CASE REPORT

Primary diffuse large B-cell lymphoma in the anterior hard palate: A rare case report with review of literature

Sujit Ranjan Sahoo, Satya Ranjan Misra[1], Lora Mishra[2], Sobhan Mishra[3]
Department of Oral Pathology, [1]Department of Oral Medicine and Radiology, [2]Department of Conservative Dentistry and Endodontics, and [3]Department of Oral and Maxillofacial Surgery, Institute of Dental Sciences, Bhubaneswar, Odisha, India

Address for correspondence:
Dr. Satya Ranjan Misra,
Prasanti, Kathogola Road, Mangalabag,
Cuttack - 753 001, Odisha, India.
E-mail: drsatyaranjanmds@gmail.com

ABSTRACT

Diffuse large B-cell lymphomas (DLBCLs) are defined as neoplasms of large transformed B cells, i.e. with nuclear diameter more than twice that of a normal lymphocyte. These account for 30-40% of all adult non-Hodgkin's lymphomas (NHL). Intraoral lymphomas are relatively rare and often difficult to diagnose in clinical settings. In this case report, we describe a case of primary DLBCL affecting the anterior part of the hard palate of an elderly male patient. DLBCL of anterior part of hard palate is yet to be reported in the English literature, even though DLBCL cases involving the posterior palate have been recorded, thus making the present case to be first of its kind. Emphasis has also been given on the subclassification, differential diagnosis and prognostic antibody factors determining the outcome of DLBCL.

Key words: Anterior hard palate, diffuse large B-cell lymphoma, non-Hodgkin's lymphoma

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a subtype of non-Hodgkin's lymphoma (NHL) characterized by diffuse proliferation of large neoplastic B-lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte (>20 μm).[1] Affected patients are usually in their seventh decade of life and clinically a rapidly enlarging and often symptomatic mass is typically seen.[2] It is frequently reported in the mediastinum, gastrointestinal tract, bone marrow, central nervous system, breast and testes.[3] NHLs of the oral cavity are rare and account for only 2-3% of all the lymphomas reported.[4] In the maxillofacial region, the most commonly affected site of NHL is the Waldeyer's ring, nasopharynx and base of the tongue.[5] However, the incidence of primary DLBCL in the oral cavity has not been previously specified in the literature. Apart from Waldeyer's ring, in the oral cavity, DLBCL can involve maxillary alveolus, maxillary vestibule and posterior palate.[4] Currently, the treatment of DLBCL consists of radiotherapy, chemotherapy or both. Importantly, DLBCL may be cured in a significant percentage of patients, depending on the initial characteristics of the tumor and the host.[6]

This article reports a case of primary DLBCL affecting anterior part of hard palate in a 76-year-old male patient, which is first case of its kind considering the unusual location.

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CASE REPORT

A 76 year old eastern-Indian male patient reported to the dental hospital with a complaint of swelling in the palate since 2 months. History revealed that the swelling started as a small lesion and gradually grew in size. There was no toothache or pain associated with it, but as the size increased there was trauma from the mandibular anterior teeth causing ulceration and pain in the swelling. There was no history of any discharge from the swelling. The patient had nasal stuffiness and seromucous discharge from the nose on the left side since 15 days, which did not respond to medications.

On examination, a single well-circumscribed swelling was seen on the anterior hard palate, ovoid in shape, measuring about 3 cm in greatest diameter, with the surface color resembling that of normal mucosa, margins were well defined and the swelling crossed the midline on the left side with surface ulceration [Figure 1]. On palpation there was slight tenderness, the swelling was firm in consistency, sessile, attached to the underlying bone, not yielding to pressure, non-fluctuant and non-reducible. Fine-needle aspiration cytology was done, but no aspirate was obtained. Correlating the history and clinical

features, a provisional diagnosis of a malignant soft tissue neoplasm was made.

Antral carcinoma, malignant neoplasm of the salivary glands, lymphoma, sarcoma and malignant melanoma were considered in the differential diagnosis. Because the site was anterior part of the hard palate where salivary glands are absent and due to the mucosal color of the swelling, salivary gland neoplasm and malignant melanoma were ruled out. Radiologic and histopathologic investigations were done to confirm the diagnosis.

Periapical, occlusal and panoramic radiographs revealed generalized destruction of alveolar bone in the anterior maxilla with perforation of the antrum bilaterally. A contrast-enhanced computed tomography scan was performed and it revealed a large contrast-enhancing lobulated soft tissue attenuated mass measuring 57 × 45 mm in size, involving the maxillary alveolus extending up to the maxillary antrum bilaterally [Figure 2]. Extensive contiguous bone destruction was seen along with extension into the premaxillary soft tissue subcutaneous fat [Figure 2]. The submandibular salivary glands were enlarged bilaterally.

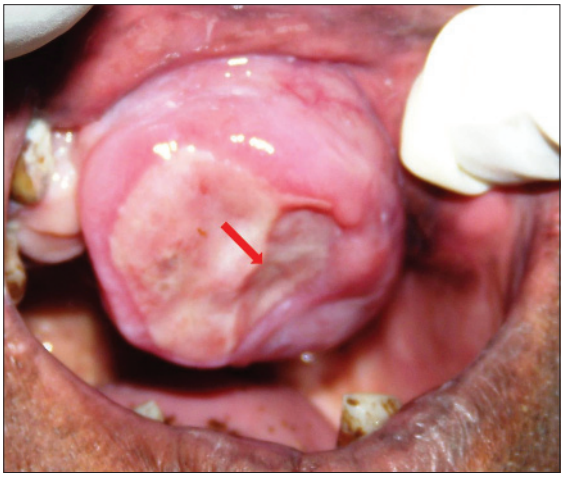

Figure 1: Swelling in the anterior hard palate with surface ulceration

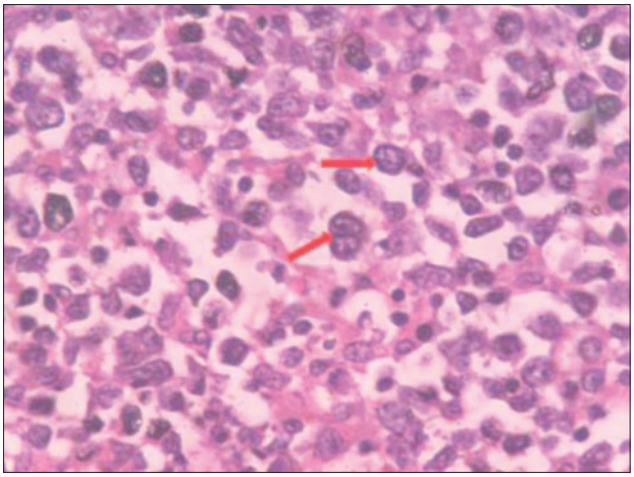

Figure 3: Photomicrograph showing centroblasts (red arrows), i.e. large atypical pleomorphic lymphocytic nucleus with multiple nucleoli (H & E stain, x400)

An incisional biopsy was done and histological examination of biopsy specimen revealed diffuse proliferation of large atypical lymphoid cells with high nuclear cytoplasmic ratio, coarse chromatin and prominent nucleoli with few abnormal mitotic figures [Figure 3]. The features were suggestive of large cell lymphoma. Immunohistochemistry showed weak cluster of differentiation (CD) 3 positivity, strong CD20 and CD45 positivity confirming the B-cell origin of lymphocytes [Figure 4]. Correlating the clinical, histopathological and immunohistological features, a final diagnosis of primary diffuse large B-cell lymphoma of anterior palate was given.

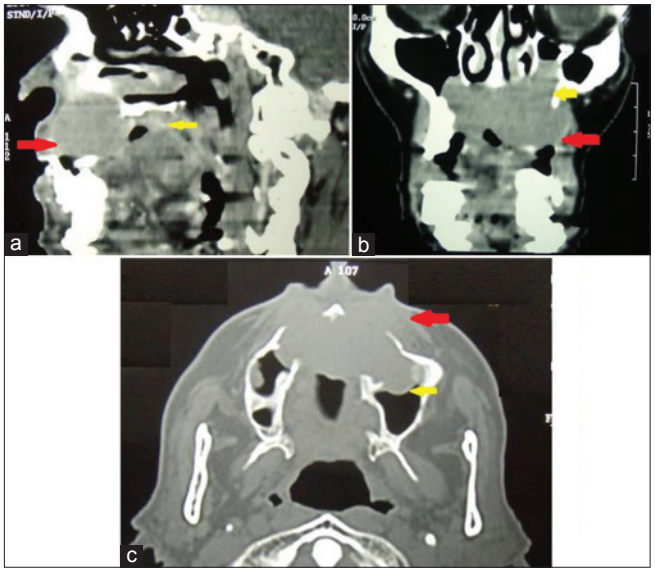

Figure 2: CT scan of the maxilla, sagittal, (a) coronal (b) and axial (c) sections showing a space occupying hypodense lesion in the anterior maxilla (red arrow) with perforation and extension into the maxillary antrum. CT: Computed tomography

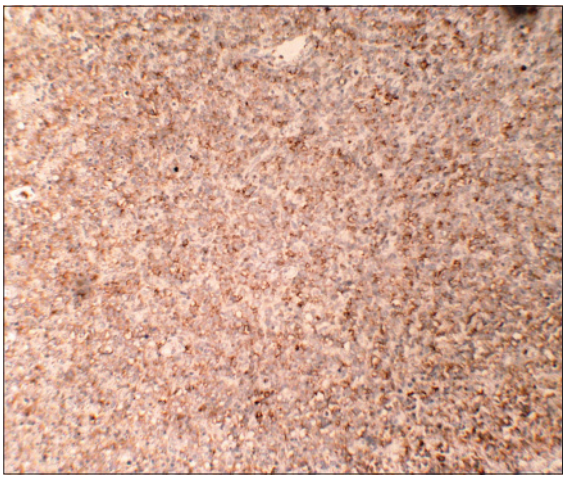

Figure 4: CD20 immunostaining showing strong positivity indicating B-cell origin of lymphocytes (IHC stain, x200)

The patient was sent to a medical oncologist for chemotherapy. He was given cyclophosphamide 1200 mg, adriamycin 75 mg and vincristine 2 gm thrice weekly for a total of six cycles. Following chemotherapy, the palatal swelling resolved completely but areas of hypermelanosis were observed [Figure 5]. Patient was asymptomic without any evidence of recurrences during the 18 months follow-up period.

DISCUSSION

Malignant lymphomas constitute a group of neoplastic proliferation process of the lymphocytes and their precursor cells. Hodgkin's disease is characterized histologically by the presence of multinucleated Reed–Sternberg cells. All other neoplasms of lymphoid system are referred to as NHL and are derived predominantly from the cells of B-lymphocyte series.[6] Till date seven case series containing a total of 202 cases on extranodal NHL have been published in English literature. Of these 202 cases only five (2.4%) are reported in palate (all in posterior hard palate), which makes it a rare site for occurrence. However, primary DLBCL occurring in anterior part of hard palate is yet to be published in literature. DLBCL, being a heterogenous neoplasm shows variable clinical, morphologic, immunophenotypic, cytogenetic and genetic features.[7] This is often reflected in their marked biological heterogeneity and highly variable clinical course.[3]

Frequently, the initial symptoms of a large B-cell lymphoma of the oral cavity are a painless swelling, a nonhealing ulcer, fever, sweats and weight loss. A painless lymph node enlargement or a submucosal lesion in the junction between hard and soft palate are highly suspicious. Oral lymphoma often is a component of a disseminated disease process that may involve regional nodes as well. Other times, it may represent a primary extranodal disease confined to oral cavity or jaws, which is very rare.[8]

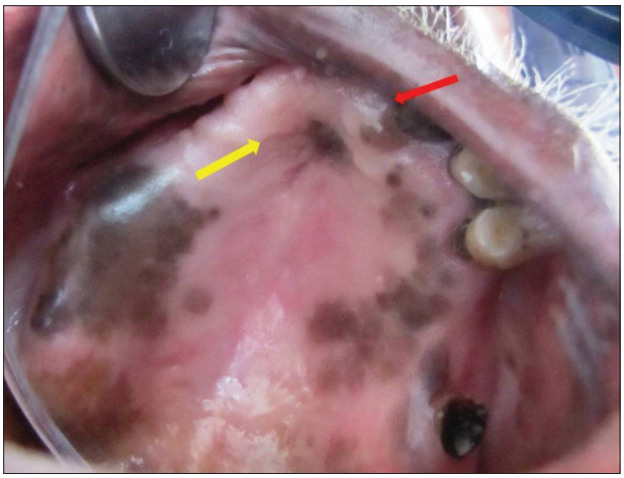

Figure 5: Post-chemotherapy photo showing complete resolution of the lesion followed by hypermelanosis after resolution of the swelling (red arrow)

The etiology of DLBCL remains unknown. They may originate *de novo* or represent progression from a less aggressive lymphoma, such as follicular lymphoma or small lymphocytic lymphoma. Underlying immunodeficiency is a significant risk factor and DLBCL in the setting of immunodeficiency is more often Epstein–Barr virus-positive than sporadic DLBCL.[9]

Lymphomas can be diagnosed using hematoxylin and eosin-stained sections, but immunophenotyping is currently the most common technique. Modern hematology relies on immunophenotyping to distinguish between benign and malignant diseases, as well as for a more detailed subtyping.[10] The DLBCL can be subclassified depending on cytomorphology, gene expression profile and reactiveness toward specific antibodies [Table 1] [11]. The histologic and immunohistochemical differential diagnosis for DLBCL includes Burkitt's lymphoma, lymphoblastic lymphoma, diffuse mixed lymphoma, true histiocytic lymphoma and the classical Hodgkin's lymphoma [Table 2].

DLBCLs express CD45 (leukocyte common antigen) and pan-B-cell antigens (CD19, CD20 and CD79). In some cases, expression of one or more of these antigens may be lacking.[14] CD20 is expressed on B cells from the mature precursor B cell until the pre-plasma cell stage of differentiation. It is a highly specific marker for B-cell lineage and most DLBCL show homogenously bright staining for CD20.[15] Table 3[13,16] shows the normal B-cell differentiation process, respective expression of specific antibody and prognosis in each stage. The post-germinal center (GC) B-cells are multiple myeloma

Table 1: Subclassification of diffuse large B-cell lymphoma affecting oral cavity

Based on cytomorphology
Centroblastic variant
Medium to large-sized centroblasts
Oval to round nuclei
Fine vesicular chromatin pattern
2-4 nucleoli opposed toward nuclear membrane
Rarely multilobated nuclei
Two subtypes: Monomorphic (>90% centroblasts) and polymorphic with admixed immunoblasts (<90% centroblasts)
Immunoblastic variant
Uniform cytology
Prominent central nucleoli with distinct rim of basophilic cytoplasm
Anaplastic variant
Variably large cells with bizarre pleomorphic nuclei
May mimic reed-stenberg cells or undifferentiated carcinoma
Increased number of intermixed T cells or histiocytes
Based on gene expression profiles[12]
GCB
Non-germinal center (non-GCB) or ABC like
Type 3 gene expression profile
Based on prognosis[13]
Prognostically favorable-CD10(+) or BCL6(+) or both (+)
Prognostically unfavorable-MUM1(+)

GCB: Germinal center B-cell like; ABC: Activated B-cell; CD: Cluster of differentiation; MUM1: Multiple myeloma oncogene 1

Table 2: clinical, histological and immunological differential diagnosis of DLBCL

DLBCL	Burkitt's lymphoma
Starry sky pattern infrequent	Starry sky macrophages present
Vesicular chromatin	Fine chromatin
Cytoplasm shows no vacuoles	Cytoplasm shows vacuoles in Giemsa staining
Proliferation fraction moderately high	Proliferation fraction nearly 100%
15% of cases have myc translocation	Translocation involving c-*myc* and *IgH* gene
DLBCL	Lymphoblastic lymphoma
Median age 60 years	Median age 39 years
B lineage	90% T lineage, 10% B lineage
Blast cells are negative in PAS stain	Blast cells show positivity on PAS stain
Vesicular chromatin	Fine chromatin
Few prominent nucleoli	None or small nucleoli
DLBCL	Diffuse mixed lymphoma
Over 50% large atypical B cells	75% of cells small atypical B cells
Confluent foci of large cells	No confluent foci of large cells
DLBCL	True histiocytic lymphoma
Variable cytoplasm	Abundant cytoplasm
Median age 60 years	Most under 30 years
CD20 and CD79a positive	CD20 and CD79a negative
DLBCL	Classical hodgkin's lymphoma
CD45RB, CD20 and CD79a>90%	CD45RB, CD20 and CD79a 10-20%
CD15 5%, CD30 30%	CD15 80%, CD30 90%
Light chains monotypic or negative	Light chains polytypic or negative

DLBCL: Diffuse large B-cell lymphoma; PAS: Periodic acid-Schiff stain

Table 3: DLBCL affecting different stages of B-cell differentiation, subsequent antibody positivity and prognosis

DLBCL affecting B-cell at Different stages of maturation	Antibody positivity	Prognosis
Pre-GC stage or virgin B-cell stage	CD22, CD23, CD40	Favorable
GC stage	CD45, CD10, BCL 6	Favorable
Post-GC stage	MUM1, CD138, Ki67, p53	Unfavorable

GC stage: Germinal center stage; MUM1: Multiple myeloma oncogene 1; DLBCL: Diffuse large B-cell lymphoma; CD: Cluster of differentiation

oncogene 1 (MUM1) positive, which when expressed more can be prognostically unfavorable. MUM1 expression denotes the final step of intra-GC B-cell differentiation and subsequent steps of B-cell maturation toward plasma cells.[17] CD138 expression is usually restricted to cells exhibiting plasmablastic differentiation and to plasma cells. CD3 is a T-cell marker that is associated with the T-cell receptor and transmits the activation signal to the cytoplasm. It is highly restricted in its expression to T-lymphoid cells and is an excellent marker, as it is retained following neoplastic transformation.[18]

Variability in the immunophenotypes of DLBCL, indicates that this comprises a heterogeneous group of tumors. More than 25% of DLBCL have a translocation t(14;18) and most of them express bcl-2 with or without a translocation. Chromosomal rearrangements affecting the bcl-6 gene (regulator of germinal centre formation) at 3q27 are seen in 30% of DLBCL extranodal tumors. The bcl-6 is required for GC formation, antibody-affinity maturation and T-helper-2-mediated responses.[19] The bcl-6 also inhibits lymphocyte activation by inhibiting the expression of CD69 and CD44 and inhibits differentiation of GC B-cells towards plasma cells.[20] Mutations and deletion of p53 are common in DLBCL. The bcl-6 and bcl-2 are the strongest predictors of survival.[21]

DLBCLs may exhibit more than one chromosomal rearrangement and are then referred to as 'double-hit' or 'triple-hit' lymphomas. 'Double-hit' lymphomas are associated with older age, usually present with an advanced stage of disease and show an aggressive clinical behavior. They normally have a poor prognosis, even when treated with intensive chemotherapy regimens.[22] Nevertheless, in the case presented, the patient was free of symptoms 18 months after initial diagnosis.

With the help of complementary deoxyribonucleic acid (cDNA) microarray techniques, the gene expression profiles of DLBCL have been evaluated and the two distinct molecular forms, the GC-like (GCB) and the activated B-cell-like (non-GCB) DLBCL were identified. GCB lesions express genes normally expressed by GC B cells and the non-GCB DLBCL express genes normally induced during *in vitro* activation of peripheral blood B cells.[8]

Bhattacharyya and colleagues in their study of 13 primary DLBCLs proposed that non-GCB lesions predominate and may exhibit a poorer prognosis with half of the patients succumbing to their disease, whereas majority of the GCB group continues to be disease free.[11] Pathologists and clinicians should be aware of this trend and should consider adding GCB classification to their reports when referring patients with oral DLBCL for further treatment and evaluation. However, stratification of DLBCL by immunohistochemitry is possible and is a relatively inexpensive, readily available and effective method of delineating the subtypes of DLBCL.

Current treatment of DLBCL usually begins with multi agent chemotherapy, typically CHOP (cyclophosphamide, hydroxydoxorubicin, oncovin and prednisone). Despite the initial response to therapy, more than half the patients succumb to the disease.[23] Early stage disease care involves either chemotherapy alone or a combination of chemotherapy and radiotherapy. The chemotherapy usually involves three cycles of CHOP. Patients are considered for bone marrow transplantation if remission is not maintained. The role of surgery is severely limited in the treatment of DLBCL. Other

drugs used in multi agent chemotherapy for advanced stage disease usually involve various combinations of methotrexate, bleomycin, doxorubicin, vincristin, dexamethasone, leukcovorin, etoposide, mechlorethamine, procarbazine and cytarabine.[16]

Considering the rare occurrence of primary DLBCL in oral cavity, it has become essential for an oral physician to be aware of this aggressive lesion to aid in the early diagnosis thereby contributing to an increased life expectancy of these patients. The diagnosis of these tumors is complicated considering the nonspecific nature of the presenting symptoms. Therefore, a proper clinical evaluation, histology as well as immunohistochemical evaluation of biopsy specimen may aid in early diagnosis and effective management.

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