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Evaluation of Immunohistochemical Expression of C-MYC, BCL2, and BCL6 in High Grade B-cell Lymphoma

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ABSTRACT

Background: High-grade B-cell lymphoma (HGBCL) is characterized by chromosomal rearrangements involving specific oncogenes. The most commonly identified oncogenes in B-cell lymphomas are MYC, BCL2, and BCL6. Translocations involving these genes are associated with aggressive tumor behavior and poor clinical outcomes. In these lymphomas, the MYC gene is involved in one rearrangement, while BCL2 and, less commonly, BCL6 participate in additional rearrangements.
Objectives: To evaluate the immunohistochemical expression of C-MYC, BCL2, and BCL6 markers in HGBCL cases, as well as to determine the percentage of double-hit and triple-hit lymphoma among HGBCL cases.
Materials and methods: Immunohistochemical investigations were conducted for biopsies of 70 selected cases of HGBCL, using the three markers of C-MYC, BCL2, and BCL6. Also, CD20 in conjunction with CD3 was performed for all cases to confirm their B-cell origin.
Results: Out of 70 HGBCL patients, C-MYC alteration was expressed in 41% of cases. Eighty-three percent of them expressed BCL2, whereas BCL6 was expressed in 64% of cases. Conversely the double expression of C-MYC/BCL2 was established in 3 cases only (2.1%), while the C-MYC/BCL6 expression was found in 6 cases (4.2%). Most cases of double-hit lymphoma (MYC/BCL2 and MYC/BCL6) occurred in males (67% and 83%, respectively), whereas triple-hit cases were more common in females (61.1%).
Conclusion: Regular evaluation of C-MYC, BCL2, and BCL6 expression by immunohistochemistry is fundamental for pathological assessment, risk stratification, and therapeutic planning for affected patients.
Keywords: High grade B-cell lymphoma; Double hit lymphoma, Triple hit lymphoma.

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INTRODUCTION

Lymphoma is a diverse group that includes malignant neoplasms that impact lymphocytes, each characterized by distinct clinical behaviors and treatment responses. The prognosis depends on histological type, clinical variables, and, more recently, molecular attributes [1]. Large B-cell lymphomas encompass a wide array of tumors. Typically, it consists of medium to large cells with round to avoid nuclei and vesicular chromatin; nevertheless, instances with intermediate-sized and blastoid cells may also qualify that category [2].

The predominant subtype of non-Hodgkin lymphoma (NHL), which constitutes about 40% of them, is diffuse large B-cell lymphoma (DLBCL) [3]. This category is typically aggressive and encompasses a diverse array of biologically different entities that lead to the clonal expansion of malignant B-cells, either of germinal or post-germinal origin [3]. Previous radiation therapy, familial history of hematological malignancies, autoimmune disorders, history of organ transplantation, treatment with immunosuppressive medications, obesity, tobacco use, viral infections, human herpesvirus 8, occupational chemical exposure, and vitamin D deficiency are all significantly associated with DLBCL [4].

The overall 5 years survival of DLBCL is bad and has a poorer prognosis compared to Burkitt lymphoma (BL) [3]. Two unique molecular subtypes of DLBCL have been identified by gene expression profiling: the germinal center B-cell-like (GCB) subtype and the activated B-cell-like (ABC) subtype, with 10-15% of cases remaining not classified yet [4]. ABC subtype exhibiting a poorer prognosis (3-years survival

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rate of roughly 40-50%, compared to approximately 75% for the GCB subtype) [4]. In 2004, Hans et al. categorized DLBCL into germinal center B-cell (GCB) and non-GCB subtypes utilizing cDNA (deoxyribonucleic acid) microarray data and three antibodies: cluster of differentiation 10 (CD10), polyclonal B cell lymphoma 6 (BCL6), and multiple myeloma oncogene 1 (MUM1) [5]. The WHO classification was revised in 2016, recognizing GCB and ABC as distinct molecular subtypes of DLBCL. A new entity known as high-grade B-cell lymphoma (HGBCL) has been inserted [6]. HGBCL is mostly characterized by C-MYC, BCL2, and/or BCL6 rearrangements, referred to as double-hit lymphoma (DHL) or triple-hit lymphoma (THL) [7].

C-MYC gene, a proto-oncogene, represents a type of gene that is most often associated with human tumorigenesis. The C-MYC gene was first recognized in 1978. C-MYC coordinates various cellular activities, including the cell developmental process, division, lifespan, metabolism, biosynthesis, adherence, and mitochondrial function [8]. MYC rearrangement in DLBCL is associated with diminished cancer-free survival and long-term survival in individuals receiving R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) therapy. C-MYC amplifications, as opposed to C-MYC gains, are linked to a worse prognosis [8].

BL is a mature B-cell lymphoma with a high proliferation rate, which characterizes this category. Unlike B-lymphomas that primarily affect lymph nodes, BL predominantly targets extranodal areas [8]. BL originates from germinal center or post-germinal center B-cells. The BL cells exhibit expression of germinal center B-cell markers, including CD10 and BCL6, while generally being negative for BCL2 [8]. The determination of C-MYC gene transposition and C-MYC protein generation is crucial for HGBCL assessment and prediction [8]. Applying immunohistochemical (IHC) staining for C-MYC expression is crucial for detecting the outcome in DLBCL, particularly in cases exhibiting co-expression of C-MYC and BCL2, referred to (DHL) [8]. C-MYC expressions can be considered positive if more than 40% of the lymphoma cells exhibit maculation [8]. It is a significant proto-oncogenic transcription factor for the development of germinal center B cells [9].

BCL6 interacts with and inhibits genes involved in the DNA damage response, regulation of cell cycle checkpoints, and genes implicated in germinal center exit and plasma cell differentiation [10]. BCL6 expressions associated with an unfavorable survival outcome [11]. BCL2 protein is not expressed in BL or normal GCB cells; however, it can be found in more than 50% of DLBCLs and roughly 75% of HGBLs. Overexpressing cells need to undergo additional genetic changes before they may form overt lymphoma. BCL2's main job is to keep cells alive by preventing them from dying [12], and its principal role is to enhance cell viability by suppressing apoptosis [13]. BCL2 expression in BL is usually negative or weak expression in up to 20% of cases [14].

Accordingly, the C-MYC, BCL6, and BCL2 mutations have significant effects on the treatment and prognosis of HGBCL patients, and due to the lack of relevant local research in our city (Nineveh province, Iraq), we conducted this study to evaluate the frequency of C-MYC, BCL6, and BCL2 IHC expression in HGBCL and the relationship between IHC expression and variable demographic and clinicopathological parameters such as age of the patients, sex, site, and histopathological types.

MATERIALS AND METHODS

This retrospective case series study was approved by the Ethics Committee of the Nineveh Health Directorate Training and Development Center, Ministry of Health, Iraq, (protocol number 2024146 issued on October 8, 2024). Seventy cases of HGBCL were assembled over the period from September 2024 to February 2025. These cases were gathered from the labs of Al-Jumhori Teaching Hospital and Al Salam Teaching Hospital in Nineveh, Mosul, north of Iraq.

Information concerning the age of the patients, sex, and tumor locations was gathered from hospital records. Sections of 4-micron thickness were cut from the paraffin blocks of each case and stained with hematoxylin and eosin (H & E) for revision to demonstrate the histological type. Cases with sufficient tissue and high tumor density, regardless of patient age, sex or biopsy site, were included in this study. On the contrary, cases that lack information and those with less tumor material, significant necrosis, or poorly preserved specimens were excluded. The evaluated patients received classification using the Modified Ann Arbour staging system for lymphoma [15].

We calculated the required sample size according to the Stephen Thompson equation in the IBM-Statistical Package for Social Studies (SPSS) for Windows version 26. According to the Iraqi Cancer registry 2023, non-Hodgkin lymphoma prevalence in Nineveh province, Iraq, was 4.2 per 100,000 (https://storage.moh.gov.iq/2024/11/24/2024_11_24_12127028949_4299728097670824.pdf). Assuming that the error rate is (0.05), then the required sample size (n) will be approximately 150 cases; this number is applied for all NHL cases. In the present study, only DLBCL and BL cases were included, which constitute 30-40% of all NHL cases [3]. Then the required sample size (for DLBCL and BL) was 60 cases. The sample size was increased to 70 cases to increase the validity of the current investigation.

Tissue sections with 4-micron thickness were made from the paraffin blocks of each specimen and affixed to positively charged slides. After routine antigen retrieval an IHC study was performed using an automated IHC stainer (Autostainer, Dako Cytomation, USA). A rabbit monoclonal (anti-human C-MYC Vitro, Master Diagnostics, Clone (Y69), code (MAD-000487QD)) for C-MYC. A mouse monoclonal antibody (antihuman BCL6 protein clone PG-B6p code IR625, antihuman BCL2 Protein Clone 124, code IR614) was used as the primary antibody for BCL6 and BCL2, respectively, with a dilution of 1:10-1:20. The results were assessed manually by a list of markers for IHC study, including C-MYC, BCL2, and BCL6. Also, for scoring DH and TH expressions. The cutoffs for C-MYC, BCL2, and BCL6 positivity were 40, 50, and 30%, respectively. Nuclear staining was considered positive, and a minimum of 500 malignant cells were evaluated to determine the quantity of positive malignant cells [16].

Statistical analysis was completed using the Windows version of IBM-SPSS (Statistical Package for the Social Sciences) version 26 (IMB Inc., Armonk, NY, USA). The expressions of C-MYC, BCL6, and BCL2 and the categorical variables were presented in tables as frequencies and percentages. To ascertain statistically significant differences among continuous variables, we used Fisher's exact test, which were expressed in numbers. Statistically significant events had a P-value < 0.05.

RESULTS

Out of 70 cases of HGBCL. 64 (91.4%) of cases were DLBCL (Figure 1). Their ages ranged from 5 to 88 years (46.5 ± 24) as shown in (Figure 2). Thirty-eight patients (54.3%) were males, and thirty-two (45.7%) were females, with a male to female ratio of 1:0.84. Based on the tumor's location, 17 (24.3%) non-specific lymph nodes, 24 (34.4%) abdominal, 10 (14.3%) mediastinal, 5 (7.1%) supraclavicular, 5 (7.1%) inguinal, and 5 (7.1%) submandibular and axillary 4(5.7%).

Among the evaluated cases, C-MYC was positive in 29 of them (41%). While 58 cases (83%) were positive for BCL2, and 45 cases (64%) were positive for BCL6. Eighteen cases (12.6%) had triple positive expressions of the studied markers (C-MYC, BCL-2, and BCL-6), whereas only 3 cases (2.1%) showed C-MYC and BCL-2 positive expressions, and 6 cases (4.2%) showed C-MYC and BCL6 expressions. On the other hand, only 3 cases (2.1%) were triple negative for these markers. However, when considering the expression of each marker separately in the studied cases. C-MYC was expressed in 23 (79%) of DLBCL and 6 (21%) of BL, Bcl2 was expressed in 57 (98%) of DLBCL & 1 (2%) of Burkitt lymphoma, and Bcl6 was expressed in 39 (87%) of DLBCL & 6 (13%) of Burkitt lymphoma, with significant P-value (P-value = 0.001). The cases show an insignificant association with age and sex related distributions of these markers. Also, it is noticed that 16 (55%) of C MYC positive cases show nodal disease; however, it didn't reach the significance value (P-value = 0.428), whereas both Bcl2 (62%) and Bcl6 (67%) show significant nodal disease (P-values = 0.007 and 0.001, respectively) as indicated in Table 1.

Eighteen cases showed triple expression of C-MYC/BCL2/BCL6, 94% were DLBCL, and 6% were BL (P-value = 0.0001). Fifty-six (56%) of them were above sixty with no significant P-value (P-value = 0.740). Regarding the patient's sex, males accounted for 39% of cases, while female accounted for 61% (P-value = 0.318). Triple positive lymphoma cases were predominantly nodal (61%) in comparison with extra nodal disease (39%); however, the P-value was insignificant (P-value = 0.318) as shown in Table 2.

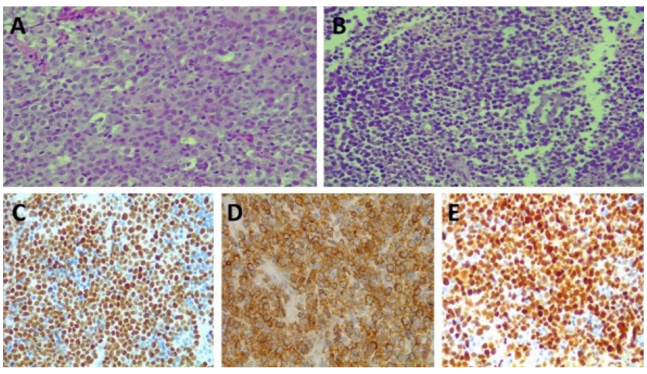

Figure 1. A: Diffuse large B-cell lymphoma (H&E) X400. B: Burkitt lymphoma (H&E) X400. C: C-MYC with positive nuclear staining (X400). D: BCL2 with positive cytoplasmic and membranous staining (X400). E: BCL6 with positive nuclear staining (X400).

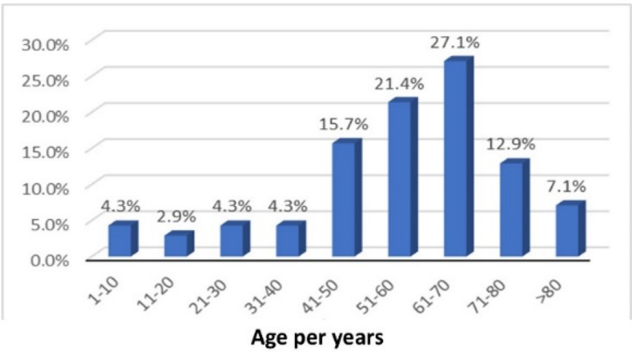

Figure 2. Distribution of 70 cases of high-grade B-cell lymphoma according to age groups.

DISCUSSION

HGBCL was isolated as a separate group in the latest WHO classification of hematological neoplasms, as they have a particular prognostic and therapeutic value. DLBCL performs the most common incident subtype of NHL worldwide, accounting for more than one third of cases. DLBCL comprises a heterogeneous collection of morphologically analogous lymphomas exhibiting a wide range of prognosis [17]. Many genetic changes have been described in HGBCL; among them recurring gene abnormalities that characterize a particularly aggressive disease entity, i.e. MYC (8q24), in addition to other markers, BCL2 (18q21), and/or BCL6 (3q27) gene relocations [17]. IHC staining was used in this study to evaluate the expression of C-MYC, BCL2, and BCL6 proteins in DLBCL and BL cases. Translocation of C-MYC has been associated with aggressive lymphomas and poor outcome in B-cell malignancies, since it facilitates cell cycle progression and tumor proliferation in DLBCL. In addition, C-MYC is the defining characteristic of BL [18]. This study has the same feature of 70 cases; all BL patients that are (6 cases) are positive for C-MYC protein. BCL6 promotes the malignant phenotype by inhibiting proliferation and DNA damage checkpoints, as well as obstructing B-cell terminal differentiation [19]. In the current study, BCL6 expression was associated with patients younger than 60 years. These findings were conducted concurrently with another investigation done by Mahmoud and Elsakhawy in Egypt, in which BCL6 positive instances were substantially correlated with patients under 45 years of age [20]. The Bcl-2 protein serves as an anti-apoptotic factor crucial for the proper growth and differentiation of B-cells. Overexpression of Bcl-2 confers a survival benefit to malignant B-cells and is believed to be pivotal in conferring resistance to chemotherapy [20]. According to the age group, the BCL2 expression is higher in the fifth decade. These results are similar to the results found by Holmqvist et al. which was done in south-east Sweden, in which BCL2 expression is higher in the fifth decade in other decades [21]. Identifying the co-existence of concurrent rearrangements of MYC, BCL2, and/or BCL6 is essential for diagnosing DHL and THL [22]. DHL cannot be considered a diagnosis defined in the WHO classification; it is a common term for a large B-cell lymphoma characterized by translocations. According to this definition, 2-12% of DLBCL (with most research indicating 6%) and 32%-78% of BL are classified as DHL [23]. In a recent study, 2.1% of cases had a double expression of

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Table 1. The relationship between C-MYC, BCL2, and BCL6 expressions and demographic and clinical parameters*.

Variables	C-MYC		BCL2		BCL6	
	n (%)	P-value	n (%)	P-value	n (%)	P-value
Age						
≤ 60	16 (0.55)	0.428	30 (0.52)	0.710	23 (0.51)	0.833
> 60	13 (0.45)		28 (0.48)		22 (0.49)	
Sex						
Male	16 (0.55)	0.428	29 (0.50)	1.000	24 (0.53)	0.526
Female	13 (0.45)		29 (0.50)		21 (0.47)	
Type						
DLBCL*	23 (0.79)	0.001	57 (0.98)	0.001	39 (0.87)	0.001
BL**	6 (0.21)		1 (0.02)		6 (0.13)	
Site						
Nodal	16 (0.55)	0.428	36 (0.62)	0.007	30 (0.67)	0.001
Extra-nodal	13 (0.45)		22 (0.38)		15 (0.33)	

* Fisher's exact test, *Diffuse Large B-cell Lymphoma **Burkitt Lymphoma.

Table 2. Relationship between triple and double expressor and demographic and clinical parameters*.

Variables	Triple hit lymphoma (C-MYC/BCL2/BCL6)		Double expressor lymphoma (C-MYC/BCL2)		Double expressor lymphoma (C-MYC/BCL6)	
	n (%)	P-value	n (%)	P-value	n (%)	P-value
Age						
≤ 60	8(0.44)	0.740	2(0.67)	1.000	5(0.83)	0.080
> 60	10(0.56)		1(0.33)		1(0.17)	
Sex						
Male	7(0.39)	0.318	2(0.67)	1.000	5(0.83)	0.080
Female	11(0.61)		1(0.33)		1(0.17)	
Type						
DLBCL*	17(0.94)	0.0001	3(1.00)	- - - - -	1(0.17)	0.080
BL**	1(0.06)		0(0)		5(0.83)	
Site						
Nodal	11(0.61)	0.318	2(0.67)	1.000	3(0.50)	1.000
Extra-nodal	7(0.39)		1(0.33)		3(0.50)	

* Fisher's exact test, *Diffuse Large B-cell Lymphoma **Burkitt Lymphoma.

C-MYC and BCL2; all of them were DLBCL. Whereas 4.2% of cases with double expression of C-MYC and BCL6, 83.4% of them were BL, and 17% were DLBCL. These results were similar to the results mentioned above by Swerdlow [23]. C-MYC, when combined with BCL2 and BCL6 rearrangements, is categorized as THL [24], which constitutes 21% of cases in the study done by Riedell and Smith [25]. These results were closely similar to the current study where THL constitutes about 25.7% of cases.

DHL patients frequently exhibit aggressive clinical criteria like male preponderance, average patient age around 60s, higher lactate dehydrogenase (LDH) values, extra-nodal disease, and high-risk IPI scores [25]. According to these criteria, this study revealed an aggressive characteristic represented by male predominance and old age.

In this study, the double expressor MYC/BCL2 occurs in the fifth and sixth decades. Huang et al. observed that the double expression of MYC/BCL2 has an aggressive clinical course is associated with poor prognosis and occurs most often in the old age group, in contrast to the double expression of MYC/BCL6, which correlates with better prognosis [16]. Concerning THL patients in this study, 29% of cases were between 60-70 years. And approximately 58.6% of cases were above the age of 60s. The same results were found by Huang et al., in which 50% of cases were above 60s [16]. Tsai et al. conclude that THL patients are found to be older i.e. > 60 years [17]. A possible explanation for the discrepancy is due to the difference in patient selection.

Concerning to sex, in this study there were male predominance in DHL. Huang et al. observed that the double expression of MYC/BCL2 has male predominance [16]. Same results were concluded by Lue et al. with male predominance [26]. Mehta et al concluded the same results [27]. While according to THL, in our study females constitutes 61% of the cases and males constitutes only 39% of all THL cases. Huang et al. found that 57.5% of patients were males [16]. However, Tsai et al. found equal occurrence between males and females [17]. Strüßmann et al. founds that the females had more predominance. This variation in results may be due to the environmental influence of the region [28].

According to the site of lymphoma, the nodal and extra nodal sites show no significant difference in THL, DHL (P-value = 0.318), and BCL6 (P-value = 1.000) respectively. While BCL2 and BCL6 separately show significant differences (P-value = 0.007), and (P-value = 0.001) respectively. Similar results were found by Salam et al, in which significant differences were detected in the BCL2 cases, but not for the BCL6. Despite this, nodal sites had more BCL6 gene abnormalities than extra nodal sites [18]. The behavioral changes of the cell types from the places where they originate could easily account for the variances [18].

This study has several limitations. Firstly, due to the type of study (retrospective study design) there was a selection bias, cases included depend on available archived samples and complete records. Secondly, a single-center study, that may not accurately represent population trends. Lastly, the availability of cases, tissue insufficiency, and necrosis because of out-of-date.

CONCLUSION

Evaluating the IHC expression of C-MYC, BCL2, and BCL6 markers in HGBCL cases offers essential discernment into the molecular characteristics and hesitancy of these aggressive neoplasms. Through systematic evaluation of these markers, we can recognize the subgroup of patients that fulfil the criteria for DHL and THL, which exhibit unique clinical behaviors and prognosis. Assessing the prevalence of DHL and THL facilitates precise categorization and has significant implications for directing focused treatment approaches and predicting patient prognosis.

ETHICAL DECLARATIONS

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Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the Nineveh Health Directorate Training and Development Center, Ministry of Health, Iraq, (protocol number 2024146 issued on October 8, 2024). Informed consent was waived because we worked on paraffin blocks.

Consent for Publication

Not applicable (No personal information was published).

Availability of Data and Material

The data generated and analyzed during this study are available from the authors upon reasonable request.

Competing Interests

The authors declare that there is no conflict of interest.

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Use of Artificial Intelligence

Artificial intelligence has been used in limited ways to correct spelling, grammar, and punctuation, as well as to edit specific texts.

Authors' Contributions

Hanna RS analyzed data and wrote the manuscript. Kachachi MSF provided expertise about laboratory data; Al-Omar ZMS supervised the research study and edited the manuscript. All authors have approved the final version of the manuscript.

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