Case Series

An evidence based immunohistochemical panel for diagnosing oral lymphoma along with a case series

V. M Aneesh, Karla M. Carvalho, Anita Dhupar, Anita Spadigam

Department of Oral and Maxillofacial Pathology, Goa Dental College and Hospital, Bambolim, Goa, India

Abstract

Oral lymphomas are rare and present a diagnostic challenge. Immunophenotyping is essential to decipher their biology and identify therapeutic targets. Histopathology can prove to be diagnostically difficult to type these lesions, and hence, immunohistochemistry (IHC) proves useful in deciphering their biology. Here, we present an evidence-based approach using a novel immunohistochemical marker panel to diagnose oral lymphomas by discussing four unique cases.

Keywords: Diagnosis, genetic heterogeneity, lymphoma, mouth

Introduction

Lymphoma is a heterogeneous malignancy characterized by an aberrant proliferation of mature lymphoid cells or their precursors.[1]

The 2016 revised World Health Organization (WHO) classification of lymphoid neoplasms classifies these lesions based on cell biology.[2] To treat lymphoma, deciphering the cell of origin is imperative for chemotherapy, radiotherapy, biologic therapy, and immunotherapy.[1,2]

In the oral cavity, these lesions can present with symptoms that simulate inflammatory conditions of the jaw most commonly seen in the gingiva and hard palate, such as advanced periodontitis and osteomyelitis.[3]

In this study, a specific and sensitive set of cell lineage markers was selectively used in a logical and evidence-based sequence to generate an immunohistochemical panel to aid in the diagnosis and prognosis of oral lymphomas. This panel was tested on a series of four cases of oral lymphomas.

Address for correspondence: Dr. V. M Aneesh, Vettathukavil, Naduvilachery, Kanjaveli Post, Kollam - 691602, Kerala, India.
E-mail: draneeshvm@gmail.com

Received: 21-09-2023 **Revised:** 10-01-2024
Accepted: 12-01-2024 **Published:** 24-05-2024

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_1570_23

Case Report

Case 1

A 48-year-old female patient complained of a large extraoral swelling over the right lower third of her face. The patient gave a 2-year history of trauma to the region and complained of intermittent pain, loss of sensation in her lower lip, and weight loss. She had her lower right second premolar extracted due to pain and mobility, the socket of which remained unhealed. On extraoral examination, a large diffuse swelling, 6 × 5 cm in dimension, extending from the right body of the mandible to the posterior ramus, was noted inferiorly to the submental region. The swelling was firm and tender. The skin over the swelling appeared smooth, erythematous, and warm to touch. Intraoral examination revealed that the swelling had obliterated the buccal vestibule and appeared fixed to the underlying tissues. Multiple tender and firm lymph nodes were present in the right submandibular region.

How to cite this article: Aneesh VM, Carvalho KM, Dhupar A, Spadigam A. An evidence based immunohistochemical panel for diagnosing oral lymphoma along with a case series. J Family Med Prim Care 2024;13:2143-8.

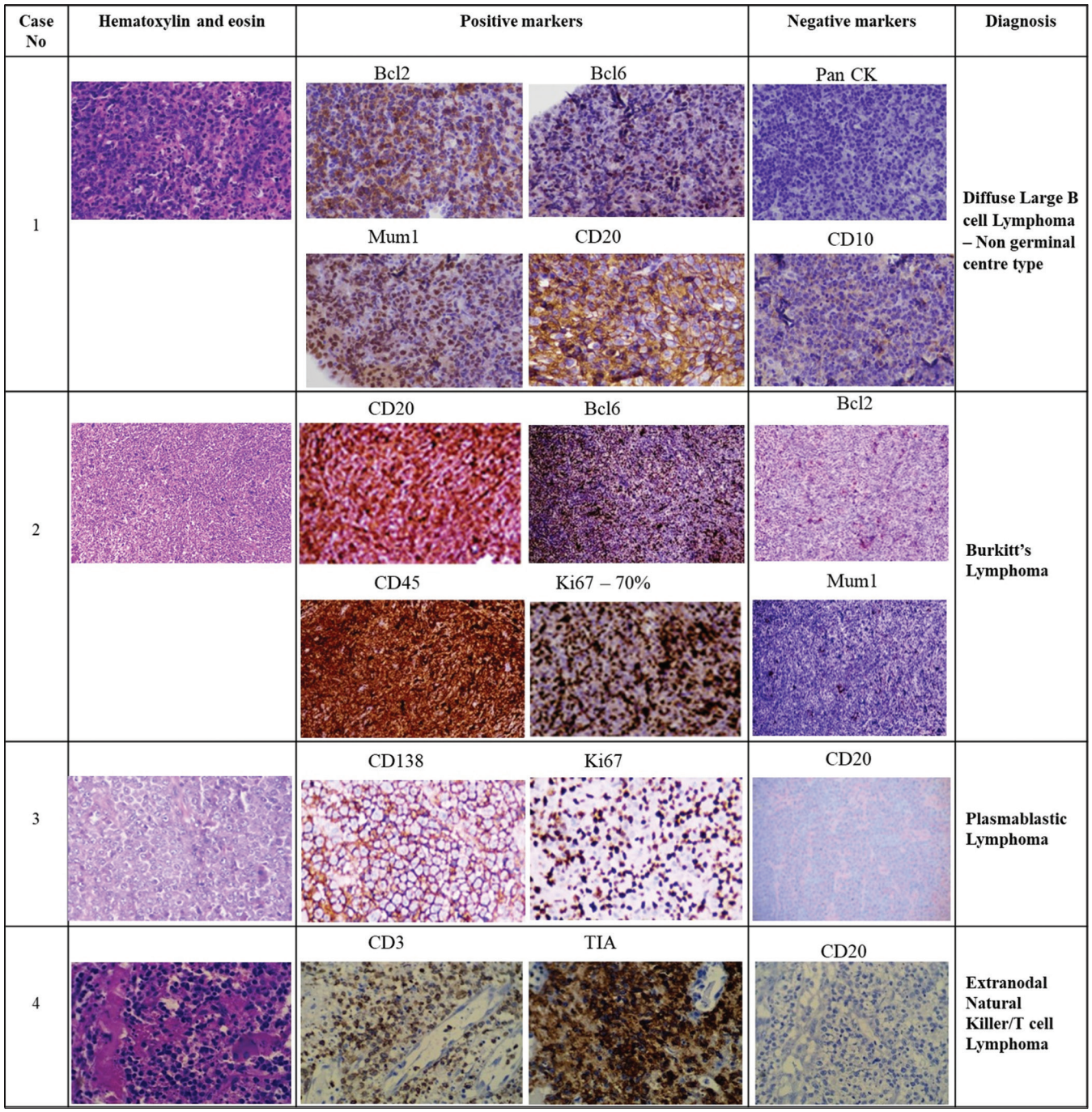

Figure 1: Pictorial representation of the results obtained after using the diagnostic IHC flowchart [Figure 2]. The use of proliferative marker Ki67 has been used to substantiate diagnosis when required

Case 2

A 68-year-old male patient reported a 5-month history of painful swelling on the right posterior alveolar ridge. He complained of pain during mastication, deglutition, and disturbed sleep. The pain radiated over his right periauricular area. He was a smoker for the last 30 years. Intraoral examination revealed a large tender erythematous swelling, 5 × 4 cm in dimension, over the edentulous alveolar ridge, which was firm and fixed to the underlying structures. The patient had palpable, tender, and fixed right submandibular lymph nodes.

Case 3

A 60-year-old female patient complained of a diffuse tender swelling on her right lower lip. Intraoral examination revealed an ulcerated lesion measuring 2 × 2 cm in dimension, which involved her right lower labial mucosa and vestibule in relation to her lower canine and first premolar. The right submandibular and submental lymph nodes were palpable and tender. The patient gave a history of loss of weight of more than 5 kgs and weakness, which she experienced for 2 months.

Case 4

A 49-year-old man complained of an ulcer, which was evident extraorally over the right nasolabial fold and extended intraorally into the upper right vestibular area. The patient had been prescribed a course of antibiotics for a right buccal space infection, which involved the right maxillary canine but had no alleviation of symptoms. He gave a history of fever, epistaxis, nasal congestion, and pain radiating to the upper right side of his face. The extraoral examination revealed that the nasolabial ulcer measured 2 × 3 cm in dimension and was tender. The ulcer extended from the right ala of the nose to the right nasolabial fold and had an indurated margin. The floor of the ulcer was covered with slough, and the surrounding skin showed a crusted appearance. The base of the ulcer was fixed to the underlying musculature. Intraorally, the ulcer extended to the right labial vestibule in relation to the right maxillary central incisor to the first premolar. Bilateral submandibular lymph nodes were tender.

Investigative workup of cases

Incisional biopsies were evaluated for histopathological findings, and a novel immunohistochemical panel of markers was used to delineate cell lineage for the four cases discussed above [Figures 1 and 2].

Discussion

The literature states that a correlation exists between certain histologic variants of oral lymphomas and specific clinical parameters. For example, Hodgkin lymphoma shows a predominance in younger individuals. Follicular lymphoma favors the female gender. Almost every site in the oral cavity, including jaw bones (i.e. central variant), is affected. Clinically, these lesions show a wide range of symptoms, which include painful ulcerated swellings, paraesthesia, tooth displacement, hypermobility, and palpable tender lymph nodes.[4,5] However, a few asymptomatic cases have also been reported, as evidenced in the review of the literature [Table 1].[1,4-13]

Immunohistochemistry (IHC) can aid in the diagnosis of oral lymphomas, which include atypical cases; however, it often involves the use of a broad range of markers.[7] To the best of our knowledge, a standardized diagnostic panel of markers for oral lymphomas does not exist, which often results in the use of nonspecific and often erroneous markers. In India, diagnosis with IHC is still considered an expensive investigative modality for the majority of the population, which prompted the authors of this publication to formulate an evidence-based IHC panel and flowchart for typing oral lymphomas using a limited number of specific and sensitive markers [Figure 2].

Rationale for Novel Diagnostic IHC marker Flowchart for Oral Lymphomas [Figure 2]: Application of Pan T and B lymphocytic markers helps in distinguishing T from B lymphocytes. Among Pan T- and B-cell markers, cluster differentiation (CD) 2, CD3 and CD19, CD20 were most specific for T- and B-cell identification, respectively. Immunopositivity of B-cell leukemia/lymphoma protein (Bcl)-6, Bcl-2, and cellular myelocytomatosis oncogene markers suggests diffuse large B-cell lymphoma, which is further differentiated into germinal and non-germinal center types by CD10 and multiple myeloma oncogene 1 (MUM1), respectively. Cyclin D1 is a highly specific marker for mantle cell lymphoma, the diagnosis of which can be confirmed by sex determining region Y gene-Box transcription factor 11 positivity. Negativity for all the aforementioned markers for

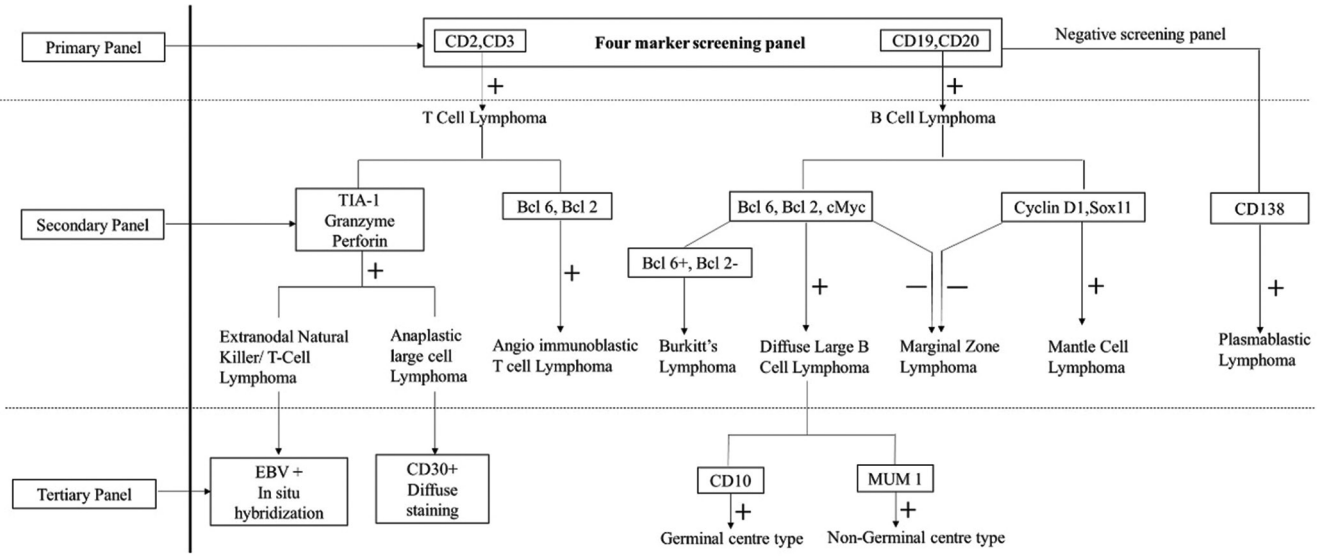

Figure 2: Primary panel consists of cluster of differentiation (CD) 2, CD3 and CD19, CD20, which delineate T- and B-cell lineage, respectively. Negativity to these markers indicates plasmablastic differentiation, confirmed by CD138. Differentiation of T-cell lineage can be demonstrated by a secondary panel: T-cell intra-cellular antigen-1 (TIA-1), granzyme, perforin, Bcl-6, and Bcl-2. B-cell lineage can be differentiated by a secondary panel: Bcl-6, Bcl-2, c-Myc, cyclin D1, and SOX11.[7,10,12,14,15]

Table 1: A summary of the existing caseload of oral lymphomas reported in the literature that includes a few atypical cases.

Reference	Age and gender	Clinical features	Radiographic features	Histopathology	IHC	Final diagnosis
Yassine Oueslati, Raouaa Belkacem Chebil, Iyadh Abidi, 2020[1]	72, F	Painful ulcerated mass Tooth mobility Lymphadenopathy Hypoesthesia	Osteolysis, tooth displacement, and multiple enlarged lymph nodes	Large tumor cells with clear and abundant cytoplasm, nuclei with marked atypia Numerous mitoses and apoptotic bodies	CD45+ CD20+ CD3- CK- Ki67+	NHL
Natheer Hashim Al-Rawi 2016[6]	43, M	Asymptomatic slow-growing nodular mass on the tongue No lymphadenopathy	Not mentioned	Sheets of pleomorphic lymphoid cells and abnormal mitotic figures, large number of histiocytes	Ki67+ CD3+ CD20+ CD43+ Granzyme B+ CD68+ CD4- CD8- CD30- CD56- Alk1 (CD246)-	NHL
Nisha Modi, Ujjawal Khurana, Sramana Mukhopadhyay 2021[7]	6, M	Gingival hypertrophy, cervical lymphadenopathy	Not mentioned	Atypical large lymphoid cells with plasmacytoid morphology, conspicuous apoptotic and mitotic activity	CD45+ EMA+ CD10- CD19- CD20- CD22- CD23- FMC7- CD4- CD5- CD8- CD3-	Plasmablastic lymphoma
J. Quenot, N. Sigaux, E. Hugot 2020[8]	66, F	Vestibular mucosal tender swelling No tooth mobility No lymphadenopathy	No bone destruction	Small lymphocytes without atypia mixed with large lymphocytes, few small follicles with germinal centers	CD20+ CD3+ Bcl-2+ CD5+ CD10+ CD23+ Bcl-6+	Mucosa-associated lymphoid tissue lymphoma (MALT)
Abubakar Badshaha Shaikh, Sneha Waghmare, Supriya Koshti-Khude 2016[4]	92, M	Large, tender, reddish-pink swelling on the alveolar ridge No lymphadenopathy	Local bone destruction	Diffuse, uniform monotonous proliferation of medium-sized lymphocytes in loose fibrocellular stroma	CD3+ CD20+ MB1+ CD138+ CD56-	NHL
Masato Watanabe, Ai Enomoto, Yuya Yoneyama 2019[9]	51, F	Asymptomatic firm mass in the left posterior maxilla No lymphadenopathy	No bone involvement	Scattered lymphoid follicles with germinal centers and predominant small well-differentiated lymphocytes in the parafollicular area	CD20+ CD79A+ CD10+ Bcl-6+ Ki67+ Bcl-2- CD3+ CD5+ CD21+ CD15- CD45R0+	Follicular lymphoid hyperplasia (FLH)
A. Richards, Costelloe, J.W. Eveson 2000[5]	61, M	Painful irregular deep ulcers on the left maxillary anterior alveolus Left submandibular lymphadenopathy	Bone destruction	Ulcer overlying an angiocentric infiltrate of large atypical lymphoid cells with pleomorphic nuclei and occasional mitoses and areas of necrosis	CD3+ CD45R0+	NHL

Contd...

Table 1: Contd...

Reference	Age and gender	Clinical features	Radiographic features	Histopathology	IHC	Final diagnosis
Manuel Antonio Gordon-Nunez, Onilson Da Rocha Mendes Jr, Leonardo Miguel Madeira Silva 2012[10]	70, F	Soft, nodular, asymptomatic, slow-growing, sessile lesion on the right soft palate No lymphadenopathy	No bone involvement or lymphadenopathy	Lymphoid aggregates with numerous lymphocytes in the periphery with scanty cytoplasm and homogeneously basophilic nuclei, germinal center—cells with large and lightly stained nuclei, conspicuous nucleoli and scanty cytoplasm, occasional mitotic figures	Bcl-2+ in mantle zone and within follicular centers	FLH
Ranjitha Rao, Deviprasad Dosemane, Bhagyashree Jaipuria 2018[11]	52, M	Asymmetric tonsillar enlargement with surface nodularity and vascularity	Not mentioned	Small- to medium-sized lymphoid cells with irregular nuclear contours, condensed nuclear chromatin, inconspicuous nucleoli, and scant cytoplasm	Bcl-2+ CD20+ CD5+ Cyclin D1+ Bcl-6- CD3- CD10-	Mantle cell lymphoma (MCL)
Sangeeta Patankar, Poornima Venkatraman, Gokul Sridharan, 2015[12]	38, M	Painful diffuse swelling in anterior gingiva, displaced central incisors, nontender, submandibular, and cervical lymphadenopathy	Generalized horizontal alveolar bone loss	Homogenous tumor cells with round-to-oval nuclei with coarse chromatin and minimal cytoplasm. Tumor cells were separated by thin fibrous septae within which were present large pale-staining macrophages resembling starry sky pattern	LCA+ CD3+ CD10+ CD20+ MIB 1+ CK- MPO- Tdt- CD138-	Burkitt's lymphoma
Yuk-Kwan Chen, Chung-Ho Chen, Yu-Ju Lin 2004[13]	43, M	Painful swelling on the left buccal mucosa extending to the maxillary tuberosity Bilateral submandibular lymphadenopathy	Poorly defined radiolucency over 25, bony destruction of the maxilla including the wall of the left maxillary sinus and the mandibular ramus	Monotonous small lymphocytes with clumped chromatin, angulated nuclei, and scanty cytoplasm. Some exhibit pleomorphic appearance and abnormal mitosis	LCA+ CD5+ CD20+ CD79a+ CD23+ CD43+ Bcl-2+ Bcl-6+ CD10- Bcl-1- (cyclin D1) CD3- CD30- CD68- SMA-	Small lymphocytic lymphoma (SLL)

B- and T-cell differentiation suggests a diagnosis of marginal zone lymphoma[14,15]

Unlike other B-cell lymphomas, plasmablastic lymphoma forms a distinct diagnostic entity as it shows negativity for CD19 and CD20. It is identified by a positivity for CD38, CD138, and B-cell lymphocyte-induced maturation protein-1 (BLIMP-1).[7]

Once the T-cell lymphoma is identified, the application of follicular dendritic cell marker CD21 can confirm angioimmunoblastic T-cell lymphoma (AITL). Testing for T-cell intracellular antigen-1 (TIA-1), granzyme, and perforin (i.e., cytoplasmic proteins present in cytotoxic T lymphocyte and natural killer (NK) cells) leads to the diagnosis of two distinct entities—the extra-nodal NK or T-cell lymphoma (ENKTCL) and anaplastic large cell lymphoma (ALL).[14,15]

The rationale behind the novel diagnostic flowchart described in this study is optimized to confirm the cell of origin in the case of oral lymphoma. This IHC marker template is a simple, easy-to-use, and modifiable tool that can be expanded to include new variants of oral lymphomas and extraoral lymphomas. Thus, this flowchart can prove useful to both diagnosticians, including primary healthcare providers and oncologists.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Oueslati Y, Chebil RB, Abidi I, Sriha B, Khochtali H, Oualha L, *et al.* Mandibular non-Hodgkin's lymphoma: Two observations of a challenging disease. Pan Afr Med J 2020;37:102.
2. Yap DRY, Lim JQ, Huang D, Ong CK, Chan JY. Emerging predictive biomarkers for novel therapeutics in peripheral T-cell and natural killer/T-cell lymphoma. Front Immunol 2023;14:1068662
3. de Araújo GR, Morais-Perdigão AL, de Cáceres CVBL, Lopes MA, Aguirre-Urizar JM, Carlos R, *et al.* Lymphomas affecting the sublingual Glands: A clinicopathological study. Head Neck Pathol. 2023;17:154-64.
4. Shaikh AB, Waghmare S, Koshti-Khude S, Koshy AV. Unusual presentation of non-Hodgkin's lymphoma: Case report and review of literature. J Oral Maxillofac Pathol 2016;20:510-7.
5. Richards A, Costelloe MA, Eveson JW, Scully C, Irvine GH, Rooney N. Oral mucosal non-Hodgkin's lymphoma--a dangerous mimic. Oral Oncol 2000;36:556-8.
6. Al-Rawi NH. Primary non-Hodgkin's lymphoma of the tongue: A diagnostic dilemma of unusual case presentation. BMJ Case Rep 2017;2017: bcr2016218218.
7. Modi N, Khurana U, Mukhopadhyay S, Joshi D, Soni D, Chaudhary N, *et al.* An unusual case of paediatric plasmablastic lymphoma presenting with malignant effusion and the challenges in its diagnosis. Diagn Cytopathol 2021;49:E389-94.
8. Quenot J, Sigaux N, Hugot E, Meyer C, Louvrier A. Gingival Mucosa-Associated Lymphoid Tissue (MALT) lymphoma developed around a mandibular extraosseous dental root canal overfilling: A case report. J Stomatol Oral Maxillofac Surg 2020;121:743-5.
9. Watanabe M, Enomoto A, Yoneyama Y, Kohno M, Hasegawa O, Kawase-Koga Y, *et al.* Follicular lymphoid hyperplasia of the posterior maxillary site presenting as uncommon entity: A case report and review of the literature. BMC Oral Health 2019;19:243.
10. Gordón-Núñez MA, Méndes OR, Silva LM, Galvão HC. Follicular lymphoid hyperplasia in palate: a case report with immunohistochemical analysis and review. J Clin Case Rep 2012;2:2.
11. Rao R, Dosemane D, Jaipuria B, Saha D, Narayan M, Rao KS. Mantle Cell Lymphoma of the Palatine Tonsil: A Rare Case Report. Iran J Otorhinolaryngol 2018;30:297-300.
12. Patankar S, Venkatraman P, Sridharan G, Kane S. Burkitt's lymphoma of maxillary gingiva: A case report. World J Clin Cases 2015;3:1011-6.
13. Chen YK, Chen CH, Lin YJ, Hsue SS, Wang WC, Lin CC, *et al.* Intra-oral small lymphocytic lymphoma. Oral Oncology Extra 2004;40:73-8.
14. Cho J. Basic immunohistochemistry for lymphoma diagnosis. Blood Res 2022;57:55-61.
15. Sun R, Medeiros LJ, Young KH. Diagnostic and predictive biomarkers for lymphoma diagnosis and treatment in the era of precision medicine. Mod Pathol 2016;29:1118-42.