Case Report

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Burkitt's lymphoma: A case report and review

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Abstract

B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL) and classical Burkitt's lymphoma (BL), is a diagnostic provisional category in the World Health Organization 2008 classification of lymphomas. This category was designed as a measure to accommodate borderline cases that cannot be reliably classified into a single distinct disease entity after all available morphological, immunophenotypical and molecular studies have been performed. Typically, these cases share features intermediate between DLBCL and classical BL or include characteristics of both lymphomas. The rarity of such cases poses a tremendous challenge to both pathologists and oncologists because its differential diagnosis has direct implications for management strategies. In this article, we present a "classical unclassifiable lymphoma with features intermediate between DLBCL and BL" in a young male patient and review of literature.

Key Words: Diffuse large B-cell lymphoma, gray zone lymphoma, non-Hodgkin lymphoma, oral lymphomas, unclassifiable lymphomas

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INTRODUCTION

Lymphomas are a heterogeneous group of lesions with varied geographic, etiologic, phenotypic, clinical and histopathological features, demanding diverse management strategies. They represent 3.5% of all oral malignancies.[1] Traditionally, lymphomas are divided into Hodgkin's and Non-Hodgkin's lymphoma (NHL), with almost 86% representing NHL.

The global cancer statistics states that the highest incidence of NHL is noted in Northern America with 1.62:11.5, male (M) to female (F) ratio and lowest in South Central Asia with M:F of 3.3:2.1[2-4] Among various Indian Registries, the average age-adjusted incident ratio for NHL was found to be highest in New Delhi (4.45M/2.93F), followed by Mumbai (2.8M/1.8F) and lowest at Bhopal (2.49M/1.44F) Registry.[5]

The lymphomas arising centrally in a single bone, without visceral or lymph node involvement, are known as primary intraosseous lymphoma[6] Primary oral cavity lymphomas account for only 1% of all lymphomas and 12.2% of extra-nodal lymphomas.[1] The most frequent intraoral sites for lymphomas are the hard palate, vestibule and gingiva.[1,6]

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The frequency of primary extranodal NHL in Asia varies from 28.5% to 45%.[3] The understanding and histopathological diagnosis of NHL have improved with the use of advanced technology. As a result, the classification of lymphomas has undergone a significant reassessment over the past 40 years from Rappaport's classification in 1973 to World Health Organization (WHO) classification in 2008, wherein the classifications were renewed and updated.[7]

The WHO now recognizes a group of high-grade B-cell lymphomas that were not readily classified as either Burkitt's lymphoma (BL) or diffuse large B-cell lymphoma (DLBCL), into a provisional category termed as B-cell Lymphoma unclassifiable, with features intermediate between DLBCL and BL (WHO 2008).[7] These lesions usually occur in adults and are rare in young individuals more so as intraoral primary lesions. Herewith, we present such an unusual primary isolated, intraoral lesion without systemic involvement in a very young patient.

CASE REPORT

A 21 year old male patient reported to our Institute with an intraoral, nontender swelling on the right side of the palate for 15 days. The past medical and family history was not contributory. The lesion extended from mesial aspect of the maxillary right first premolar posteriorly up to permanent maxillary first molar and medially just 5 mm away from the midline [Figure 1]. On palpation, it was soft in consistency, fluctuant with areas of ulceration and superficial slough along with indentation of teeth. Both maxillary premolars in the lesional area showed Grade I mobility. No significant lymph node enlargement was noted. The intraoral periapical x-ray showed only interdental bone loss in relation to (i.r.t) 14, 15 and periodontal widening i.r.t.16 [Figure 2]. Based on these findings, an endo-perio problem was suggested. Routine hematological investigations showed the complete blood count (CBC) to be within normal range with no abnormal morphology of the red blood cells, white blood cells or platelets.

However, as the lesion was rapidly growing, with no response to antibiotic therapy, magnetic resonance imaging and computed tomography scan were done. The findings showed a moderately large mass in the lateral portion of the right maxillary sinus with minimal destruction of anterior and posterior lateral walls, extending along the right side of hard and soft palate [Figure 3a and b]. Three-dimensional cone beam CT showed destruction of infraorbital margin [Figure 4]. The above findings were suggestive of a neoplastic lesion, with a differential diagnosis of keratocystic odontogenic tumor, ameloblastoma, other odontogenic lesions and central giant cell tumor.

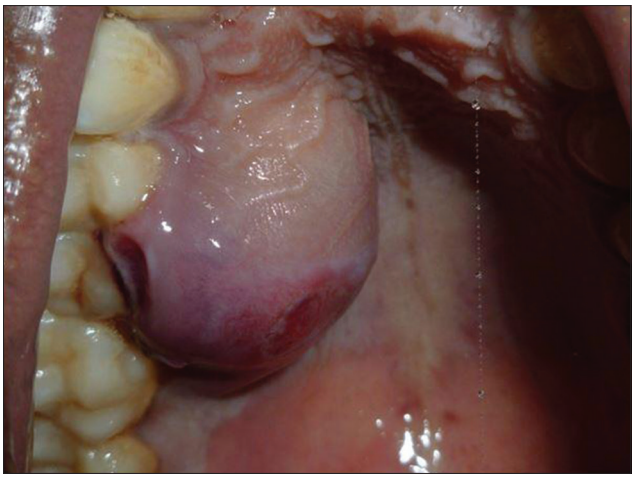

Figure 1: Intraoral exophytic palatal mass with ulceration and tooth indentation

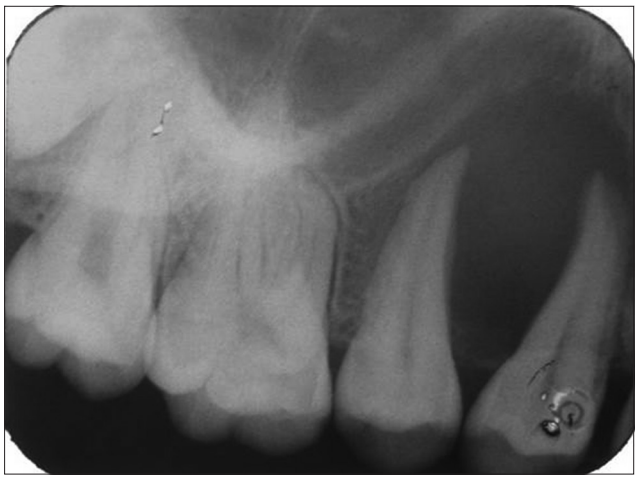

Figure 2: Intraoral periapical x-ray showing interdental bone loss in 14, 15 region and periodontal widening i.r.t 16

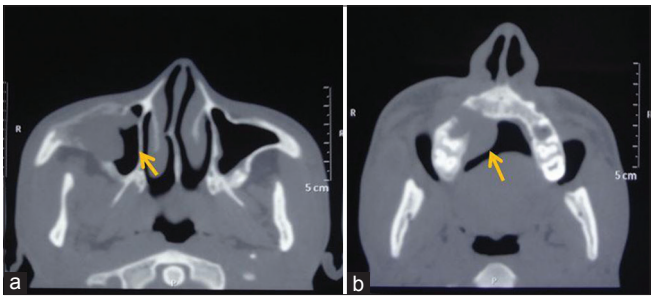

Figure 3: (a) Cone beam computed tomography showing a large mass in the lateral portion of the right maxillary sinus extending to the hard palate. (b) Cone beam computed tomography showing - destruction of anterior and posterior lateral walls of maxillary sinus with involvement of hard palate

The laboratory investigations during the course revealed white cell count: 8200/μl, hemoglobin: 11.10 g/dl, platelet count: 213,000/μl, calcium: 9.8 mg/dl, serum uric acid: 1.8 mg/dl (normal value 3.5–7.2mg/dl), serum aspartate transaminase:

42 U/L (normal value 10–37 U/L), serum alanine transaminase: 60 U/L (normal value 10–37 U/L), serum creatinine: 0.8 mg/dl (0.7–1.3) and β-2 microglobulin levels were slightly raised. β-2 microglobulin was 2.04 mg/L, slightly raised than the normal reference value of 0.83–1.15 mg/L.

Serological test using chemiluminescent microparticle immunoassay reported was nonreactive for hepatitis B surface antigen anti-hepatitis C antibodies and HIV antibodies. Further, an incisional biopsy was performed under local anesthesia.

The hematoxylin and eosin (H and E) stained sections under scanner view showed palatal mucosa with diffuse arrangement of neoplastic cells in the lesional area [Figure 5]. The low power view showed diffusely arranged sheets of hyperchromatic neoplastic cells interspersed with a number of histiocytes giving a typical starry sky appearance of BL [Figure 6]. However, under high power, the size of the cells was abnormally larger with nuclei double the size of the lymphocytes and moderate degree of pleomorphism. Macrophages could be seen phagocytosing the necrotic tumor cells with a Burkitt-like morphology [Figure 7a and b]. The neoplastic tumor cells under ×100 magnification showed abundance of abnormal mitotic figures, 2-3 prominent nucleoli along with macrophages phagocytosing the necrotic tumor cells [Figure 8a, b and c]. Histologically, features were rather confusing, showing a picture of both BL and DLBCL. Therefore, immunohistochemical (IHC) staining was performed to rule out the type of lymphoma. IHC showed the cells positive for CD 20 [Figure 9] (B-cell antigen) and focally positive for Bcl-2 [Figure 10] and leukocyte common antigen (LCA) and terminal deoxynucleotidyl transferase (Tdt). MIB-1 proliferation index (PI) [Figure 11] (for Ki-67 labelling) was approximately 95%. The lesional tissue was negative for Bcl 6 [Figure 12], CD3 (T-cell co-receptor), CD 10 or common acute lymphocytic leukemia antigen (CALLA) and CD 138 (plasma cell antigen).

Bone marrow biopsy done at a higher center did not reveal any definitive morphologic and immunophenotypic evidence of involvement by B-cell/T-cell NHL.

On the basis of CT scan, histopathology, IHC, bone marrow biopsy and positron emission tomography (PET) scan, the lesion was diagnosed as primary intraosseous, B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL. The patient underwent chemotherapy, regular follow-up for past 2 years did not show recurrence or spread of the lesion.

DISCUSSION

Lymphomas of the oral cavity are uncommon and very few cases of primary lymphomas in the oral cavity have been reported in the English literature accounting for <5% of all the published cases. In general, HL corresponds to 14% and NHL to 86% of all lymphomas.[8]

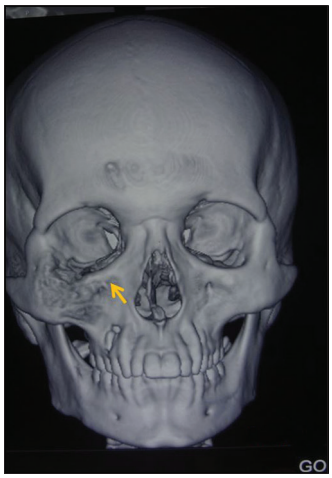

Figure 4: Three-dimensional cone beam computed tomography showing destruction of infra-orbital margin

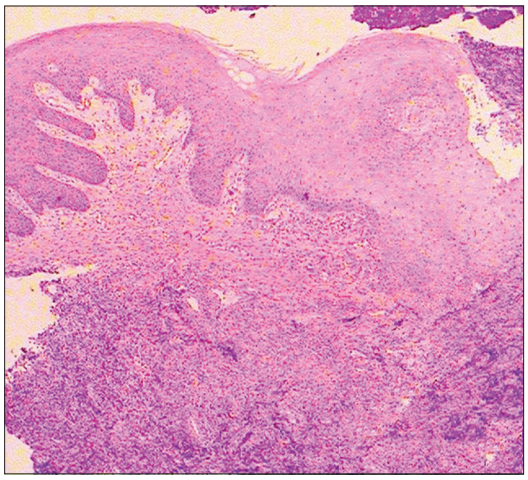

Figure 5: Section showing palatal mucosa with diffuse arrangement of neoplastic cells in the lesional area (H&E stain, x40)

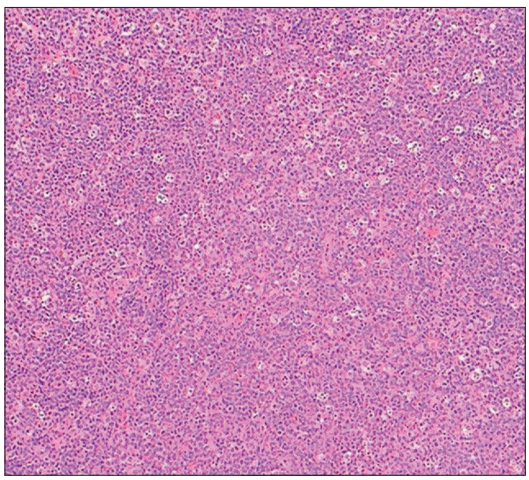

Figure 6: Diffusely arranged sheets of neoplastic cells with starry sky appearance. A Burkitt's lymphoma-like morphology (H&E stain, x100)

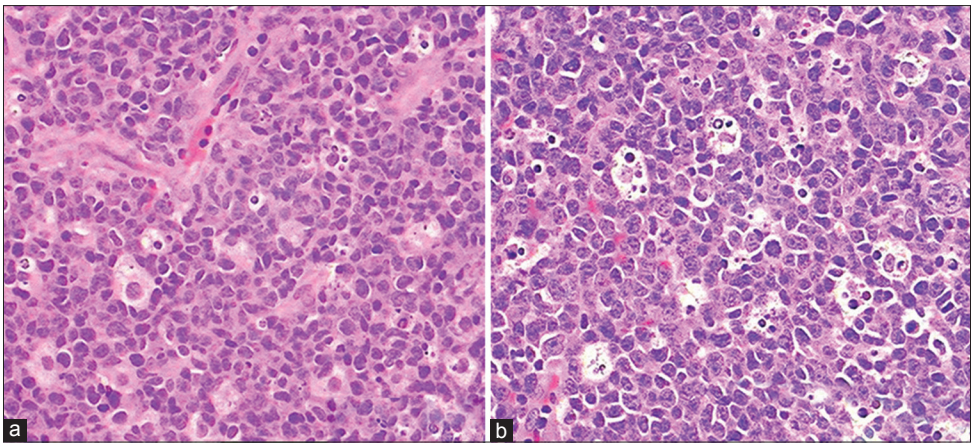

Figure 7: (a) Pleomorphic large tumor cells with nuclei double the size of the lymphocytes (H&E stain, x400) (b) Macrophages can be seen phagocytosing the necrotic tumor cells with a Burkitt-like morphology (H&E stain, x400)

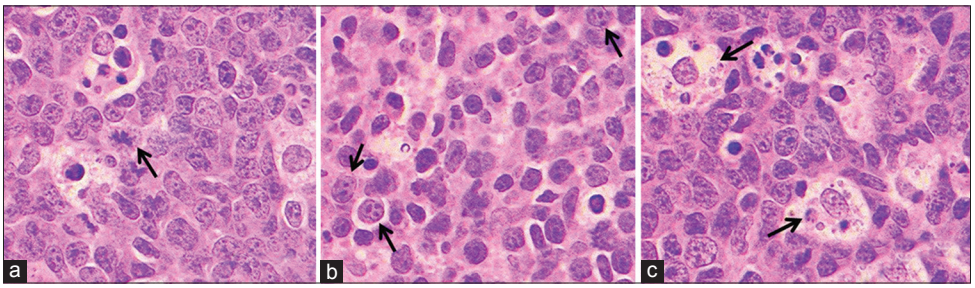

Figure 8: (a) Large and polymorphic tumor cells with abnormal mitotic figures (H&E stain, x1000). (b) Abnormal mitotic figures, 2–3 prominent nucleoli (H&E stain, x1000). (c) Macrophages can be seen phagocytosing the necrotic tumor cells (H&E stain, x1000)

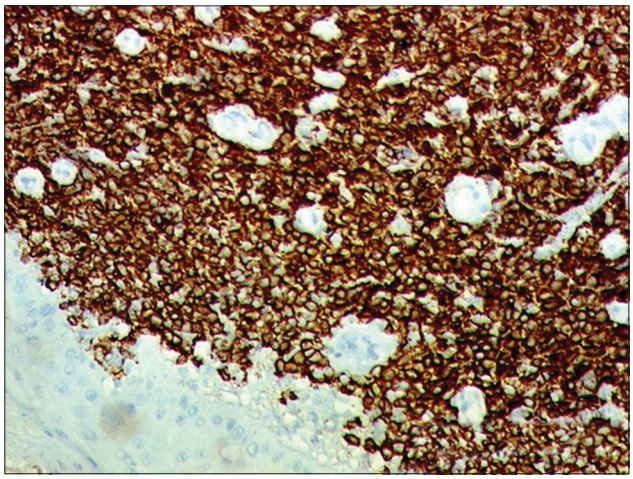

Figure 9: Section showing strongly positivity for CD20 (IHC stain, x100)

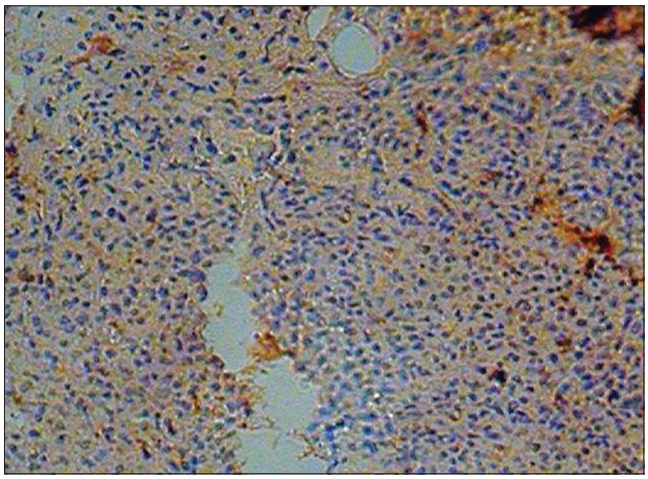

Figure 10: Lesional tissue showing weak Bcl-2 positivity (IHC stain, x100)

Extra-nodal NHL was first described by Isaacson and Wright in 1983 as quoted by Shah *et al*.[9] and has varied geographical and ethnic differences. The frequency of primary extra-nodal lymphoma was found to be highest in Italy (48%) and lowest in India (22%).[3] Guevara-Canales *et al*. studied 3513 new cases of lymphomas for a period of 25 years and found that 4.3% (151) occur in the oral cavity and maxillofacial region.[8] While Shah *et al*. did a retrospective analysis at a tertiary care center between 1990 and 2008 and found only 15 cases of isolated primary lymphomas from the archives, although they register nearly 2000 new cases of oral cancer every year.[9]

The age of presentation of oral lymphomas is highly variable ranging from 3 years to 70 years as published in the literature,[1,9] with 53.64% occurring in males,[8] and the patient in our case was a young male of 21 years.

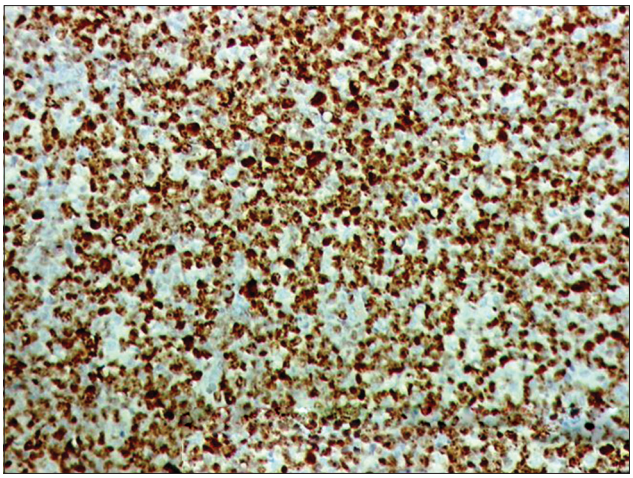

Figure 11: Mib-1 proliferation index is close to 95% (IHC stain, x100)

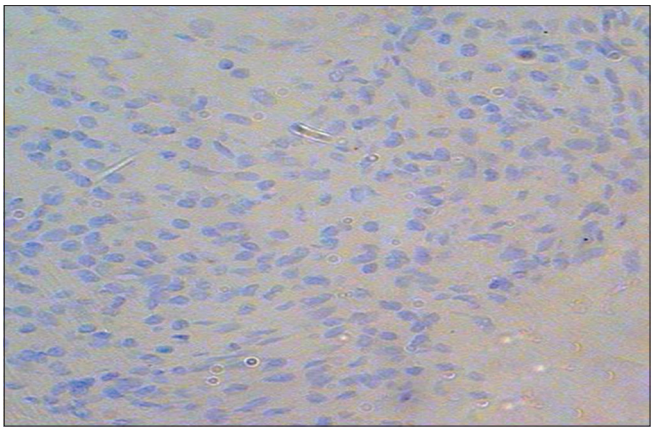

Figure 12: Tumor cells were negative for Bcl-6 (IHC stain, x200)

In almost 2% of extranodal lymphomas,[9,10] the primary lesions may involve the gingiva, buccal mucosa, tongue,[1] salivary glands, bones and floor of the mouth.[10] Janet *et al.* found 43.05% in the tonsils, followed by 13.91% in parotid glands and 8.61% on palate,[8] while Shah *et al.* found involvement of gingivo-buccal complex in 80% of the cases.[9] However, till date, only 202 cases of extranodal lymphomas have been published in English literature, of these only 5 (2.4%) are reported in the palate.[11] Gingival masses due to HIV-associated lymphomas are also well recognized.

Little is known about the etiologic factors of primary lymphomas involving the oral cavity, it appears to be multifactorial and includes immune suppression, both viral and bacterial infections, exposure to pesticides and other environmental agents. Few geographic differences with incidence of Epstein–Barr virus (EBV) and human T-cell lymphotropic virus-1 associated with T-cell lymphoma are higher in Asia than in Europe and North America.[3] Some cases of oral lymphomas, such as plasmablastic lymphomas, have been reported in association with the acquired immune deficiency syndrome.[10] Velez and Hogge reported 5 cases of primary maxillofacial large B-cell lymphoma in immunocompetent patients.[6] However, in our case, the patient did not show reactivity toward HIV antibody and no definite etiological factor could be attributed.

Oral lymphomas apart from those arising in Waldayer's ring are notorious for mimicking inflammatory disease of periodontal tissues or jaws,[10] hence before diagnosing primary lymphomas, the periapical and periodontal infections should be ruled out. In our case, the patient clinically presented with a lesion, mimicking an inflammatory disease of dental origin provoking a clinical diagnosis of periapical cyst, periodontal cyst and odontogenic keratocyst. Nearly, 70% of the patients report with painless swelling without systemic signs, such as fever and weight loss.[9] The patient in our case also did not show any systemic signs, thus complicating the clinical diagnosis.

Radiographically, the lesions may appear as a radiolucent area that may mimic endodontic lesion, periodontal pathology or odontogenic cyst or tumor.[6] Lesions involving bone show diffuse bone destruction and disappearance of lamina dura or may appear as solitary radiolucency.[8] The present case also had similar radiographic manifestations of interdental bone loss in 14, 15 region and periodontal widening i.r.t 16.

In fact, the diagnosis of lymphoma involves a multi-parameter approach and includes most importantly a meticulous H and E examination followed by IHC, cytogenetics and molecular diagnostics. Also important are history, clinical features and laboratory parameters such as CBC, erythrocyte sedimentation rate serum albumin and β-2 microglobulin. Bone marrow examination, X-ray chest and abdominal ultrasonography are required for staging of the disease.[12] Diagnosis and further classification of lymphomas is important as treatment protocols are different.

Classification systems represent the language of both pathology and clinical medicine and provide a critical communication medium in establishing, applying and validating therapeutic protocols.[13]

The latest WHO classification of lymphoid neoplasms was published in 2001 and updated in 2008.[14] The basic principle of this classification is the recognition of "distinct" diseases utilizing a multiple parametric approach that is based on clinical information, morphology, immunophenotype and molecular genetic characteristics.

Although most lymphomas can be accurately classified, some lymphomas present with features transitional between DLBCL and classical Hodgkin lymphoma (cHL) or DLBCL and BL and are difficult to classify. These lymphomas have

been reported in the literature using different terms, such as borderline lymphomas, B-cell lymphomas unclassifiable (BCLu), atypical BL, Burkitt-like lymphomas (BLLs) or gray zone lymphomas. The term "Gray Zone Lymphoma" was first used in 1998 at the "Workshop on Hodgkin's disease and related diseases" to designate lymphomas at the border of cHL and other entities. This term was then further extended to lymphomas with overlapping features between BL and DLBCL. The 2008 updated WHO classification of Tumors of the Hematopoietic and Lymphoid Tissues proposed to assign these gray zone lymphomas to provisional categories called BCLu with features intermediate between DLBCL and cHL (BCLu-DLBCL/cHL) and BCLu with features intermediate between DLBCL and BL (BCLu-DLBCL/BL).[15]

B-cell lymphoma, BCLu-DLBCL/BL, is a difficult category to use which is well reflected by its description in the WHO handbook 4th edition: "This is a heterogeneous category that is not considered a distinct disease entity, but is useful in allowing the classification of cases not meeting criteria for classical BL or DLBCL."[12]

BCLu-DLBCL/BL is relatively rare and mainly diagnosed in adults and often invade extranodal tissue, but Yung-Tang Kung reported a case in a young Korean patient.[16] They represent up to 5% of adult aggressive B-cell lymphomas and usually occur in extranodal sites, sometimes associated with leukemic involvement. By definition, BCLu-DLBCL/BL harbors intermediate morphological and IHC features between BL and DLBCL.[15]

Various studies are being done on archival material to reclassify and place the lesions under this category. Sur *et al*. retrospectively studied 170 cases of lymphomas and reclassified 34 cases as BCLu-DLBCL/BL based on the biopsy revealing lymphoma with a combination of morphologic and IHC features intermediate between DLBL and BL, according to the features outlined in the 2008 WHO classification[17] BCLu-DLBCL/BL included cases with cellular morphology intermediate between BL and DLBL with a monomorphic population of intermediate to large cells, many times with a component of "starry sky" appearance caused by tingible-body macrophages. Cells showed a more open chromatin pattern and more variation in nuclear size and shape than that seen in BL with more than occasional prominent single nucleoli. Mitoses were abundant and the PI characteristically very high.[3,17] They are typically composed of diffuse proliferation of medium- to large-sized transformed cells with few admixed small lymphocytes and no stromal reaction of fibrosis.[18] It is used for those cases that are morphologically not right for BL - too many big cells, too polymorphic as noted in the present case and also reported by Hashimoto in a 3-year-old patient. Some DLBCLs may exhibit a very high proliferative index and starry-sky growth pattern or have medium-sized tumor cells showing slight nuclear pleomorphism mimicking those of classical BL or a BL/BLL. In addition to morphologic features, DLBCL may share immunophenotypic features of BL.[19]

Morphologically, the tumor cells of BL are medium-sized cells and show a diffuse monotonous pattern of growth. The cells appear to be cohesive, but sometimes exhibit squared-off borders of retracted cytoplasm while DLBCL presents large B-cell lymphoid cells with big nuclei and a diffuse growth pattern.[18] They generally resemble BL (most cells Burkitt-like), but have either significant population of large cells or abnormal immunophenotype (esp. BCL2+).[20] The immunophenotype in these lesions is spot on (B-cell, CD10 +ve, bcl-2 −ve, bcl-6 +ve and Ki67 >95% +ve). Other cases that lodge here could be those with a perfect BL morphology, but the immunophenotype is odd for the present case, for example , the cells are bcl-2 +ve.[15]

The characteristic immunophenotype of BL is that of strong CD10 expression, expression of BCL6, negativity for BCl2, CD138 or Tdt and a Ki67 PI of nearly 100% (at least 90% of tumor cells). Cases with BL molecular signature did poorly as a group when treated with CHOP-like regimens.[13]

IHC is performed to confirm the diagnosis, for therapeutic purposes, and sometimes to differentiate between a reactive and a malignant lymphoid proliferation.[12] It is also important in nodal and extranodal sites with diffuse small lymphocytic proliferation, with presence of diffuse sheets of B-cells (CD20+) suggestive of lymphoma.[12] Minimum IHC panel for any suspected hemato-lymphoid lesion is LCA, CD20 and CD3.[12] These "borderline cases" are always diagnostically difficult, but various literature reports based on existing literature evaluation for intermediate DLBCL/BL should include an immunophenotypic panel with CD10, BCl 6, BCl2 and Ki 67.[21]

In the present case, CD 20 was positive forming the first basis to diagnose the case as B-cell lymphoma. CD10 and Bcl-2 expression were studied for nodular growth patterns and to differentiate Burkitt's from DLBL. BL is CD10+ and bcl-2 negative.[16,17] In our case, IHC was positive for Bcl-2, but negative for CD10. Ki-67 (MIB1, proliferation marker) was approximately 95% putting the lesion more in favor of DLBCL. BL cases can also present as a leukemia without significant lymphadenopathy.[13] Hence, CALLA was done, but it was negative. Plasmablastic variants of DLBCL have also been reported to be associated with EBV infection; hence, to rule out this, CD138 was done, but found to be negative. Thus, it was difficult to place this lesion with the older classification. The common and distinguishing features of BL, DLBCL and

Table 1: Common and distinguishing features of Burkitt's lymphoma, diffuse large B-cell lymphoma, B-cell lymphoma unclassifiable-diffuse large B-cell lymphoma/Burkitt's lymphoma and present case

Features	BL	DLBCL	BCLu with features intermediate between DLBCL and BL	Present case (BCLu-DLBCL/BL)
Age	Young children, rare in young adults	Adults of all age groups, rare in children	Mainly adults	Young adult
Gender	Male predominance	No real predominance	No real predominance	Male patient
Location	Often extranodal (jaw andiliac region)	Nodal and extranodal	Often extranodal (no predominate site)	Extranodal
Morphology	Frequent mitotic figures and apoptosis often with starry sky pattern	Frequent mitotic figures and apoptosis may be present	Frequent mitotic figures and apoptosis often with starry sky pattern resembling BL	Frequent mitotic figures and starry sky pattern resembling BL
Immunophenotype	CD 20, Bcl-6 positive, bcl-2, CD 138 negative Tdt not expressed	BL immunophenotype" CD 10, CD20, bcl-2 may be positive Negative for BCL-6 CD3, CD 138	Variable depending on morphologic features	Positive for CD20, focally for bcl-2 and LCA Tdt and Mib-1 proliferation index approximately 95% Negative for CD3, CD 10, CD 138
CD20	Positive	Positive	Positive	Positive
Mib-1 proliferative index	Positive	Positive	Positive	Positive
Bcl-2	Negative	Positive	Positive	Positive
Bcl-6	Positive	Negative	Negative	Negative
LCA	Variable	Variable	Variable	Focally positive
Tdt	Negative	Positive	Positive	Positive
CALLA	Negative	Negative	Negative	Negative
CD 138 (plasma cell antigen)	Negative	Negative	Negative	Negative
CD3	Negative	Negative	Negative	Negative

LCA: Leucocyte common antigen, Tdt: Terminal deoxynucleotidyltransferase, CALLA: Common acute lymphocytic leukemia antigen, BL: Burkitt's lymphoma, DLBCL: Diffuse large B-cell lymphoma, BCLu: B-cell lymphoma unclassifiable, CD3: T-cell co-receptor, CD20: B-cell antigens

BCLu-DLBCL/BL[15] in the present case were studied, analyzed and evaluated as shown in Table 1.[15]

Various groups have applied gene expression profiling to distinguish BL from DLBCL. There was an intermediate to define and only partly overlapping group of aggressive B-cell lymphomas with features intermediate between DLBCL and BL based on morphologic and genetic features, but not on gene expression characteristics. A strong overlap was suggested to exist with the gene-expression.[18]

Chuang *et al.* studied 28 consecutive cases of BL obtained retrospectively from 4 hospitals in Southern Taiwan. They suggested that we can confidently distinguish BL from DLBCL-HPSS (high PI and with or without a starry-sky pattern) by using histopathologic and IHC (CD10, bcl-2, bcl-6 and Ki-67 PI ≥95.0%) studies without the aid of Epstein-Barr encoded early RNAs (EBER) and fluorescence *in situ* hybridization (FISH) in the great majority of cases.[18,21] In our case, we did not go for EBER and FISH studies as the histological and IHC staining were quite evident of the lesion not being a BL nor a DLBCL, hence placed as unclassifiable B-cell lymphoma with features intermediate between DLBCL and BL. The patient was diagnosed with intermediate DLBCL/BL of primary type based on its aggressive clinical behavior, intermediate histomorphological features of both BL and DLBCL expression of CD20, bcl 2 and MIB-1labeling index, exclusion of CD3, CD10, CD138, bcl 6, Tdt and PET scan.

BCLu-DLBCL/BL is believed to have a poor prognosis when treated with conventional therapies for DLBL. Some early data are beginning to suggest that BCLu-DLBCL/BL may respond better to intense chemotherapy,[17] In this case, the patient was treated with extensive chemotherapy and found to be disease-free even after 2 years of follow-up.

CONCLUSION

Lymphomas arising primarily in extra-nodal sites are of diagnostic challenge due to their morphological diversities and lack of uniformity in histopathological classification system. The primary oral lesion in the 21-year-old male was difficult to place as either a BL or DLBCL. The clinical presentation, histopathologic picture and IHC staining were all conclusive to place the lesion in the gray zone according to the 2008 WHO classification.

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Conflicts of interest

There are no conflicts of interest.

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