CASE REPORT

Follicular lymphoma transforming into anaplastic diffuse large B-cell lymphoma of oral cavity: A case report with review of literature

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Received: 15-06-2014
Accepted: 04-12-2015

ABSTRACT

Follicular lymphoma (FL) is a common form of non-Hodgkin's lymphoma (NHL) with the ability to transform into a more aggressive disease, frequently to B cell-lymphoblastic lymphoma. Diffuse large B-cell lymphoma (DLBCL) is a subtype of NHL, which is characterized by diffuse proliferation of large neoplastic B-lymphocytes. It accounts for 30% of all NHL and its occurrence in the mandible is very rare. It is often seen in young adults, but in the present case, a 50-year-old male patient presented with painless swelling in left lower jaw since 25 days following extraction of left lower molar teeth. There was a history of fever and submandibular lymph nodes were enlarged. On incisional biopsy, features of NHL-like lesion were observed and confirmed by immunohistochemistry using CD20, bcl-2, CD10, CD3, CD5, Ki67 markers to be FL (3A) lymphoma transforming into DLBCL. This is a very uncommon presentation.

Key words: Diffuse large B-cell lymphoma, follicular lymphoma, non-Hodgkin's lymphoma

INTRODUCTION

Lymphomas are a heterogeneous group of neoplasm of the immune system.[1] The non-Hodgkin's lymphomas (NHL) are a group of B-cell and T-cell neoplasms that arise primarily in the lymph nodes. They constitute 5% of all head and neck cancers. NHLs of the oral cavity are rare and account for only 3–5% of the lymphomas reported.[2]

Follicular lymphoma (FL) accounts for approximately 30% of adult NHL and is generally indolent in its clinical course with long survival rates, but it is currently incurable. A subset of FL cases transform into diffuse large B-cell lymphoma (DLBCL/DLBL) in 25–60% of patients associated with a rapidly progressive clinical course, refractoriness to treatment and short survival.[3]

DLBL is the one of the common variants of NHLs involving around two-third of the cases. Although DLBL is characterized by an aggressive behavior, it responds well to chemotherapy.[2] NHLs usually manifest as a localized or generalized lymphadenopathy. Primary lesion principally occurs in the areas of lymphoid tissue such as oropharynx, bone marrow, intestine and skin. DLBL is often associated with systemic symptoms such as night sweats, weight loss (10%) and fever.[3]

Intraorally, lesions can occur as hard and diffuse tumors involving buccal vestibule, gingiva and the posterior region of the hard palate. In bone tissue, they may cause mild pain, paresthesia and swelling; the radiographic examination often shows irregular radiolucid images. DLBL can occur in soft tissue as well as bone and sometimes it is difficult to determine its initial site of origin. DLBL corresponds to 68% of cases of NHL of the oral cavity and the average age of highest prevalence is 66 years.[4] Women are affected more than men in a 2:1 ratio.[5]

Access this article online
Quick Response Code:
Website: www.jomfp.in
DOI: 10.4103/0973-029X.174617

How to cite this article: Mittal M, Puri A, Nangia R, Sachdeva A. Follicular lymphoma transforming into anaplastic diffuse large B-cell lymphoma of oral cavity: A case report with review of literature. J Oral Maxillofac Pathol 2015;19:379-84.

DLBCL is characterized by a diffuse proliferation of large neoplastic B cells having nuclear size equal to or exceeding normal macrophage nuclei or it can be more than twice the size of a normal lymphocyte.[6] It is a heterogeneous neoplasm with marked biological heterogeneity and highly variable clinical course.[7]

Here, we report a case of FL transforming into anaplastic DLBCL affecting the oral cavity of a 50-year-old man, along with clinical, histopathological and immunohistochemical features.

CASE REPORT

A 50-year-old male patient reported to the dental hospital with a complaint of painless swelling in the lower left body of the mandible since 25 days following the extraction of left lower 1st and 2nd molar teeth. The patient had a history of enlarged submandibular lymph node and fever since 15 days which was earlier thought to be due to infection after extraction. The swelling was insidious in onset and gradually increased in size causing facial asymmetry [Figure 1]. Examination revealed a nontender, solitary diffuse swelling measuring 3.5 cm × 3.5 cm in the lower left body of the mandible. The swelling was fixed, firm to hard in consistency. Intraorally, the swelling extended from left premolar till left ascending ramus of mandible obliterating the buccal vestibule, with buccal cortical plate expansion [Figure 2].

Orthopantomogram of the patient was done to evaluate the invasion of the lesion and pathological fracture of lower left body of mandible [Figure 3] was seen.

Fine-needle aspiration cytology was done, but no aspirate was obtained. The hematological tests (complete blood count, fasting blood glucose, prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate) were normal and the patient was HIV negative. The incisional biopsy of the lesion was performed. Correlating the history and clinical features, a provisional diagnosis of squamous cell carcinoma was made.

Histopathological picture showed the lesion to be composed of dysplastic parakeratinized stratified squamous epithelium overlying connective tissue stroma. Basement membrane is indistinct at few places with infiltrating epithelial cells seen in the connective tissue. The connective tissue stroma is highly cellular in nature. There are diffuse proliferations of large atypical lymphoid cells showing dysplastic features such as nuclear and cellular pleomorphism, nuclear hyperchromatism, increased number of nucleoli and abnormal mitotic figures. Some areas show invasion of neurovascular bundles. Cells are highly anaplastic. Multinucleated giant cells are also seen. The above-mentioned findings favored the diagnosis of large cell lymphoma [Figure 4a and b].

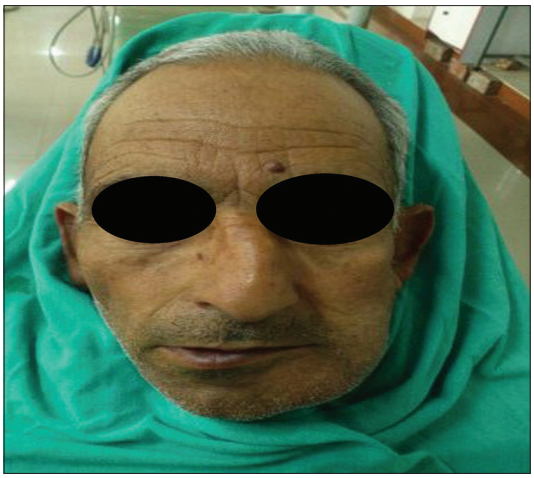

Figure 1: Swelling on the left side of mandible causing facial asymmetry

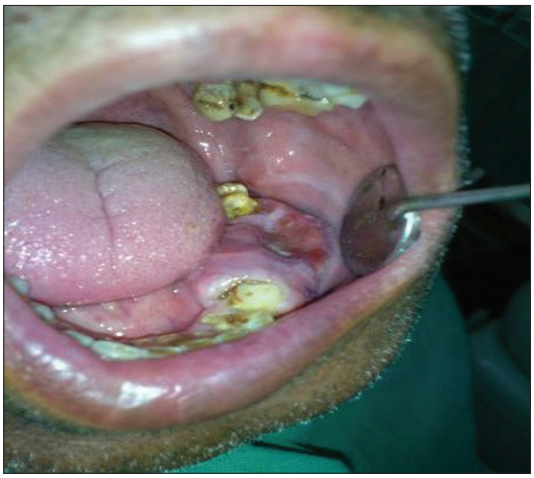

Figure 2: Intraoral swelling involing left alveolar process of the mandible

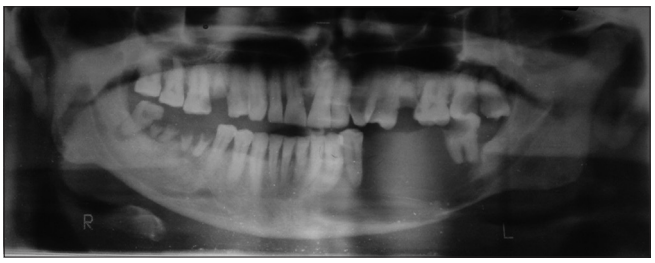

Figure 3: Orthopantomogram showing pathological fracture of the left lower jaw

Following this, immunohistochemical analysis was done for the expression of pan B-cell markers CD20, CD3, bcl-2, CD5, CD10 and Ki67. CD20 and bcl-2 were positive in medium and large lymphoid cells in follicle and diffuse pattern. CD3 and CD5 were positive in few scattered lymphocytes. CD10 was positive in few focal areas and Ki67 was positive in 30% area [Figure 5a-f]. Based on immunohistochemical report, the lesion was diagnosed as DLBCL anaplastic variant (70%) and FL, grade 3A (30%).

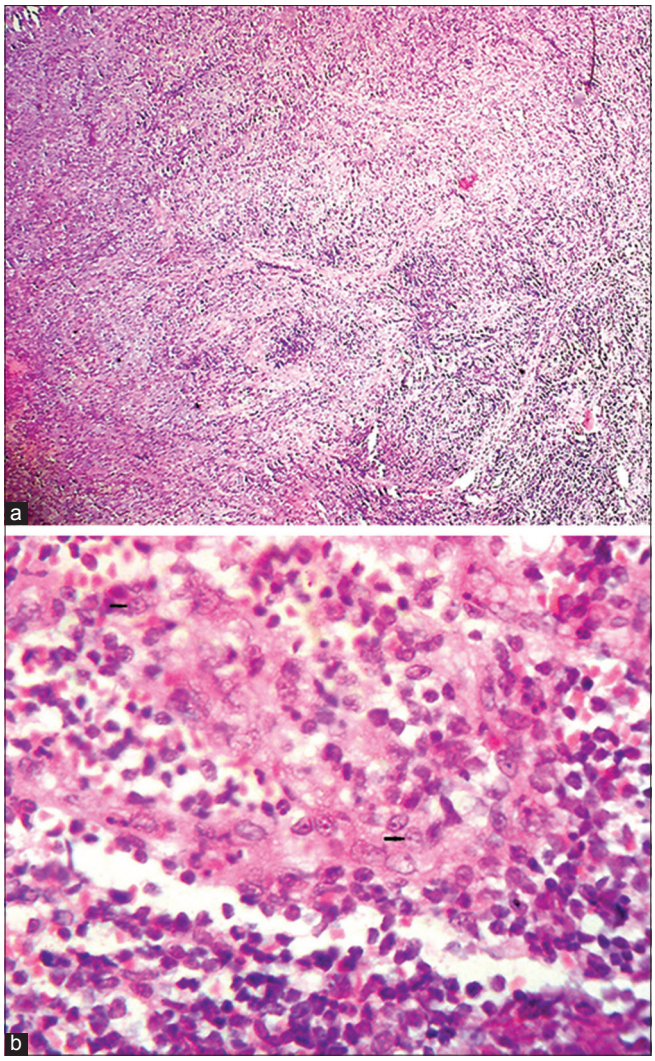

Figure 4: (a) Photomicrograph shows diffuse large lymphocytes (H&E stain, x100). (b) Photomicrograph shows diffuse large lymphoblast in sheets showing nuclear and cellular pleomorphism with multiple nucleoli (black arrow) (H&E stain, x400)

Based on histopathological examination and immunohistochemical study, the following lesions under differential diagnosis were ruled out squamous cell carcinoma, Hodgkin's lymphoma, large cell lymphoma of T-cell type, Burkitt's lymphoma, undifferentiated carcinoma and amelanotic melanomas.

Based on the final diagnosis, chemotherapy was advised by the oncologist, but the patient died within 1 month.

DISCUSSION

Malignant lymphomas involve a group of neoplastic proliferation process of the lymphocytes and their precursor cells.[8] Histologically, Hodgkin's lymphoma is characterized by the presence of multi-nucleated Reed–Sternberg cells while all other neoplasms of lymphoid system named as NHL are derived predominantly from the cells of B-lymphocyte series.[9] NHL arises primarily within the lymph nodes and up to 40% of cases present with extranodal presentation. NHL showing oral manifestations accounts for only 3–5% of cases and are rarely the initial manifestation of the disease.[1]

In the oral cavity, 15–45% of NHL occur in the maxilla and mandible.[10] The most common locations are maxilla (11%), mandible (8%), palatal soft tissue (8%), vestibule and gingiva (7%).[11] Isolated mandibular NHL accounts for only 0.6% of the cases reported.[4]

FL is one of the most common subtypes of NHL accounting for 22% of all cases worldwide. Several analyses of genetic alterations that appear to affect the risk for FL transformation to DLBCL have been reported, including c-MYC translocation, p53 mutation, deletions of the tumor suppressor genes p15 and p16 and chromosomal 6q23-26 and 17q aberrations. However,

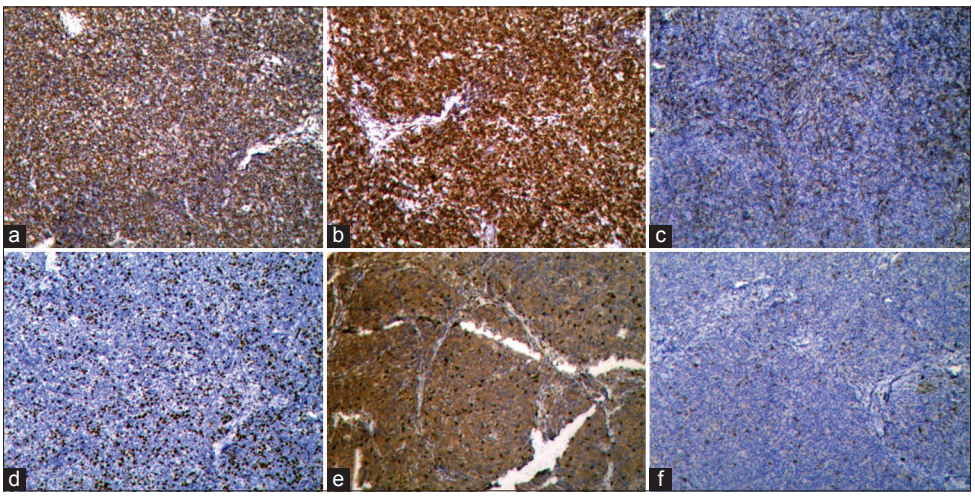

Figure 5: (a) Immunohistochemistry showing CD20 positivity (IHC stain, x40), (b) bcl-2 positivity in medium and large lymphoid cells in follicle and diffuse pattern (IHC stain, x40), (c) CD10 was positive in few focal areas (IHC stain, x40), (d) Ki67 was positive in 30% areas (IHC stain, x40), (e) CD3 was positive in few scattered lymphocytes (IHC stain, x40), (f) CD5 were positive in few scattered lymphocytes (IHC stain, x40)

immunohistochemical analyses of FL shows it to be positive for the pan-B-cell marker CD20, CD10, bcl-2 and bcl-6.[12]

The WHO classifications of 2001 and 2008 recognized three grades - FL1-2, FL3A and FL3B [Table 1][5], based on the number of centroblasts present per high power field; the difference between FL3A and FL3B is the presence of a mixture of centrocytes and centroblasts in FL3A and the presence of follicles existing exclusively of centroblasts, immunoblasts or both in FL3B. The fact which supported the continuation of a grading system is that grades predict outcome, higher grades being associated with poor clinical outcome and more rapid progression to DLBCL.[13]

Table 1: Grading of follicular lymphoma (WHO 2008)

Grade	Definition
Grade 1-2	0-15 centroblasts/0.159 mm^2
Grade 1	0-5 centroblasts/0.159 mm^2
Grade 2	5-15 centroblasts/0.159 mm^2
Grade 3	>15 centroblasts/0.159 mm^2
Grade 3A	Centrocytes present
Grade 3B	Solid sheets of centroblasts
DLBCL with follicular component	Diffuse area with solid sheets of centroblasts outside histologically or immunophenotypically (CD21, CD23 + FDC) recognizable follicles

DLBCL: Diffuse large B-cell lymphoma, CD: Cluster of differentiation, FDC: Follicular dendritic cell

Table 2: Subclassification of diffuse large B-cell lymphoma affecting oral cavity

Basis of classification	Types
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-Sternberg cells or undifferentiated carcinoma Increased number of intermixed T cells or histiocytes
Based on gene expression profiles	GCB Non-GCB or ABC like Type 3 gene expression profile
Based on prognosis	Prognostically favorable - CD10(+) or BCL6(+) or both(+) Prognostically unfavorable - MUM1(+)

GCB: Germinal center B-cell, ABC: Activated B-cell, CD: Cluster of differentiation, MUM1: Multiple myeloma oncogene 1, BCL6: B-cell lymphoma 6

DLBCL constitutes a heterogeneous group of lymphoid neoplasms with a diverse spectrum of features, response to therapy and survival. The normal architecture of lymph nodes is morphologically replaced by cells in a diffuse pattern. Neoplastic cells are characterized by at least twice the size of normal lymphocytes with vesicular nuclei, prominent nucleoli and basophilic cytoplasm.[14]

The most common presenting symptoms of extranodal NHL in the head and neck region include pain, discomfort and local swelling in the region of involvement. Clinical signs include localized swelling causing facial asymmetry, destruction of hard and soft tissue and ulceration.[7]

Lymphomas can be diagnosed using hematoxylin and eosin-stained sections, but the most common technique currently is immunophenotyping. Modern hematology relies on immunophenotyping to distinguish between benign and malignant diseases, as well as for a more detailed subtyping.[15] The DLBCL can be subclassified depending on cytomorphology, gene expression profile and prognosis [Table 2].[5,8,16]

DLBCL usually expresses pan B-cell markers lacking one or two such as CD19, CD20, CD75, CD79a, PAX5 and CD22. In 50–70% cases, surface and or cytoplasmic immunoglobulins (immunoglobulin M > immunoglobulin G > immunoglobulin A) can be demonstrated.[17] DLBCL show homogeneously bright staining for CD20 showing differentiation from mature precursor B-cell until the preplasma cell.[18]

CD10 is a membrane metalloproteinase expressed in germinal centers (GCs) of secondary follicles. Majority of FLs are CD10 positive whereas DLBCL are 20–40%. CD3 is expressed by T-cell lineage and transmits the activation signal to the cytoplasm. It is an excellent marker since it is retained following neoplastic transformation. Ki67 is a proliferation marker and it defines growth fraction of actively cycling cells. In DLBCL, the expression varies from 30 to 100% and tumors with Ki 67 expression of >80% are termed as "highly proliferative" or aggressive tumors. Bcl-2 protein functions as an anti-apoptotic protein associated with worse overall prognosis according to some studies and 30–60% of DLBCL cases show its expression. Bcl-6 is selectively expressed by GCB cells in normal lymphoid tissues. Their expression in DLBCLs has been found in a majority of the cases ranging from 57% to 100%, but the biological significance of this expression is not clear. Multiple myeloma oncogene 1 (MUM1) is a lymphoid-specific member of the interferon regulatory factor family of transcription factors and is associated

with worse overall survival rate. In DLBCLs, MUM1 is expressed in 50–75% of cases and is seen both with and without Bcl-6 expression.[7]

In normal B-cell differentiation, the B-cells go through the pre- and post-GC stages (non-GCB or activated B-cell-like). Pre- germinal center B (GCB) cells are virgin B-cells while GC consists of small blast cells, centroblasts, centrocytes and occasionally plasma cells. The B-cells that leave the GC and enter the post-GC phase, differentiate either toward the memory cells or plasma cells.[15] GCB lesions express genes normally expressed by GCB cells and the non-GCB DLBCL expresses genes normally induced during *in vitro* activation of peripheral blood B cells.[19]

More than 25% of DLBCL have a translocation t (14;18) and most of them show bcl-2 with or without a translocation. Chromosomal rearrangements affecting the bcl-6 gene (regulator of germinal center formation) at 3q27 are seen in 30% of DLBCL extranodal tumors.[20] The bcl-6 inhibits lymphocyte activation by inhibiting the expression of CD69 and CD44 and inhibits differentiation of GCB-cells toward plasma cells.[21] Mutation and deletion of p53 is common in DLBCL. The bcl-6 and bcl-2 are the strongest predictors of survival.[22]

Current treatment of DLBCL usually begins with multiagent chemotherapy which includes typically cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP). More than half the patients succumb to the disease in spite of initial response to therapy. Early stage disease care involves either chemotherapy alone or a combination of chemotherapy and radiotherapy. The chemotherapy usually involves 3 cycles of CHOP.[7]

If remission is not maintained, patients are considered for bone marrow transplant. The role of surgery is severely limited in the treatment of DLBCL. For advanced stage chemotherapy, other drugs which can be used in multiagent chemotherapy usually involve various combinations of methotrexate, bleomycin, doxorubicin, vincristine, dexamethasone and leucovorin, etoposide, mechlorethamine, procarbazine and cytarabine.[7]

CONCLUSION

This case report shows that diagnosis of these tumors is difficult considering the nonspecific nature of the presenting symptoms. An accurate morphologic and immunophenotypic diagnosis is required as early as possible so that to increase the life expectancy of the patient.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mahima VG, Patil K, Raina A. Extranodal non-Hodgkin's lymphoma. An unfamiliar presentation in the oral cavity: A case report. Int J Clin Cases Invest 2010;vol1 (1) 7-12.
2. Razmpa E, Saedi B. Clinical features of extranodal presentation of non-Hodgkin's lymphoma in head and neck. Acta Med Iran 2009;47:489-92.
3. Martinez-Climent JA, Alizadeh AA, Segraves R, Blesa D, Rubio-Moscardo F, Albertson DG, *et al.* Transformation of follicular lymphoma to diffuse large cell lymphoma is associated with a heterogeneous set of DNA copy number and gene expression alterations. Blood 2003;101:3109-17.
4. Adouani A, Bouguila J, Jeblaoui Y, Ben Aicha M, Abdelali MA, Hellali M, *et al.* B-cell lymphoma of the mandible: A case report. Clin Med Oncol 2008;2:445-50.
5. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, *et al*. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: IARC Press; 2008.
6. Coiffier B. Diffuse large cell lymphoma. Curr Opin Oncol 2001;13:325-34.
7. Bhattacharyya I, Chehal HK, Cohen DM, Al-Quran SZ. Primary diffuse large B-cell lymphoma of the oral cavity: Germinal center classification. Head Neck Pathol 2010;4:181-91.
8. Ioachim LH. Ioachim's Lymph Node Pathology. 4th ed. Philadelphia: Lippincott; 2009. p. 423.
9. Eisenbud L, Sciubba J, Mir R, Sachs SA. Oral presentations in non-Hodgkin's lymphoma: A review of thirty-one cases. Part II. Fourteen cases arising in bone. Oral Surg Oral Med Oral Pathol 1984;57:272-80.
10. Barber HD, Stewart JC, Baxter WD. Non-Hodgkin's lymphoma involving the inferior alveolar canal and mental foramen: Report of a case. J Oral Maxillofac Surg 1992;50:1334-6.
11. Kemp S, Gallagher G, Kabani S, Noonan V, O'Hara C. Oral non-Hodgkin's lymphoma: Review of the literature and World Health Organization classification with reference to 40 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008;105:194-201.
12. Maeshima AM, Omatsu M, Nomoto J, Maruyama D, Kim SW, Watanabe T, *et al.* Diffuse large B-cell lymphoma after transformation from low-grade follicular lymphoma: Morphological, immunohistochemical, and FISH analyses. Cancer Sci 2008;99:1760-8.
13. Harris NL, Swerdlow S, Jaffe E. Follicular lymphoma. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H, editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Systems. 4th ed. Lyon: IARC; 2008. p. 220-8.

14. Dominis M, Dzebro S, Gasparov S, Pesut A, Kusec R. Diffuse large B-cell lymphoma and its variants. Croat Med J 2002;43:535-40.
15. Hsi ED, Yegappan S. Lymphoma immunophenotyping: A new era in paraffin-section immunohistochemistry. Adv Anat Pathol 2001;8:218-39.
16. de Leval L, Harris NL. Variability in immunophenotype in diffuse large B-cell lymphoma and its clinical relevance. Histopathology 2003;43:509-28.
17. Jaffe ES. Pathology and Genetics of Tumours of Hematopoietic and Lymphoid Tissues. Lyon: IARC Press; 2001. p. 172-3.
18. Chang KL, Arber DA, Weiss LM. CD20: A review. Appl Immunohistochem 1996;4:1-15.
19. Lin AY, Tucker MA. Epidemiology of Hodgkin's disease and non-Hodgkin's lymphoma. In: Canellos GP, Lister TA, Sklar JL, editors. The Lymphomas. 1st ed. Philadelphia: Saunders; 1998. p. 43-60.
20. Niu H. The proto-oncogene BCL-6 in normal and malignant B cell development. Hematol Oncol 2002;20:155-66.
21. Dent AL, Vasanwala FH, Toney LM. Regulation of gene expression by the proto-oncogene BCL-6. Crit Rev Oncol Hematol 2002;41:1-9.
22. Lossos IS, Czerwinski DK, Alizadeh AA, Wechser MA, Tibshirani R, Botstein D, *et al.* Prediction of survival in diffuse large-B-cell lymphoma based on the expression of six genes. N Engl J Med 2004;350:1828-37.