Case Report

Evaluation of a case of diffuse large B-cell lymphoma

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Abstract

Lymphomas are a group of malignant blood cell tumors that develop from lymphocytes representing 2.2% of all malignant neoplasms of the head and neck. Two main categories of lymphomas are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL) of which 90% are of the NHL type. Several classification systems have existed for lymphomas, the objectives of which are to help in identification of homogeneous group of well-defined entities and facilitating the recognition of uncommon diseases that require further classification as it affects prognosis and therapeutic implications. Diffuse large B-cell lymphoma (DLBCL) is the most common NHL in the oral cavity involving Waldeyer's ring, base of the tongue, buccal mucosa and hard palate. DLBCL can be divided into germinal center B-cell-like, activated B-cell-like or type 3 gene expression profiles. This paper highlights a case report of DLBCL revisiting the intricacies and difficulties involved in establishing a diagnosis.

Keywords: Activated B-cell like, diffuse large B-cell lymphoma, lymphoma

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INTRODUCTION

Malignant tumors of oral cavity are infrequent, representing only 5% of all those occurring in human body. Among malignant tumors of oral cavity, squamous cell carcinomas are the most frequent type (90%–98%), and malignant lymphomas outstand among the remaining 2%–10%. Lymphomas are a group of malignant blood cell tumors that develop from lymphocytes which are a type of white blood cell. These are characterized by the clonal proliferation of lymphocytes and of their cell precursors and of lymphocyte cell lines, arising as a result of somatic mutation of lymphocyte progenitors.[1]

Previous classifications used for classifying lymphoma were Rappaport 1956, Lennert/Kiel 1974, Working Formulation 1982 and Revised European American Classification 1994.[2] In 1995, the WHO started the project of classifying hematopoietic and lymphoid tissue tumors which was first published in 2001. It was re-edited in 2008 with the participation from the Hematopathology Society and the European Association of Hematopathologists. Apart from 2001 classification, it defined new entities and gave solutions to diagnosis accuracy problems, which included the recognition of small clonal lymphoid populations and identification of diseases characterized by the participation of certain anatomical sites or the clinical characteristics such as age.[3]

Recently, the classification was reassessed and modified in 2016 with limited alterations. This present classification

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incorporated a large body of information published over the last 8 years relating to existing entities with some important diagnostic, prognostic and therapeutic implications. It clarifies the diagnosis and management of lesions at very early stages of lymphomagenesis, refines the diagnostic criteria for some entities, details the expanding genetic/molecular landscape of numerous lymphoid neoplasm and their clinical correlates and refers to investigations leading to more targeted therapeutic strategies.[4]

Lymphomas are a heterogeneous group of neoplasms that are broadly classified as Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) due to their biological, histological and immunophenotypical differences and clinical behavior patterns.[3,5,6] Although lymphomas of the oral cavity and maxillofacial region are rare pathological entities, it is important to describe the complete manifestation of their natural history in order to provide knowledge of their development.[7]

HL corresponds to approximately 14% of all lymphomas and NHL approximately 86% of lymphomas.[3] About 85% of all lesions primarily affect tonsils and palate. Waldeyer's ring is the second most common site for the incidence of extranodal NHL. In approximately 2% of extranodal lymphomas, the oral cavity is involved with the primary sites being palate, gingiva, tongue, cheek, floor of mouth and lips.[7]

NHL is further classified as B- or T-cell lymphomas. In B-lymphocyte group, two major categories are recognized: precursor and mature B-lymphocytes. Diffuse large B-cell lymphoma (DLBCL) is the most frequently diagnosed type of NHL in the human body and is most frequent type of NHL of oral cavity.[8] DLBCL is further classified as germinal center B-cell (GCB)-like and activated B-cell (ABC)-like and molecular subgroups, based on gene expression profiling (GEP) as well as group of cases that could not be classified into either category, i.e., type 3 gene expression profiles. GCB and ABC subgroups differ in their chromosomal alterations, activation of signaling pathways and clinical outcome.[4]

In this report, a case of DLBCL is highlighted with insight on the intricacies and difficulties involved in establishing a diagnosis.

CASE REPORT

A 60-year-old male reported with a complaint of mobility of teeth for 5 months and a growth in the lower left posterior region of the jaw for the last 2 months. Initially, the growth was small in size which progressively grew to the present size of 3 cm × 2 cm. The patient also gave a history of extraction of #31 and #32 as they were decayed due to dental caries. Extraoral examination revealed facial asymmetry and a slight diffuse swelling in the left lower region of the face. Intraoral examination revealed a proliferative growth in the lower buccal vestibule and alveolus in relation to tooth #34, #35 and #36 [Figure 1]. The growth was mixed white and red in color, ovoid, raised, nontender and indurated with no serosanguineous discharge. #34 was Grade III mobile. Lymph nodes were not palpable, and hematological findings and viral markers for HIV and hepatitis were nonsignificant. No other systemic abnormality was detected. Radiographically, orthopantomography revealed hazy radiolucencies in the alveolar process from #34 to #36 region with floating tooth appearance [Figure 2]. Provisional diagnosis of carcinoma buccal vestibule and alveolus was made on this basis.

Incisional biopsy was performed under local anesthesia. Microscopic examination exhibited a diffuse population of small round cells underneath stratified squamous epithelium. The round cells were predominantly monomorphic, large with cleaved, vesicular nuclei and abundant eosinophilic cytoplasm [Figure 3]. Immunohistochemistry was performed which showed these round cells to be immunopositive for CD20, MUM1 and BCL-6 and immunonegative for CD10 and CD3 [Figure 4]. The Ki67 proliferative index was approximately 80% [Figure 4] A definitive diagnosis of DLBCL, ABC like, high grade, was arrived at. An extensive staging workup failed to reveal evidence of any other organ involvement. The disease was staged as Stage II lymphoma according to Ann Arbor staging. Local radiation and chemotherapy were advised. The patient received 6 courses

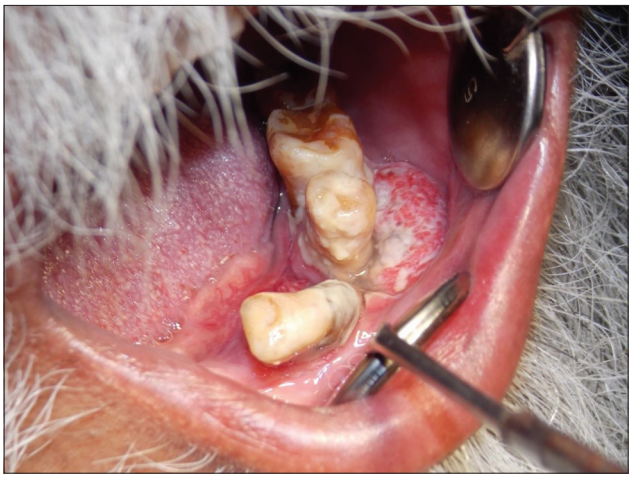

Figure 1: A proliferative growth in lower buccal vestibule and alveolus in relation to tooth #34, #35 and #36

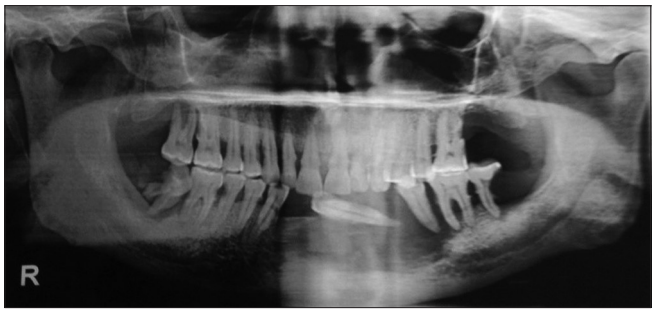

Figure 2: Orthopantomography showing hazy radiolucencies in the alveolar process from #34 to #36 region with floating tooth appearance

of CHOP chemotherapy, i.e., Cytoxan (cyclophosphamide), Adriamycin (hydroxydoxorubicin), vincristine (Oncovin) and prednisone plus local radiation. Six-month posttreatment follow-up of the patient did not show any evidence of recurrence.

DISCUSSION

Worldwide, DLBCL represents the most common subtype of NHL, accounting for 30%–40% of all newly diagnosed cases. DLBCL typically presents as an aggressive lymphoma, evolving over months and resulting in symptomatic disease that would imminently be fatal without treatment.[9] NHLs of the oral cavity account for only 3%–5% of the lymphomas. They can be primary or secondary to extension from Waldeyer's ring. The most frequent type of primary NHL lymphoma of the oral cavity is DLBCL occurring in the buccal mucosa, hard palate, gingiva and the maxillary vestibule.[8] Using a cDNA microarray, DLBCL can be divided into prognostically significant subgroups with GCB, ABC or type 3 gene expression profiles. The GCB group has a significantly better survival than the ABC group. The type 3 group is heterogeneous and not well defined but has a poor outcome similar to the ABC group.[10] GCB DLBCLs are believed to derive from lymphoid cells residing in the germinal center and therefore express genes normally detected in germinal center B-cells such as CD10 and LMO2 and the transcriptional repressor BCL-6. Whereas, ABC DLBCLs are believed to derive from B-cells at a plasmablastic stage, just before germinal center exit, and therefore express genes that are frequently expressed in mature plasma cells. The pathogenetic hallmark of ABC DLBCL is the constitutive activation of the NF-kB signaling pathway, which promotes cell survival, proliferation and inhibition of apoptosis.[9]

DLBCL has marked biological heterogeneity and highly variable clinical course. In the past, DLBCL was subclassified based on cytomorphologic features into centroblastic, immunoblastic and anaplastic. Centroblasts

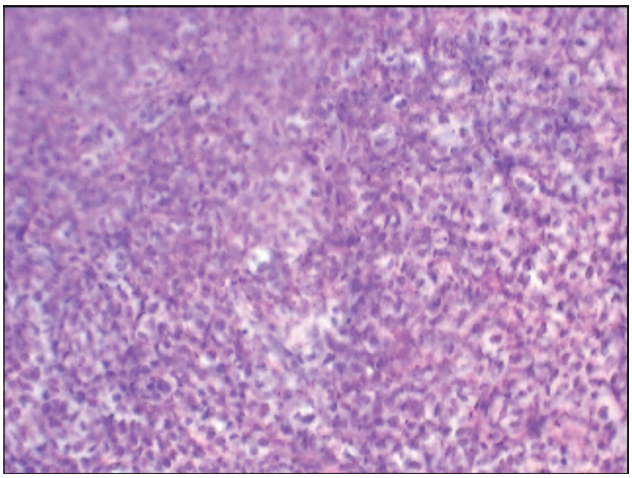

Figure 3: Microscopic examination exhibited a diffuse monomorphic population of small round cells having vesicular nuclei and eosinophilic cytoplasm (H and E, ×40)

are medium to large in size with oval-to-round nuclei and fine vesicular chromatin patterns having two to four nucleoli opposed toward the nuclear membrane, which can predominate in extranodal disease. The tumor can be monomorphic or polymorphic with admixed immunoblasts. Immunoblasts display a uniform cytology, and almost all cells exhibit prominent central nucleoli with distinct rims of basophilic cytoplasm. In the anaplastic variant, the tumor cells are variably large cells with bizarre pleomorphic nuclei. They may mimic Reed–Sternberg cells or undifferentiated carcinoma.[8]

Hans's algorithm has used antibodies CD10, BCL-6 and MUM1 to subclassify the cases of DLBCL into two groups: GCB or non-GCB (ABC like). CD10 is a membrane metalloprotein that is detected in early lymphoid progenitors and its expression is restricted to germinal center of the secondary follicle and is strongly associated with GCB DLBCL.[11] BCL-6 protein is a zinc finger transcription factor and acts as a sequence-specific repressor of transcription.[12] Its expression in DLBCL has been found in a majority of cases ranging from 57% to 100%.[13] MUM1 denotes the final step of germinal center B-cell differentiation which is considered as a marker of the non-GCB phenotype, especially when used in conjugation with CD10 and BCL-6. If CD10 alone is positive or if both BCL-6 and CD10 are positive, then it is a GCB subgroup. If both BCL-6 and CD10 are negative, the case is assigned to the non-GCB subgroup. MUM1 is expressed in plasma cells and the later stages of B-cell development, and it is associated with the ABC group in GEP studies. If BCL-6 is positive and CD10 is negative, the expression of MUM1 determined the group: if MUM1 is negative, the case is assigned to the GCB group, and if MUM1 is positive, the

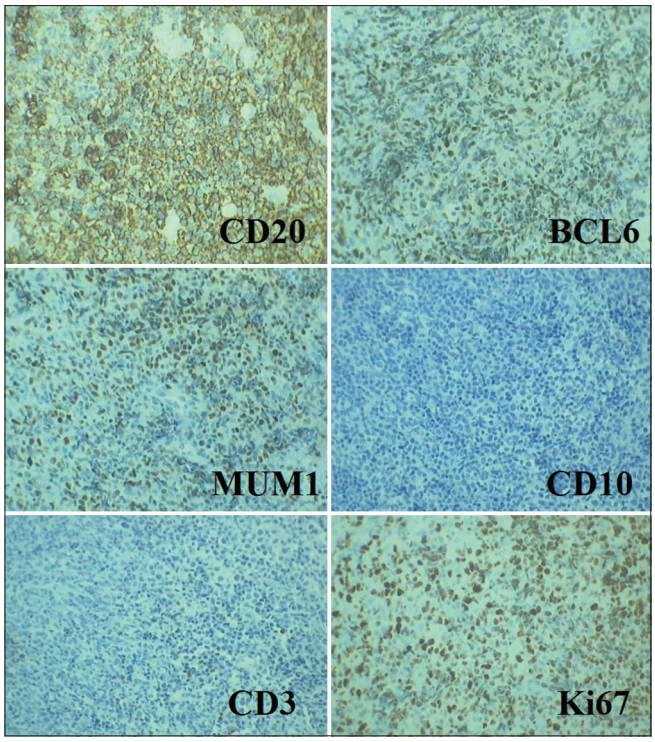

Figure 4: Immunohistochemistry shows immunoreactivity for CD20, BCL-6 and MUM1 and immunonegativity for CD10 and CD3. Ki67 proliferative index is 80%

case is assigned to the non-GCB group.[10] The present case showed immunopositivity for CD20/MUM1/BCL-6 and immunonegativity for CD10/CD3, so it was diagnosed as DLBCL, ABC like.

CD20 is involved in signal transduction and is expressed on B-cell from mature precursor B-cell (hematogone) until the preplasma cell stage of differentiation. It is a "pan B" cell marker, and DLBCL shows homogeneously bright staining for CD20[8,12] which is positive in this case.

CD3 protein is a part of T-cell receptor complex. It is a useful pan T-cell marker and is expressed from an early stage during T-cell ontogeny[8,12] and is negative in this case, hence differentiating it from T-cell lymphoma.

Ki67 is a nuclear nonhistone protein first identified in 1991 by Gerdes *et al*.[14] because it is expressed in all phases of the cell cycle except the resting stage (G_0) and has been used as a proliferation marker in numerous cancers including lymphomas. High Ki67 expression in patients with lymphoma is associated with worse prognosis.[15] In the present case, Ki67 index was 80%, which suggests a poor outcome, but the patient was lost to follow-up after 6 months.

In the present case of DLBCL like, high grade of the oral cavity, it is concluded that effort should be made to diagnose this disease as rapidly as possible for a better prognosis.

CONCLUSION

With the rising incidence of extranodal lymphomas, it has become imperative not to take any swellings of the orofacial region at face value but to properly examine its pathology and treat it judiciously. Immunophenotyping although indispensable in the diagnosis and classification of lymphoid neoplasms has to be used cautiously with knowledge of the antibodies used. Diagnostic criteria and differential diagnosis of each lymphoid tumor should be correlated with morphology, ancillary molecular genetics and clinical history to confirm the diagnostic impression.

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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Conflicts of interest

There are no conflicts of interest.

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