accumulate at the site of the trauma.[9]

Few cases have been reported in Japanese patients, under the term pyothorax-associated lymphoma. Moreover, DLBCL features are also seen in other chronic inflammatory conditions such as metallic implants in bone and joints,

chronic osteomyelitis and use of metallic mesh implant, thus in 2008 the "World Health Organization classification of tumors of hematopoietic and lymphoid tissue" categorized DLBCL associated with chronic inflammation as distinct entity [Table 1].[2,5]

Lymphomas are round cell lesions which can be diagnosed by H&E stain, but modern hematology relies on immunophenotyping for subtyping and also to distinguish between benign and malignant diseases. DLBCL can be subclassified depending on cytomorphology, gene expression profiles and based on prognosis [Table 2].[3]

DLBCLs express CD45 and pan-B-cell antigens (CD19, CD20 and CD79), but some cases lack the expression of one or more of this antigens. CD20 is expressed on B cells from the mature precursor B cells until the pre-plasma cell stage of differentiation, thus a specific marker for B-cell lineage and most DLBCL show diffuse positivity.[14] In normal B-cell differentiation, the B cells go through the pregerminal center (GC), GC and post-GC stages, where [Table 3] represents the expression of specific antibody and prognosis in each stage.[5]

Even, T-cell marker (CD5 and CD3) have been expressed in DLBCL and may have prognostic significance which is associated with more aggressive clinical course and poor outcome. Lately, few cases of large BCL showed expression of CD3 and B-lineage markers. The proposed mechanism for expression of T-cell marker is due to depression of genetic material, the transformation of progenitor cell before the divergence of B lymphocyte pathway, neoplastic expansion of normal B cells that express T-cell antigen.[15]

DLBCL comprises a heterogeneous group of tumor due to discrepancy in immunophenotyping. More than 25% of DLBCL have a translocation t(14;18) and most of them show bcl-2 with or without a translocation.[16]

Cytogenetic studies of NHL have instituted that chromosomal alterations affecting band 3q27 are relatively frequent in DLBCL (10%–20%). These alterations mainly involve reciprocal translocations between 3q27 and various other chromosome partners, including the sites of the immunoglobulin (Ig) genes (14q32, 2p12 and 22q11), and non-Ig genes (8q24, 11q13 and 5q31). Molecular cloning of the 3q27 chromosome breakpoints by several groups revealed the bcl-6 gene. At the molecular level, the bcl-6 gene rearrangement was found at a high frequency in DLBCL (30%–40%), as well as in FL at a lower frequency (5%–10%). Normally, bcl-6 is required for GC formation, antigen-specific antibody response and Th2-mediated cytokines. Both bcl-2 and bcl-6 have a pro-apoptotic effect thus inhibiting cell growth and initiating cell cycle progression.[17,18]

DLBCL may show more than one gene rearrangement, which referred as "double" (*BCL6*+/*MYC*+) or "triple hit" (*BCL2*+/*MYC*+/*BCL6*+) lymphomas. The *MYC* translocation is characteristic of Burkitt lymphomas (BLs) but can be seen in other NHLs, including DLBCL and so-called double-hit lymphomas that have both *BCL2* and *MYC* translocations.[19]

The differential diagnosis includes nonhematolymphoid malignancies where tumor cells show cohesive growth, cytoplasm often eosinophilic rather than amphophilic or basophilic and expression of specific

Table 1: WHO classification of diffuse large B-cell lymphoma

WHO classification 2008 (categorized aggressive B-cell lymphomas as)
DLBCL not otherwise specified
DLBCL associated with chronic inflammation
DLBCL arising in human herpes virus-8 associated Castleman's disease
B-cell lymphoma unclassified
Burkitt's lymphoma

DLBCL: Diffuse large B-cell lymphoma

Table 2: Subclassification of diffuse large B-cell lymphoma

Based On	Types	Characteristics
Cytomorphology	Centroblastic variant	Cells are medium to large sized with oval to round nuclei and fine vesicular chromatin pattern with 2-4 nucleoli opposed toward the nuclear membrane Tumor may show monomorphic (>90% centroblasts) or polymorphic (<90% centroblasts) with admixed immunoblasts
	Immunoblastic variant	Cells show uniform cytology with prominent central nucleoli and distinct rims of basophilic cytoplasm
	Anaplastic variant	Cell are variable large with bizarre pleomorphic nuclei Tumor cells may mimic reed-Stenberg or undifferentiated carcinoma cells Shows increased number of intermixed T cells or histiocytes
Gene expression profiles	GCB	CD10 and Bcl-6 $+^{ve}$ or alone CD10 $+^{ve}$
	Non-GCB or ABC like	MUM-1 $+^{ve}$
	Type 3 gene expression profile	
Prognosis using antibodies	Good prognosis	CD10 and Bcl-6 $+^{ve}$
	Bad prognosis	MUM-1 $+^{ve}$

GCB: Germinal center B cells, MUM-1: Multiple myeloma oncogene1, Bcl-6: B-cell lymphoma 6, CD: Cluster of differentiation

Table 3: Stages of B-cell differentiation, subsequent antibody positivity and prognosis

B-cell - different stages of maturation	Antibody positivity	Prognosis
Pre-GC stage	CD22, CD23, CD40	Favorable
GC stage	CD45, CD10, BCL6	Favorable
Post-GC stage	MUM1, CD138, Ki67, p53	Unfavorable

GC: Germinal center, MUM-1: Multiple myeloma oncogene1, Bcl-6: B-cell lymphoma 6, CD: Cluster of differentiation

immunohistochemical (IHC) markers (e.g., cytokeratin for squamous cell carcinoma, HMB 45, S-100 for melanoma). Nonreactive neoplastic process shows aggregates of bland lymphocytes without atypical features. BLs are more common in younger age groups, shows starry sky appearance, tumor cells show fine chromatin and cytoplasm shows vacuoles. IHC shows BCL2 protein negative, Ki-67: ~100% and translocation of MYC gene. Anaplastic plasmacytoma may have a history of multiple myeloma, tumor cells are smaller and CD 20−, CD138+. Histiocytic sarcoma shows often larger cells with abundant cytoplasm and shows positive macrophage lineage marker (e.g., CD68+ and CD20−).[19,20]

Recent molecular studies evidenced that chromosomal abnormalities play an important role in the pathogenesis of the disease and its subclassification is important to guide the treatment.[4] The current treatment of DLBCL usually begins with multi-agent chemotherapy; typically, CHOP (cyclophosphamide, hydroxydoxorubicin, oncovin and prednisone) which involve three cycles.[4,11] Early stage disease requires either chemotherapy alone or a combination of chemotherapy and radiotherapy, but bone marrow transplantation considered if remission is not maintained. The role of surgery is markedly limited in the treatment of DLBCL.[11] Newer treatment includes the use of proteasome inhibitors which targets NF-κβ pathways which is required by B-cell type DLBCL, small molecule inhibitors of signal transduction pathways and agents like lenalidomide, which modulate the cytokines and tumor microenvironment.[19] Even the same line of treatment is followed for DLBCL associated with chronic inflammation. The prognosis of NHLs depends on clinical staging, where Stage I have a better prognosis than those in Stages II to IV, with 5-year overall survival rates ranging from 26% to 73%.[21] DLBCL associated with chronic inflammation shows good prognosis with no relapse with 6 months to 5 years' follow-up. The present case showed total reduction in swelling with no relapse after 10 months of follow-up.

CONCLUSION

The occurrence of primary DLBCL in oral cavity is very rare, but the connection between trauma and tumor development in our patients remains obscure, but our cases may represent an example of a trauma-induced lymphoma in the oral cavity. It is very essential for the clinician to be aware of this type of aggressive lesion, which aid in early diagnosis to improve the life expectancy of these patients. The diagnosis of these lesions is challenging due to their nonspecific nature of presenting symptoms, so proper clinical evaluation, histology as well as IHC evaluation of biopsy specimen may aid in early diagnosis and effective management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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