



Intraoral HIV-associated Burkitt's lymphoma: a rare case report with special emphasis on differential diagnosis

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Abstract (J Korean Assoc Oral Maxillofac Surg 2019;45:225-229)

Individuals with human immunodeficiency virus (HIV) infection present with unique intraoral manifestations of various neoplasms. Intraoral HIV-associated Burkitt's lymphoma is a rare presentation, especially in patients of Indian origin and may present as an initial sign of HIV. The objective of this paper is to report a rare case of Burkitt's lymphoma in an HIV-positive Indian patient along with a special emphasis on differential diagnosis. A 30-year-old Indian female presented with a solitary, well-defined, exophytic mass extending anteroposteriorly and buccolingually from the 35th to 38th regions with no evidence of intraosseous extension. An incisional biopsy was performed, and histopathology showed sheets of neoplastic lymphoid cells with numerous tingible body macrophages with clear cytoplasm, presenting a starry sky appearance, suggesting a diagnosis of BL. The tumor cells were positive for CD10, CD20, c-myc, and Epstein-Barr virus, with a nearly 100% Ki-67 proliferative index. The patient tested positive for HIV. This report indicates the importance of immunohistochemical analysis to differentiate Burkitt's lymphoma from other similar lesions like diffuse large B-cell lymphoma. Thorough knowledge of the clinical presentation, etiopathogenesis, histopathology, and immunoprofile of intraoral HIV-associated Burkitt's lymphoma is essential among clinicians and pathologists.

Key words: Acquired immunodeficiency syndrome, Burkitt lymphoma, Gingiva, HIV, Oral cavity

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I. Introduction

Non-Hodgkin's lymphoma (NHL) is one of the most common acquired immunodeficiency syndrome (AIDS)-defining neoplasms, accounting for one-third of AIDS-related malignancies^{1,2}. Burkitt's lymphoma (BL) is an uncommon highly aggressive B-cell NHL, first described by Dr. Dennis Burkitt in 1958^{3,4}. BL has the highest proliferation rate of any human neoplasm, with a possible doubling time of 24 hours³. Three forms of BL have been described by World Health Organization (WHO): 1) Endemic, 2) sporadic, and 3) immunode-

ficiency-associated⁴. BL exhibits an elevated incidence in immunocompromised patients, especially those with human immunodeficiency virus (HIV) infection, accounting for 2.4% to 20% of HIV-associated NHLs^{2,3}. Extra nodal sites particularly in the abdomen and lymph node are the most common sites for HIV-associated BL, and intraoral lesions are very uncommon^{5,6}. This subtype is considered one of the primary/initial conditions indicating an underlying HIV infection⁶. Therefore, we report a case of HIV-associated BL presenting as an intraoral mass in a female Indian patient.

II. Case Report

A 30-year-old female reported to our institution with a chief complaint of an asymptomatic, gradually enlarging growth in the lower left back region of the jaw for 4 months. The patient did not reveal any significant medical history or drug allergies. Extraoral examination revealed facial asymmetry caused by a soft, painless swelling of the left cheek. An enlarged left submandibular lymph node was noted. Intraoral examination showed a solitary, well-defined, sessile, exo-

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phytic mass covered by slough, extending anteroposteriorly and buccolingually from the 35th to 38th region.(Fig. 1) The lesion was non-tender, soft in consistency, and measured approximately 3 cm×4 cm in diameter. Panoramic radiograph showed superficial bone loss in the area of the lesion, with no evidence of intraosseous extension. Considering these features, a provisional diagnosis of malignant tumor was suspected. Gingival enlargement, periodontal disease, fungal infection, granulomatous diseases like Wegener’s granulomatosis, epithelial malignancies such as squamous cell carcinoma, connective tissue tumors like fibromatosis and fibrosarcoma, and lymphoproliferative disorders like lymphoma and leukemia were also considered in the differential diagnosis. Since these lesions are clinically indistinguishable, a histopathologic examination in the form of an incisional biopsy was performed, and the excised tissue was subjected



Fig. 1. Intraoral clinical image showing a sessile exophytic mass covered by slough, extending anteroposteriorly and buccolingually from the 35th to 38th region.

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to histopathologic evaluation to obtain a confirmatory diagnosis.

Microscopic examination revealed diffuse proliferation of uniformly sized neoplastic lymphoid cells. The cells showed hyperchromatic round nuclei with multiple nucleoli and basophilic cytoplasm. Numerous tingible body macrophages with clear cytoplasm were seen interspersed among the tumor cells, producing a starry sky appearance.(Fig. 2. A) The cells also demonstrated pleomorphism and increased abnormal mitotic figures.(Fig. 2. B) Immunohistochemical analysis showed that the tumor cells were positive for c-myc, CD10, CD20, and Epstein–Barr virus (EBV) (Fig. 3. A-C, 3. E) and negative for CD3, Bcl2, Bcl6, and MUM1. The Ki-67 proliferative index was nearly 100%.(Fig. 3. D) Based on the histologic and immunohistochemical findings, the diagnosis was BL. Since this particular intraoral location of BL is uncommon in non-endemic regions, it was suspected that the patient might be immunocompromised. Therefore, the patient was asked to undergo serological testing for HIV, which turned out to be positive, resulting in a final diagnosis of HIV-associated BL. Unfortunately, further investigations could not be performed as the patient was lost to follow-up.

III. Discussion

Patients with HIV infection are at high risk of developing malignancies. NHL constitutes the second most common variety of these neoplasms and is considered an AIDS- defining entity¹. The most common types of NHLs seen in HIV/AIDS patients include diffuse large B-cell lymphoma (DLBCL) and BL, accounting for 7% to 20% of cases⁷⁻⁹. Abdominal, nodal, and bone marrow involvement are frequent for HIV-associated BL, and Central Nervous System (CNS) involvement is seen in 13% to 17% of cases^{4,6}. Intraoral locations are a

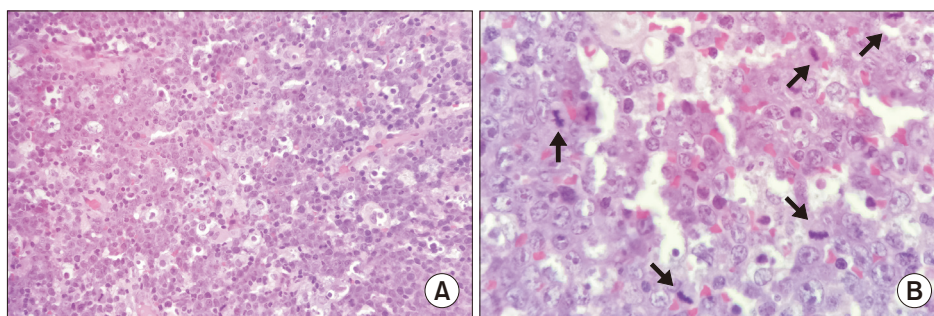


Fig. 2. Photomicrograph showing diffuse proliferation of uniformly sized neoplastic lymphoid cells with numerous tingible body macrophages, presenting a starry sky appearance (A: H&E staining, ×10) and numerous mitotic figures, marked with arrows (B: H&E staining, ×40).

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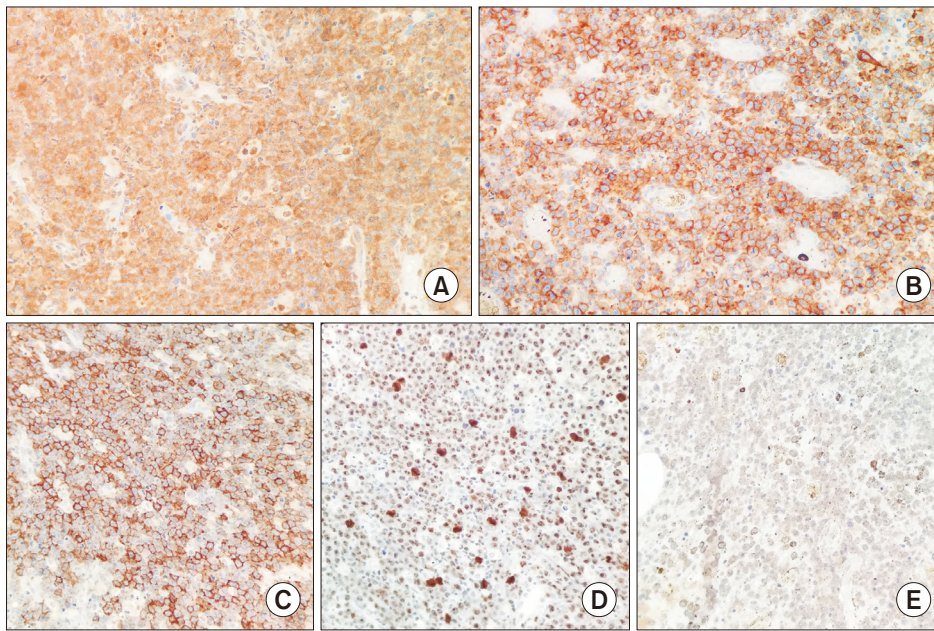


Fig. 3. Immunohistochemical staining showed that the neoplastic lymphoid cells were positive for c-myc (A: $\times 10$), CD10 (B: $\times 10$), CD20 (C: $\times 10$), Ki-67 (D: $\times 40$), and Epstein-Barr virus (E: $\times 10$).
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Table 1. Summary of cases of intraoral HIV-associated Burkitt's lymphoma reported in the literature

Study	No. of cases	Age (yr)/sex	Intraoral site	Immunohistochemical and molecular findings
Langford et al. ¹³ (1991)	1	42/M	Gingiva	Positive for CD45RA, Ki-B3, L26, and CD45 Negative for CD45RO, CD43, CD21, CD68, and CD30
Karlis et al. ¹¹ (1998)	1	51/M	Gingiva	NA
Jordan et al. ¹² (1998)	2	59/M	Gingiva	NA
Nittayananta et al. ¹⁵ (1998)	2	46/M 26/M	Gingiva Gingiva	Positive for CD20 and CD45 Negative for CD45RO and EBV
Chen et al. ¹⁰ (2005)	1	28/M	Gingiva	Positive for CD20, kappa, and c-myc Negative for CD45RO, lambda, CD30, Bcl2, Bcl6, and EBV High labelling indices with Ki-67 and p53
Venkatesh et al. ¹⁶ (2008)	1	39/M	Gingiva and hard palate	NA
Butt et al. ¹⁸ (2008)	1	NA	Palate	NA
Corti et al. ¹⁴ (2011)	3	44/M 24/F 38/M	Gingiva, palate Gingiva Gingiva	EBV+ve EBV+ve Not tested
Goto et al. ⁵ (2012)	1	45/F	Gingiva	Positive for CD10, CD79a, CD20, and Bcl6 Negative for CD3, CD5, cyclinD1, and Bcl2 Ki-67 index 98%
Ajila et al. ³ (2012)	1	42/M	Gingiva	Not tested
Komatsu et al. ¹⁷ (2013)	1	37/M	Floor of mouth	Positive for CD19, CD20, and CD10 Negative for CD3, CD4, and CD8 c-myc rearrangement +ve by FISH
Pinisetti et al. ⁸ (2013)	1	38/F	Gingiva	Positive for CD20 Negative for CD3
Sivolella et al. ⁷ (2015)	1	52/M	Mandibular jaw	Positive for CD19, CD20, CD79a, CD10, and Bcl6 Negative for CD5, CD23, Bcl2, and EBV MIB-1 index 100%
Mosalleum et al. ⁶ (2015)	1	25/F	Gingiva	Positive for CD45, CD20, CD10, and Bcl6 Ki-67 index 100% c-myc rearrangement +ve by FISH

(HIV: human immunodeficiency virus, M: male, F: female, NA: not analysed, EBV: Epstein-Barr virus, FISH: fluorescent *in situ* hybridization)
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relatively rare occurrence¹⁰. A summary of literature reporting intraoral HIV-associated BL is depicted in Table 1.

Literature strongly suggests EBV infection and dysregula-

tion of the c-myc (c-myelocytomatosis) oncogene as possible causes of BL⁷. Approximately 98% of endemic BL, 20% of sporadic BL, and 30% to 40% of immunodeficient BL ex-

hibit an association with EBV². EBV promotes B-cell hyperplasia, an essential step in lymphomagenesis. This increases the risk of chromosomal rearrangement associated with c-myc oncogene expression. The c-myc immunoglobulin (Ig) translocation is thought to arise as a result of errors in activation-induced cytidine deaminase-mediated Ig class switch recombination in germinal centers, leading to proliferation of neoplastic cells^{3,6-8}. In addition, when HIV infection is associated with BL, it causes uncontrolled polyclonal activation of B cells⁸.

Approximately 4% of NHLs associated with HIV occur in the oral cavity⁵. The data available regarding intraoral HIV-associated BL indicate the gingiva as the most frequently affected site and primary occurrence in males^{3,5-8,10-16}. Lesions on the palate, floor of the mouth, and lower jaw have also been reported^{17,18}. The most frequently affected ages were from the 3rd to 5th decades. A lesion usually presents as a rapidly growing ulcerative mass with a necrotic surface^{2,5,8,10}. Intraoral and extraoral swelling along with tooth loosening and mobility are seen with jaw lesions^{3,7}. Radiographic findings include ill-defined radiolucency with loss of trabecular pattern of the mandible or maxilla³. The present case involved an exophytic growth with surface ulceration in the mandibular gingiva in a 30-year-old female patient. Clinically, BL may mimic a variety of orofacial pathologies; hence, clinical differential diagnosis should include periodontal disease, deep fungal infection, granulomatous diseases, and malignant neoplasms¹⁵.

Microscopically, HIV-associated BL exhibits features of classic BL. These include diffuse monotonous proliferation of sheets of small to intermediate-sized malignant cells that exhibit moderately abundant basophilic cytoplasm with round, regular nuclei containing multiple nucleoli^{1,2} and abundant mitotic figures. Numerous scattered tangible body macrophages with clear cytoplasm (as a result of phagocytosis of apoptotic cells) form a starry-sky appearance^{1,5}. Previously, the WHO had suggested three histological subtypes of HIV-associated BL: classic BL, BL with plasmacytoid differentiation, and atypical BL. However, these subtypes are no longer favored, and the variants have been described as a separate entity of B-cell lymphoma, unclassifiable with features intermediate between DLBCL and BL^{1,4}.

Immunohistochemically, the tumor cells of BL show positivity for Pan B-cell antigens that include CD19, CD20, CD22, and CD79a; may co-express CD10, BCL-6, CD43, and p53; and show immunonegativity for MUM-1, CD5, CD23, BCL-2, CD138, and TdT (terminal deoxynucleotidyl trans-

ferase)^{2,7,8,19}. This immunoprofile suggests a follicle center origin of BL. The tumor cells have a high proliferation rate, as shown with the nearly 100% nuclear reactivity of Ki-67²⁰. In addition, chromosomal rearrangement of MYC is most common in the form of translocation of t(8;14) detected by fluorescent *in situ* hybridization (FISH)¹. The present case also showed immunoreactivity for CD10, CD20, c-myc, and EBV and immunonegativity for CD3, BCL2, BCL6, and MUM-1.

Features like the starry sky pattern, BL-like immunophenotype, and high proliferation fraction in some DLBCLs necessitates that BL be distinguished from DLBCL, as the two entities require different treatment modalities¹⁹. DLBCL is traditionally treated by CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy with the anti-B cell antibody rituximab, whereas adult BL frequently requires a high intensity chemotherapy regimen including CNS prophylaxis to improve overall survival^{19,20}. The WHO recommends positivity for CD10, BCL6, and Ki-67 >90%; negativity for BCL2 with the presence of a MYC breakpoint; and absence of BCL2 and/or BCL6 breakpoints for diagnosis of BL²⁰. Therefore, researchers have reached a consensus regarding the practical approach for this differentiation and have suggested that positivity for CD10, BCL6, and Ki-67 >90%; negativity for BCL2; presence of an MYC breakpoint; and absence of BCL2 and/or BCL6 breakpoints favor diagnosis of BL^{19,20}. The differences between BL and DLBCL are depicted in Table 2. Our case showed positivity for CD10 (germinal center-associated marker¹⁷), CD20 (mature B cell with monotypic surface antigens⁶), c-myc, and EBV and negativity for CD3 (T-cell associated marker¹⁷), Bcl6, Bcl2 (marker for activated B- cell), and MUM1 (plasma cell marker¹⁴). Based on these findings, we confirmed the diagnosis of BL. Therefore, the final diagnosis of BL should be established with the help of immunohistochemistry and molecular investigations.

The primary mode of treatment for BL is intensive multi-

Table 2. Differences between Burkitt’s lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL)¹⁹

	BL	DLBCL
Bcl2	Negative	Positive
Ki-67	>95%	<90%
c-myc	Immunoglobulin-MYC rearrangement (simple karyotype)	Negative rearrangement
Others		Bcl6-rearrangement Bcl2-rearrangement

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agent chemotherapy. In HIV patients, modified protocols are used to reduce toxicity⁶. However, HIV-associated BL is less sensitive to chemotherapy compared to endemic forms and shows poor prognosis with a tendency to relapse^{5,8}. In cases of extra nodal HIV-associated BL, thorough investigations should be performed to detect other sites of involvement, and patients should be treated accordingly.

In conclusion, the present case and analysis of previously reported cases suggest that intraoral BL can be the initial manifestation of HIV infection in patients. Therefore, such an oral presentation should raise the suspicion of an underlying immunocompromised state. BL should be differentiated from DLBCL, as they require different treatments. As a result, detailed knowledge on the etiopathogenesis, clinical presentation, and histopathology along with immunological and molecular profiles is critical to obtain a final diagnosis.

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Authors' Contributions

M.K. participated in data collection and wrote the manuscript. M.K., U.D., S.K., and S.B. participated in the design and performed the draft. U.D. participated in the coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Consent for Publishing Photographs

Written informed consent was obtained from the patients for publication of this article and accompanying images.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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