The Utility of CD10 and MUM1 Immunohistochemical Stains in Subtyping Diffuse Large B Cell Lymphoma

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Abstract

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma in the world. It is divided into two important prognostic categories, germinal centre B cell (GCB) and non-germinal centre B cell (non-GCB) subtypes according to the cell of origin. **Objectives:** In this study, we aimed to determine the frequency of each subtype of DLBCL using a modified Hans algorithm in addition to the association of CD10 and MUM1 immunohistochemical expression with clinicopathological parameters (age, sex, type of specimen (nodal or extranodal) in Ninevah Province (Iraq). **Methods:** A retrospective and prospective case series study of 61 cases of DLBCL which were collected from histopathological departments of governmental and private labs over 10 months extending from November 2022 to August 2023. DLBCL subtypes (GCB and non-GCB/ABC) were assessed based on immunohistochemical expressions of CD10 and MUM1. **Results:** A total of 61 patients, (59%) were non-GCB, while (41%) were GCB subtypes. Thirty-four (55.7%) cases were male, whereas twenty-seven (44.3%) were female. The median age was (61 years), 44 (72.1%) cases were nodal and 17 (27.9%) were extranodal primary sites. There is a significant inverse relation between CD10 and MUM1 expression (p-value 0.02). **Conclusions:** In the Ninevah population, there was a high frequency of unfavourable prognostic markers that included a predominance of non-GCB/ ABC DLBCL. It is necessary to investigate more since it represents high-risk subsets for whom different approaches to diagnosis and treatment should be considered. The significant inverse relation between CD10 and MUM1 supports the Modified Hans algorithm in subtyping DLBCL.

Keywords: CD10, MUM1, Diffuse Large B Cell Lymphoma, Modified Hans Algorithm.

Introduction

Non-Hodgkin's lymphoma (NHL) is the prevailing form of blood cancer globally, encompassing a wide range of abnormal cell growth in B and T cells.[1] Diffuse large B-cell lymphoma (DLBCL) is the most common and aggressive subtype of non-Hodgkin lymphoma (NHL), making up approximately 30%–40% of all cases. DLBCL is a diverse collection of diseases that vary in terms of their biology, clinical presentation, and response to treatment. It signifies the rapid growth of a cancerous B cell that originates from a germinal or post-germinal stage. The prevalence of DLBCL is around 6 cases per 100,000 individuals per year in the United States and 3.8 cases per 100,000 individuals per year in Europe.[2] The onset of this condition typically occurs during the sixth decade of life, with a higher prevalence among males. However, it is possible to detect this condition at any age. Increased risk of diffuse large B-cell lymphoma (DLBCL) is associated with autoimmune disorders that activate B-cells, testing positive for hepatitis C, having a family history of non-Hodgkin lymphoma (NHL), and having a high body mass index (BMI) during young adulthood.[3] DLBCL can be categorised into three molecular subtypes using gene expression profiling (GEP): germinal centre B cells (GCB), activated B cells (ABC), and unclassified (~10%). These subtypes exhibit a wide difference in patient survival.[4] Microarray investigation has revealed that patients with DLBCL who exhibit a gene expression profile (GEP) of germinal centre B-cell (GCB) have a more extended survival period compared to those with a GEP of activated B-cell (ABC).[5] These subtypes are believed to originate from distinct stages of lymphoid development, depending on independent cancer-causing pathways. The ABC subtype is associated with a poorer result, with a 3-year progression-free survival rate of approximately 40 to 50%, compared to 75% for the GCB subtype.

The relative frequency of the GCB and ABC subtypes, which are typically around 60% and 40% respectively, is influenced

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by factors such as geographical location, median age of the patient group, and the procedures used. The GCB subtype is less prevalent in Asian countries.[6] Immunohistochemistry (IHC) analysis has becoming more widely used in clinical practice as a replacement for gene expression profiling (GEP). This is because GEP investigations are sometimes time-consuming, costly, and rely on the availability of freshly frozen tissue samples, which are not commonly accessible.[7] The classification of DLBCL into GCB and non-GCB subtypes was achieved through the utilisation of the Hans algorithm. This algorithm was developed based on an immunohistochemical panel that included CD10 (a marker for GCB subtype), BCL6 (related with both GCB and ABC subtypes), and MUM1 (a marker for post germinal centre stage). Despite the existence of alternative algorithms, the Hans algorithm remains the predominant choice.[8,9] Several research attempted to eliminate BCL6 and developed a modified Hans algorithm. This modified algorithm shown a strong agreement with the microarray data, similar to the original methods. For instance, certain institutes in Malaysia only utilise two antibodies, namely CD10 and MUM1.[10] The performance of BCL6 is typically challenging due to its technical complexity, leading to difficulties in interpretation.[11] CD10, also known as a cluster of Differentiation, is an enzyme located on the surface of cells that requires zinc and functions by breaking down signalling peptides. It has been detected in several hematopoietic cells, as well as in a wide variety of non-hematopoietic cells and cancerous tissues.[12] MUM1, also known as interferon regulatory factor 4 protein, belongs to the family of transcriptional factors called interferon regulatory factors (IRFs). It has a crucial role in controlling multiple stages of lymphoid, myeloid, and dendritic cell development. The presence of this gene has been identified in cancerous growths of these specific tissues.[13]

The classification significantly influences the outcome as GCB types have a more favourable prognosis compared to non-GCB kinds. Additionally, it is beneficial for evaluating the result of the treatment. This study seeks to ascertain the prevalence of germinal centre B-cell (GCB) and non-GCB subtypes using a modified Hans algorithm. The algorithm relies on the immunohistochemical expression of CD10 and MUM1 in the Iraqi population of Ninevah Province. Additionally, the study aims to explore the correlation between these markers and clinicopathological characteristics.

Materials and Methods

Patients' selection: This current study registered all patients confirmed as DLBCL at governmental institutions and those referred from private laboratories in Ninevah Province (Iraq) over a 10-month period from November 2022 to August 2023. The study has a total of 61 instances of DLBCL. The clinicopathological data, including age, gender, and site, were thoroughly examined by reviewing all histopathology reports. We examined the hematoxylin and eosin-stained sections for each instance, and all cases showed positive results for CD20 (Figure 1). The cancer was diagnosed using the 2017 classification system established by the World Health Organisation.[6] For the immunohistochemistry research, two sections were chosen from each instance.

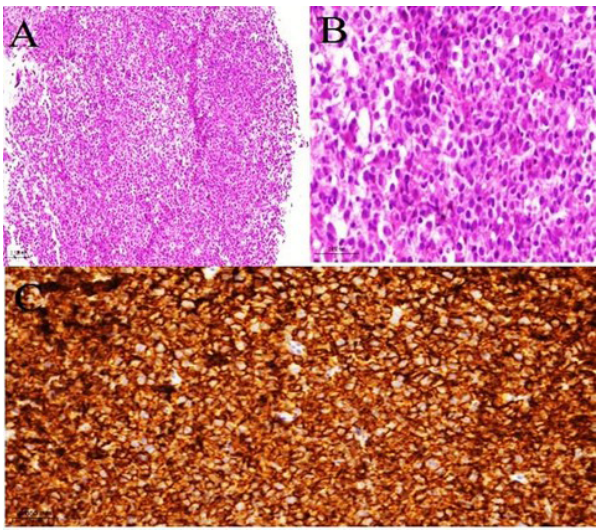

Figure 1: DLBCL (A) (H&E) X100 (B) (H&E) X 400 (C) Positive CD20 (IHC X 200).

Immunohistochemistry is a technique used to detect specific proteins or antigens in tissue samples by using antibodies that bind to the target molecules. We obtained formalin-fixed paraffin-embedded blocks of cases. Sections with a thickness of 4 microns were treated with xylene to remove paraffin and then rehydrated.[14-16] The immunohistochemistry investigation was conducted in accordance with the directions provided by the manufacturer. Heat-based methods for antigen retrieval were employed. The sections were immersed in a pressure cooker containing a solution of 10 mmol/L Tris buffer, 1 mmol/L EDTA, and pH 9.0. The immersion lasted for three minutes, once the cooker reached the desired temperature and pressure. Subsequently, the inherent peroxidase activity was inhibited using a 3% solution of hydrogen peroxide (H2O2). The sections were treated with primary antibodies, namely Monoclonal Mouse Anti-Human CD10 and MUM1 Protein from DAKO USA, both diluted at a ratio of 1:50. The incubation took place at room temperature for one hour. The primary antibody was detected using a Horseradish peroxidase (HRP) polymer solution from the DAKO Real Envision Detection System. External control tissue consisted of tonsils exhibiting reactive lymphoid hyperplasia.

Evaluation of CD10 and MUM1 expression: A positive outcome was determined by assessing the presence of CD10 and MUM1 staining in 30% of non-necrotic malignant B-lymphoid cells. Conversely, if less than 30% of the non-necrotic tissue showed staining, it was declared negative.[17] The lymphoma cases were categorised into two groups depending on the cell of origin using the modified Hans algorithm (Figure 2).[11] Transform into either germinal centre B cells or non-germinal centre B cells. Considering that CD10 is indicative of germinal centre B cells and MUM1 represents the advanced stages of B cell development outside the germinal centre, the cases were categorised into the GCB group if they were either positive for CD10 or negative for both CD10 and MUM1. Conversely, the cases were categorised as

the non-GCB subgroup based on the absence of CD10 and the presence of MUM1.

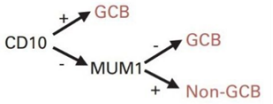

Figure 2: Decision Algorithm Modified Hans Algorithm[11]

The data acquired underwent analysis using the computer programme (SPSS) version 26. Demographic variables were summarised using descriptive statistics. The Fisher Exact test and Chi-square test were employed to assess the connections between different tumour classifications. A p-value of 0.05 or lower was considered statistically significant.

Results

During the study period, a total of 61 cases of DLBCL were included. The age of patients ranged from 5 to 93 years with mean (55 years), median (61 years) and the most frequent age group was (60-69) years. There were 34 (55.7%) males and 27 (44.3%) females. Forty-four cases (72.1%) were of nodal presentation while 17cases (27.9%) were extranodal sites, the most frequent site was cervical LN in 15 cases(34.1%) while among the extra-nodal presentation, the most frequent site was tonsil in 4 (23.5%) (Table 1). In this study, CD10 was positive in 13 cases while 48 cases showed negative CD10. MUM1 was positive in 41 cases and negative in 20 cases (Table 2). The results of CD10 and MUM1stratifiy the cases, according to the Modified Hans algorithm into two prognostic groups: Non-GCB/ABC in 36 cases(59%) and GCB in 25 cases(41%) (Table 3)(Figure 3).

Table 1: Distribution of the Study Sample According to the Sites.

	Presentation	Frequency	Percentage
Nodal presentation (n=44; 72.1%)	Cervical LN	15	34.1
	Multiple group	6	13.6
	Axillary LN	4	9.0
	Inguinal LN	4	9.0
	Intra-abdominal LN	4	9.0
	Para-aortic LN	4	9.0
	Mediastinal LN	2	4.5
	Iliac LN	2	4.5
	Lt. supra clavicular LN	1	2.3
	Lingual and parotid LN	1	2.3
	Submandibular LN	1	2.3
Extra-nodal presentation (n=17; 27.9%)	Tonsillar mass	4	23.5
	Adrenal mass	3	17.6
	Chest wall mass	2	11.8
	Extra-spinal tumor	1	5.9
	Pelvic bony mass	1	5.9
	Right sided nasal mass	1	5.9
	Rt. Fronto ethmoidal sinus mass	1	5.9
	Rt. thigh mass	1	5.9
	Spinal extradural mass	1	5.9
	Spleen biopsy	1	5.9
	Testicular mass	1	5.9

Table 2: The Results of CD10 and MUM1 IHC Markers.

		Expression	Total	
			No.	%
IHC	CD10	Positive	13	21.3
		Negative	48	78.7
	MUM1	Positive	41	67.2
		Negative	20	32.8

Table 3: Prognostic Groups.

Prognostic Groups	Immunophenotype	Number (%)
GCB	(CD10+)	13(52%)
(n:25)	(CD10-, MUM1-)	12(48%)
Non-GCB (n: 36)	(CD10-, MUM1+)	36(100%)

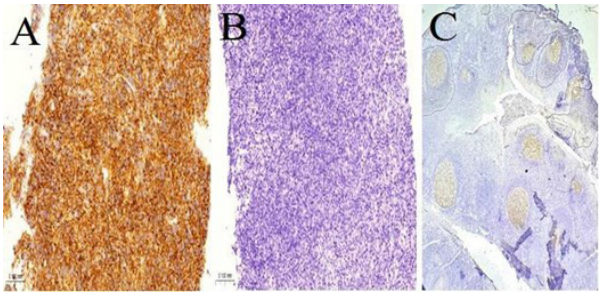

Figure 3: (A) DLBCL with Positive CD10 (IHCX100). (B) DLBCL with Negative CD10 (IHCX100). (C) CD10 Positive Control (IHCX40).

The Non GCB/ABC group was (MUM-, CD10-) in 36 cases(100%)

While the GCB group include 13 cases (52%) that were (CD10+) and 12 cases (48%) that were (CD10-, MUM1-) (Table 3).

A comparison of the study parameters between GCB and non-GCB groups was demonstrated in Table (4) and revealed that in both GCB and non-GCB groups, the patients with age >60 years were more frequent; the difference was statistically not significant. Males were predominant in both groups representing (60%) and (52.7%) respectively with no statistically significant difference about females. Nodal and extra-nodal presentations showed no statistically significant difference between the study groups although the nodal was more frequent. In this study, CD10 was positive in 13 patients while 48 patients showed negative CD10. MUM1 was positive in 41 patients and negative in 20 patients (Table 3). Comparison of the study parameters in relation to CD10, and MUM1 were demonstrated in Table 5 and Table 6. These tables elicited no statistically significant difference between the positive and negative CD10, and MUM1 concerning age, gender and presentations. Comparison of CD10 with MUM1 was demonstrated in Table 7 and revealed that among the CD10+ group, 5 (38.5%) showed positive MUM1 staining and 8(61.5%) showed negative MUM1 staining, while among the CD10- group, 36 (75%) showed positive MUM1 and 12 (25%) were MUM1 negative; the difference between positive and negative MUM1 in relation to CD10 was statistically significant (p=0.02) (Figure 4).

Table 4: Comparison of the Study Parameters between GCB and Non-GCB Groups.

		GCB (n=25)		Non-GCB (n=36)		p-value
		No.	%	No.	%	
Age	< 60years	12	48	16	44.4	0.784*
	≥ 60 years	13	52	20	55.5	
Gender	Males	15	60	19	52.7	0.576*
	Females	10	40	17	47.2	
Presentation	Nodal	18	72	26	72.7	0.984**
	Extra nodal	7	28	10	27.7	

*Chi square test has been used; ** Fisher Exact test

Table 5: Comparison of the Study Parameters in Relation to CD10.

		CD10				p-value
		Positive (n=13)		Negative (n=48)		
		No.	%	No.	%	
Age	< 60 years	5	38.5	23	47.9	0.544*
	≥ 60 years	8	61.5	25	52.1	
Gender	Males	9	69.2	25	52.1	0.270*
	Females	4	30.8	23	47.9	
Presentation	Nodal	9	69.2	35	72.9	1.000**
	Extra nodal	4	30.8	13	27.1	

*Chi square test has been used; ** Fisher Exact test

Table 6: Comparison of the Study Parameters in Relation to MUM1.

		MUM1				p value*
		Positive (n=41)		Negative (n=20)		
		No.	%	No.	%	
Age	< 60 years	18	43.9	10	50	0.654*
	≥ 60 years	23	56.1	10	50	
Gender	Males	24	58.5	10	50	0.529*
	Females	17	41.5	10	50	
Presentation	Nodal	29	70.7	15	75	0.727*
	Extra nodal	12	29.3	5	25	

*Chi square test has been used

Table 7: Comparison of CD10 with MUM1 Marker.

		CD10				p-value
		Positive (n=13)		Negative (n=48)		
		No.	%	No.	%	
MUM1	Positive	5	38.5	36	75.0	0.02**
	Negative	8	61.5	12	25.0	

* Chi square test has been used; ** Fisher Exact test

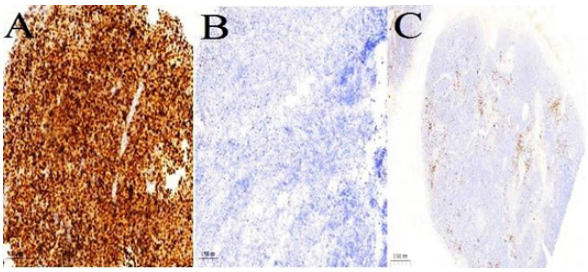

Figure 4. (A) DLBCL with Positive MUM1 (IHCX100). (B) DLBCL with Negative MUM1 (IHCX100). (C) MUM1 Positive Control (IHCX 20).

Discussion

Diffuse large B-cell lymphoma (DLBCL) is a diverse disease with a variety of biochemical, clinical, and treatment-responsive features. Several prediction models have been proposed to categorise DLBCL prognosis due to these reasons.[18] Several efficacious algorithms utilising immunohistochemistry have been developed to facilitate subtype classification.[11] In this investigation, we employed the modified Hans algorithm to classify patients as GCB or non-GCB based on the detection of two IHC markers (CD10 and MUM1), instead of the usual three markers.[11,19-21] The study revealed that the majority of the sample consisted of individuals belonging to the ABC group, accounting for 59%. Conversely, those of the GCB subtype made up 41% of the sample. The findings align with previous research conducted by Coutinho *et al.*[20] and Muris *et al.*[21], which reported the incidence of ABC DLBCL at 55% and 58% respectively. The studies conducted by Meyer *et al.*[11] and Boltežar *et al.*[19] reported that out of 171 cases, 93 were classified as GCB subtypes, and out of 127 cases, 81 were classified as GCB subtypes. Possible causes influencing the disparity in proportions between GCB and non-GCB include geographical location and environmental factors, such as the interaction with the Epstein-Barr virus (EBV).[6,22] Diffuse large B-cell lymphoma primarily affects the elderly population. The present study comprised a cohort of 61 patients diagnosed with the condition, with 54% of them being aged 60 years or older. These results align with current data, which suggests that the median age for DLBCL diagnosis is 70 years old and that 25% of diagnoses occur in patients aged 75 or older.[23] Furthermore, according to the National Cancer Institute[24], the median age upon diagnosis is 66 years.[24] The gender distribution of the current study sample revealed a male predominance, with males accounting for 55.7% and females accounting for 44.3%. Abu Sabaa *et al.*[25] found a similar discovery, with a median age of 64.6 years and 56.6% of the participants being male.[25] Regarding the place of presentation, this study discovered that nodal presentation was the most common, accounting for 72.1% of the patient sample, while extra-nodal presentation was observed in the remaining 27.9%. Consistent with the current research, Abu Sabaa *et al.*[25] reported that extranodal illness was detected in 46.4% of cases.[25] However, a research conducted by Frauenfeld *et al.*[26] revealed that extranodal presentation was observed in 58% of cases.[26] No significant differences were found in age, gender, and presentations when comparing the GCB and non-GCB (ABC) groups in this study. This aligns with the findings of a study conducted among Chinese patients by Chen *et al.*[27], which also reported no differences in gender, age, and extra-nodal involvement between GCB subtype and non-GCB subtype patients. In the current investigation, the correlation of CD10 and MUM1 with age, gender, and presentation was examined. It was shown that CD10+ was more prevalent in patients who were 60 years or older. This finding is consistent with a previous study by Xu *et al.*[28], which indicated that patients with CD10+ were, on average, 50.3 years old. Regarding gender,

the current study discovered that there was no statistically significant disparity between males and girls, despite the male gender being more prevalent. In a similar vein, Xu *et al.*[28] found that the presence of CD10+ was linked to males. In both the current investigation and the studies conducted by Xu *et al.*[28], the nodal presentation was identified as the primary site for the presentation of CD10+. Additionally, in the current study, the MUM1 marker was found to be linked to patients who were above 60 years old, male, and had nodal presentation. According to the study conducted by Ichiki *et al.*[29], they discovered that the MUM1+ marker was found in 68.2% of patients who were above 60 years old, 63.6% of males, and 53.0% of patients with extra-nodal involvement.[29] Ahmed *et al.*[30] found that there was no significant association between MUM1 and male gender (p=0.906)[33]. When comparing markers, there is a strong negative relationship between the expression of CD10 and MUM1 (p value=0.02). This discovery aligns with a study conducted by Naresh[31], which found that the expression of MUM1 (a marker indicating late germinal centre B-cells or early post-germinal centre B-cells),[32] was significantly inversely correlated with CD10 (a marker indicating germinal centre B-cells).[33] In the aforementioned investigation, out of the 11 cases that tested negative for CD10, nine of them were found to be positive for MUM1 ($p<0.0001$).[31] The current study evaluated two markers using the modified Hans method. CD10 expression was observed in 21.3% of patients, whereas MUM1 was detected in 67.2% of cases. The study conducted by Bajwa *et al.*[34] found that 37.5% of patients showed positivity for CD10, while MUM1 was positive in 62.5% of cases (specifically non-GCB type or activated type). The study also observed a strong statistical correlation between the expression of IHC markers CD10 and MUM1 and DLBCL subtypes ($p<0.001$). The study undertaken by Davies *et al.*[35] found a prevalence of 39% for CD10 and 65% for MUM1,[35] supporting these findings. The management of treatment and the subsequent consequences may present similar difficulties as those encountered with other forms of cancer.[36,37]

The present study is limited by a small sample size and the absence of genetic profiling to characterise the type of cells and subtypes of B cell lymphoma. The differentiation in the study is only based on the decision algorithm modified Hans algorithm (Figure 2).

Conclusion

The majority of the diseased patients were of ABC type. The expressions of CD10 and MUM1 show, according to the Modified Hans algorithm, the predominance of the ABC subtype of DLBCL. The nodal presentation was the most common whether among the GCB and non-GCB groups or the study markers (CD10 and MUM1). There is a significant inverse relation between CD10 and MUM1 and this supports the use of the Modified Hans algorithm in subtyping DLBCL since it considered cases of DLBCL as of GCB origin if CD10+ or MUM1- (in $CD10^-$ cases) and as of non-GCB if $CD10^-$ and $MUM1^+$.

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