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RESEARCH ARTICLE

C-MYC Protein Expression and High Ki-67 Proliferative Index are Predictives of Disease Relapse in Diffuse Large B Cell Lymphoma

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Abstract

Objective: To evaluate the status of C-MYC protein expression and Ki-67 proliferative index and to clarify their role in predicting relapse of diffuse large B cell lymphoma (DLBL). **Materials and Methods:** A retrospective study conducted on 50 cases diagnosed as DLBL in a 3 years' time period from January 2014 till December 2016, collected from the archive of Pathology Departments of the National Cancer Institute Cairo - Egypt, Misr University for Science and Technology and private labs of authors. The diagnosis of DLBL for all cases, both nodal and extranodal, was confirmed by histopathologic examination and immunophenotyping. Automated immunohistochemical staining using antibodies against C-MYC protein and MIB-1 was used to evaluate the C-MYC expression in tumor cells and to assess their proliferative ability by calculating Ki-67 labelling index. The relation between the percentage of C-MYC protein expression, Ki-67 proliferative index, clinical data and the relapse status during the follow up period were analyzed. **Results:** A total of 50 cases of DLBL in both nodal and extra-nodal sites were included. Twenty-three cases (46%) were expressing the C-MYC protein, and 29 cases (58%) showed high Ki-67 proliferative index. Twenty-two cases (44%) relapsed during the follow-up period. Positive C-MYC protein expression was significantly associated with high Ki-67 proliferative index. C-MYC protein expression and high Ki-67 proliferative index were independently associated with disease relapses in 81.8% and 86.4% of cases respectively. Cases with combined C-MYC protein expression and high Ki-67 proliferative index showed statistical prediction of relapse in 81.8% of cases. **Conclusion:** C-MYC protein expression and high Ki-67 proliferative index were independently associated with relapse of diffuse large B cell lymphoma. Furthermore, the combined positive C-MYC protein expression and high Ki-67 proliferative index is better than a single positive test in predicting relapses among DLBL patients.

Keywords: DLBL-C-MYC- Ki-67-Relapse-IHC

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Introduction

C-MYC is one of the most important transcriptional proto-oncogene involved in human carcinogenesis and is the most common mutated gene in lymphomas. This proto-oncogene is regulating a wide range of cellular functions including proliferation, growth and apoptosis [1]. C-MYC oncogene functions as a universal enhancer of already expressed genes in cells rather than directly activating silent genes [2]. Rearrangement of C-MYC gene is crucial in the pathogenesis of B cell lymphomas, but it is rarely reported in T cell lymphomas. The dysregulated gene in B cell lymphoma occurs either as a primary event in Burkitt lymphoma (BL) or secondary event in aggressive lymphomas such as DLBCL [1]. Under normal physiological conditions, C-MYC protein level is low and insufficient to promote cellular proliferation. The tumor transforming activity of C-MYC is also opposed by its ability to induce apoptosis [3]. Loss of gene regulation induces lymphomas by over expression of

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intact C-MYC protein that transforms cells through three main mechanisms such as insertional mutagenesis, gene amplification and chromosomal translocation [4]. Secondary C-MYC gene rearrangement in low grade B-cell lymphomas usually results in transformation into highly aggressive lymphomas with decreased survival rates. The gene changes in DLBCL most often confer an aggressive clinical behavior and chemotherapy resistance [1-6]. The adverse prognosis associated with C-MYC gene rearrangement is largely derived from concurrent BCL2 or BCL6 gene rearrangement [7]. DLBCL with C-MYC and either BCL2 or BCL6 rearrangements are subsequently termed double-hit lymphomas, while those with all three rearrangements are referred to as triple-hit lymphomas. Double-hit lymphoma is currently classified as high grade B cell lymphoma [8]. The detection of C-MYC gene translocation and C-MYC protein expression has become essential in the clinical diagnosis and prognosis of aggressive B cell lymphoma. Conventional karyotyping and fluorescence in situ hybridization (FISH) are the two techniques clinically available for the detection of C-MYC gene abnormalities [9]. Immunohistochemical (IHC) detection of C-MYC protein expression does not correspond to C-MY C gene rearrangement. However, there is a correlation between C-MYC protein expression immunohistochemically and its gene translocation in aggressive B cell lymphoma, as over expression of C-MYC protein suggests its gene translocation [10-11]. DLBCL with high level of C-MYC protein expression are likely double-hit lymphomas [8]. IHC staining for detection of C-MYC protein expression is important for prognosis in DLBCL. High level C-MYC protein expression is associated with inferior overall survival irrespective of BCL2 expression [6]. Double expressor lymphoma is a DLBCL that exhibits over expression of both C-MYC and BCL2 proteins. It is associated with worse clinical outcome than other DLBCL [12-13]. Unregulated C-MYC expression promotes cell proliferation, but also induces apoptosis in p53-dependent and p53-independent pathways [14]. Ki-67 is a nuclear non-histone protein that is synthesized at the beginning of cell proliferation [15]. Ki-67 expression has been widely used in clinical practice as an index to evaluate the proliferative activity of lymphoma cells. High Ki-67 proliferative index (PI) is highly associated with worse survival for Non Hodgkin lymphoma [16]. In DLBCL, Ki-67 can distinguish patients with a good and bad prognosis when combined with other prognostic factors [17].

This study aimed to evaluate the status of C-MYC protein expression and Ki-67 PI and clarify their role in predicting relapse of DLBCL using immunohistochemical study.

Materials and Methods

This study was carried out on 50 cases of DLBL diagnosed in the time period from January 2014 till December 2016 in the Pathology Departments of the National Cancer Institute (NCI) Cairo University- Cairo-Egypt, Misr University for Science and Technology (MUST) - Giza- Egypt and private labs of authors, with available follow-up data for the following 3 years from 2015 till the end of year 2017. Approval for this study was obtained from the Medical Ethics Committee of NCI and MUST University. Tissue specimens were preserved in 10% neutral buffered formalin, embedded in paraffin, cut in 4 µm thick tissue sections and stained with H&E stain for conventional histopathologic examination. The diagnosis of DLBL for all cases was confirmed by histologic examination and immunophenotyping using pan B (CD20) and pan T (CD3) markers. All cases revealed diffuse positivity for CD20, while CD3 highlighted only small reactive T lymphocytes. Immunohistochemical analysis was performed using automated Ventana GX immunostainer. The used antibody is C-MYC (EP121) rabbit monoclonal antibody of Cell Marque Tissue Diagnostics, predilute 7 ml vial. C-MYC protein expression was assessed as dense nuclear staining of tumor cells and was judged as positive if the number of stained nuclei is equal to or more than 40% [11]. The used clone for Ki-67 was anti-Ki-67 (30-9) rabbit monoclonal primary antibody from ROCHE Diagnostics. The estimation of Ki-67 PI was done by calculating the percentage of positive tumor nuclei in 1000 tumor cells. The cut-off value of high Ki-67 positivity was set to ≥ 70% [17]. Clinical data as age and gender of the patients were recorded. Excision and core biopsies were obtained from various nodal and extranodal sites, including cervical (n=21), axillary (n=7), inguinal (n=5), spleen (n=4), liver (n=3), colon (n=2), retroperitoneal (n=2), lacrimal gland (n=1), mediastinum (n=1), breast (n=1), supraclavicular (n=1), nasopharyngeal (n=1) and oropharyngeal (n=1) regions. Follow up for all patients included in the study were conducted for the following 3 years and relapsed cases were recorded. The relation between the results of IHC expression of C-MYC protein, Ki-67 PI, clinical data and relapse status during the follow up period were analyzed.

Statistical Analysis

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 25.0; IBM Corporation, Armonk, NY, USA). Demographic and clinical characteristics of the studied patients were presented as frequencies and percentages (%) or mean ± standard deviation (SD). Association between categorical variables were tested for statistical analysis by Chi-square test or Fisher's exact test (if >20% of expected values were less than 5). Shapiro-Wilk's test was used to test for data normality. Difference in mean age (a continuous variable) between binary categorical variables was tested for statistical significance by independent-samples t-test. Multivariate analysis with logistic regression was performed to calculate the age- and sex-adjusted odds ratio of combined C-MYC and Ki-67 for predicting relapses. A p-value <0.05 was considered statistically significant.

Results

This study included a total of 50 cases of DLBCL with available follow-up data. Nodal and extra-nodal biopsies were taken from 25 male and 25 female patients. The age of the patients ranged from 4 to 80 years, with a mean age of 56.7± 15 years. The most common biopsy sites were cervical, axillary, and inguinal lymph nodes (42%, 14%, and 10%, respectively). Submitted tissue materials were either core biopsies (56%) or excision biopsies (44%). The Ki-67 PI ranged from 25 to 99 with a mean of 62.40 ± 25.93. Twenty-three cases (46%) had positive C-MYC protein expression, and 29 cases (58%) had high Ki-67 PI (Figure 1). Twenty-two cases (44%) showed disease relapse during the three years follow-up period (Table 1). Positive C-MYC protein expression was significantly associated with high Ki-67 PI. All 23 cases with positive C-MYC protein expression had high Ki-67 PI, while 22.2% of cases with negative C-MYC protein expression had high Ki-67 PI (Table 2). Markers high expression and disease relapse have no significant relationship with both patients' ages and sexes. C-MYC protein expression and high Ki-67 PI were independently associated (significantly associated) with disease relapse in 81.8% and 86.4% respectively. Further, 81.8% of all relapsed patients had combined positive C-MYC protein expression and high Ki-67 PI (Table 3). Multivariate analysis revealed that patients with combined positive C-MYC protein expression and high Ki-67 PI were 19.6 times more likely to have disease relapse when compared to patients with combined negative C-MYC protein expression and low Ki-67 PI; and 16.2 times when compared to patients with either positive C-MYC protein expression alone or high Ki-67 PI alone. In contrast, patients with either positive C-MYC protein expression or high Ki-67 PI alone were only 1.17 times more likely to have relapses when compared to patients with combined negative C-MYC protein expression and low Ki-67 PI.

Table 1. Distribution of Studied Patients According to their Demographic and Clinical Characteristics (N = 50)

Age (years)	Mean ± SD (Range)	56.68 ± 14.99 (4 – 80)
Sex, No. (%)	Male	25 (50.0%)
	Female	25 (50.0%)
Site of biopsies, No. (%)	Cervical	21 (42%)
	Axillary	7 (14%)
	Inguinal	5 (10%)
	Spleen	4 (8%)
	Liver	3 (6%)
	Colon	2 (4%)
	Retroperitoneal	2 (4%)
	Breast	1 (2%)
	Lacrimal gland	1 (2%)
	Mediastinal	1 (2%)
	Nasopharynx	1 (2%)
	Oropharyngeal	1 (2%)
	Supraclavicular	1 (2%)
Type of Biopsy, No. (%)	Core	28 (56.0%)
	Excision	22 (44.0%)
C-MYC Protein Expression, No. (%)	Negative	27 (54.0%)
	Positive	23 (46.0%)
Ki-67 Proliferative Index (PI)	Mean ± SD (Range)	62.40 ± 25.93 (25 – 99)
	Low	21 (42.0%)
	High	29 (58.0%)
Relapse on Follow-up	No	28 (56.0%)
	Yes	22 (44.0%)

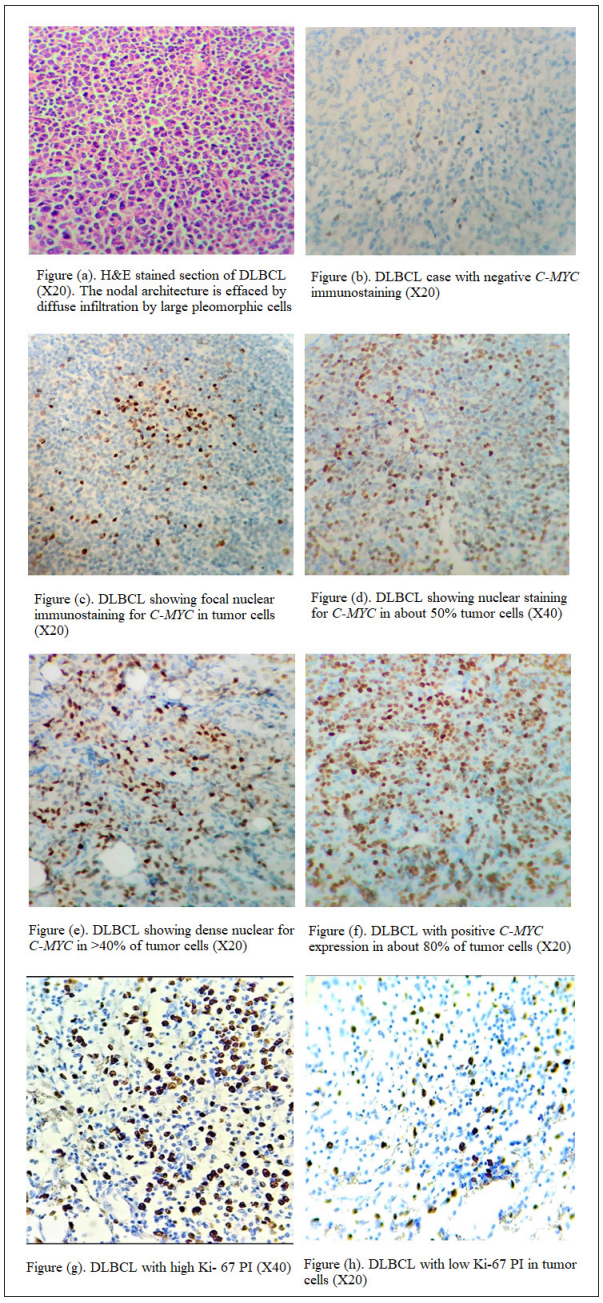

Figure 1. Histopathological and Immunohistochemical Results

Table 2. Distribution of C-MYC Protein Expression and Ki-67 PI Level by Demographic and Clinical Characteristics (N = 50)

Measured Parameters		C-MYC Expression		Sig.	Ki67 PI		Sig.
		Negative	Positive		Low	High	
Age (years)	Mean ± SD (Range)	54.0 ± 16.5 (4 – 80)	59.9 ± 12.7 (33 – 84)	0.167	53.0 ± 17.6 (4 – 80)	59.3 ± 12.5 (33 – 84)	0.147
Sex	Female	11 (40.7%)	14 (60.9%)	0.156	9 (42.9%)	16 (55.2%)	0.39
	Male	16 (59.3%)	9 (39.1%)		12 (57.1%)	13 (44.8%)	
Site of biopsy	Axillary	3 (11.1%)	4 (17.4%)		3 (14.3%)	4 (13.8%)	
	Breast	1 (3.7%)	0		1 (4.8%)	0	
	Cervical	9 (33.3%)	12 (52.2%)		6 (28.6%)	15 (51.7%)	
	Colon	2 (7.4%)	0		2 (9.5%)	0	
	Inguinal	1 (3.7%)	4 (17.4%)		0	5 (17.2%)	
	Lacrimal Gland	1 (3.7%)	0		0	1 (3.4%)	
	Liver	2 (7.4%)	1 (4.3%)		1 (4.8%)	2 (6.9%)	
	Mediastinal	1 (3.7%)	0		1 (4.8%)	0	
	Nasopharynx	1 (3.7%)	0		1 (4.8%)	0	
	Oropharyngeal	1 (3.7%)	0		1 (4.8%)	0	
	Retroperitoneal	1 (3.7%)	1 (4.3%)		1 (4.8%)	1 (3.4%)	
	Spleen	4 (14.8%)	0		4 (19.0%)	0	
	Supraclavicular	0	1 (4.3%)		0	1 (3.4%)	
Type of biopsy	Core	13 (48.1%)	15 (65.2%)		10 (47.6%)	18 (62.1%)	
	Excision	14 (51.9%)	8 (34.8%)		11 (52.4%)	11 (37.9%)	
Ki67 PI	Low	21 (77.8%)	0	<0.001*			
	High	6 (22.2%)	23 (100.0)				

*. Statistically significant at 0.05 level of significance

Discussion

DLBCL is a mature B-cell neoplasm with diffuse growth pattern and various immune phenotypes and clinical prognosis. DLBCL accounts for approximately 25–30% of non-Hodgkin lymphoma in Western countries [18]. In Egypt, lymphoma is considered the most common hematologic malignancy and accounts for about 8.4% of all new cancer cases diagnosed annually [19]. The role of C-MYC oncogene in the subtypes of B-cell lymphomas was clarified by many previous studies. In Burkitt's lymphoma, the translocation of C-MYC at 14q32 is the most common, and occurring in approximately 80% of cases [20]. In plasmablastic lymphoma C-MYC rearrangements, most commonly t (8; 14) (q24·1; q32) are found in approximately 49% of cases [21]. On the other hand Kawasaki et al., identified C-MYC gene rearrangement in 5–15% of cases in DLBCL [22]. Previous researches reported that there is a correlation between C-MYC protein expression and its gene translocation in aggressive B cell lymphoma and that over expression of C-MYC protein suggests its gene translocation [10-11].

In this study, C-MYC protein expression and Ki-67 PI were not significantly associated with specific patient's age and sex. These results were in concordance of those reported by Yun et al., who examined 26 males and 16 females with an average age of 58.9 ± 12.3. Specimens were from various sources such as superficial lymph nodes, subcutaneous soft tissue, gastrointestinal tract, mesentery, spleen, and tonsil. Statistical analysis showed that, there was no significant difference in the expression of C-MYC protein related to age or gender of patients [11].

In this study, the cut-off value of Ki-67 positivity was set to be ≥ 70% .The Ki-67 PI ranged from 25 to 99 with a mean of 62.40 ± 25.93. Broyde et al., reported that the mean Ki-67 PI ranges from 26.6% in indolent lymphomas to 97.6% in very aggressive lymphomas. In patients with DLBCL, a Ki-67 PI of 70% was found to significantly discriminate patients with good or bad prognosis [17].

In this study, 46% of cases had positive C-MYC protein expression, while 58% had high Ki-67 PI. This result was close to the ratio (47.6%) detected by Yun et al., and to the ratio (42%) reported by Julum et al., as regards IHC of C-MYC protein expression [11-23]. In this study, C-MYC protein expression was significantly associated with high Ki-67 PI. All 23 cases with positive C-MYC protein expression had high Ki-67 PI, while 22.2% of cases with negative C-MYC protein expression had high Ki-67 PI. In concordance to our findings, Yun et al. detected that high Ki-67 PI indicated a higher degree of malignancy in patients with C-MYC translocation in DLBCL [11].

In this study 44% of patients relapsed on the three years follow-up period. Relapses were not significantly

Table 3. Distribution of Follow-up Status of Studied Patients by Demographic, Clinical Characteristics, C-MYC Protein Expression and Ki-67 PI level (N = 50)

Measured Parameters		Follow-up		Sig.
		Non Relapsing (n = 28)	Relapsing (n = 22)	
Age (years)	Mean ± SD (Range)	54.5 ± 16.2 (4 – 80)	59.5 ± 13.2 (33 – 84)	0.242
Sex	Female	12 (42.7%)	13 (59.%)	0.254
	Male	16 (57.1%)	9 (40.9%)	
Site of biopsy	Axillary	6 (21.4%)	1 (4.5%)	
	Breast	1 (3.6%)	0	
	Cervical	9 (32.1%)	12 (54.5%)	
	Colon	2 (7.1%)	0	
	Inguinal	1 (3.6%)	4 (18.2%)	
	Lacrimal Gland	1 (3.6%)	0	
	Liver	2 (7.1%)	1 (4.5%)	
	Mediastinal	1 (3.6%)	0	
	Nasopharynx	1 (3.6%)	0	
	Oropharyngeal	1 (3.6%)	0	
	Retroperitoneal	1 (3.6%)	1 (4.5%)	
	Spleen	2 (7.1%)	2 (9.1%)	
	Supraclavicular	0	1 (4.5%)	
Type of biopsy	Core	15 (53.6%)	13 (59.1%)	
	Excision	13 (46.4%)	9 (40.9%)	
C-MYC Expression	Negative	23 (82.1%)	4 (18.2%)	<0.001*
	Positive	5 (17.9%)	18 (81.8%)	
Ki67 PI	Low	18 (64.3%)	3 (13.6%)	<0.001*
	High	10 (35.7%)	19 (86.4%)	
Combined C-MYC & Ki67 PI status	Negative & Low	18 (64.3%)	3 (13.6%)	<0.001*
	Positive or High	5 (17.9%)	1 (4.5%)	
	Positive & High	5 (17.9%)	18 (81.8%)	

*. Statistically significant at 0.05 level of significance

associated with patient's age and sex. However, C-MYC protein expression and high Ki-67 PI were independently associated with disease relapse. Multivariate analysis revealed that patients with combined positive C-MYC protein expression and high Ki-67 PI were more likely to have relapses when compared to patients with combined negative C-MYC protein expression and low Ki-67 PI or patients with either positive C-MYC protein expression or high Ki-67 PI alone.

Parallel results were detected by Maria et al., who reported that overall survival and disease-free survival in DLBCL were higher in patients with negative expression for Ki-67 and C-MYC protein [24]. Moreover, higher rates of relapse were observed in the high Ki-67 expression group compared to the low Ki-67 expression group. In multivariate analysis, Ki-67 expression was a significant prognostic factor for event free survival and borderline significance for overall survival. Elevated Ki-67 expression seems to be associated with higher relapse and inferior free survival in patients with DLBCL [25]. We concluded that C-MYC protein expression and high Ki-67 PI are independently associated with relapses in DLBCL patients. Furthermore, the combined positive C-MYC protein expression and high Ki67 PI test is better than a single positive test in predicting relapses among DLBCL patients.

References

1. Nguyen L, Papenhausen P, Shao H. The Role of c-MYC in B-Cell Lymphomas: Diagnostic and Molecular Aspects. Genes. 2017 04 05;8(4):116. https://doi.org/10.3390/genes8040116
2. Nie Z, Hu G, Wei G, Cui K, Yamane A, Resch W, Wang R, Green D, Tessarollo L, Casellas R, Zhao K, Levens D. c-Myc Is a Universal Amplifier of Expressed Genes in Lymphocytes and Embryonic Stem Cells. Cell. 2012 09;151(1):68-79. https://doi.org/10.1016/j.cell.2012.08.033
3. Demma MJ, Mapelli C, Sun A, Bodea S, Ruprecht B, Javaid S, Wiswell D, Muise E, Chen S, Zelina J, Orvieto F, Santoprete A, Altezza S, Tucci F, Escandon E, Hall B, Ray K, Walji A, O'Neil J. Omomyc Reveals New Mechanisms To Inhibit the MYC Oncogene. Molecular and Cellular Biology. 2019 09

09;39(22). https://doi.org/10.1128/mcb.00248-19
4. Dudley J, Mertz J, Rajan L, Lozano M, Broussard D. What retroviruses teach us about the involvement of c-Myc in leukemias and lymphomas. Leukemia. 2002 06;16(6):1086-1098. https://doi.org/10.1038/sj.leu.2402451
5. God JM, Cameron C, Figueroa J, Amria S, Hossain A, Kempkes B, Bornkamm GW, Stuart RK, Blum JS, Haque A. Elevation of c-MYC Disrupts HLA Class II–Mediated Immune Recognition of Human B Cell Tumors. The Journal of Immunology. 2015 01 16;194(4):1434-1445. https://doi.org/10.4049/jimmunol.1402382
6. Valera A, Lopez-Guillermo A, Cardesa-Salzmann T, Climent F, Gonzalez-Barca E, Mercadal S, Espinosa I, Novelli S, Briones J, Mate JL, Salamero O, Sancho JM, Arenillas L, Serrano S, Erill N, Martinez D, Castillo P, Rovira J, Martinez A, Campo E, Colomo L, . MYC protein expression and genetic alterations have prognostic impact in patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Haematologica. 2013 05 28;98(10):1554-1562. https://doi.org/10.3324/haematol.2013.086173
7. Pillai RK, Sathanoori M, Van Oss SB, Swerdlow SH. Double-hit B-cell Lymphomas With BCL6 and MYC Translocations Are Aggressive, Frequently Extranodal Lymphomas Distinct From BCL2 Double-hit B-cell Lymphomas. The American Journal of Surgical Pathology. 2013 03;37(3):323-332. https://doi.org/10.1097/pas.0b013e31826cebad
8. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 05 19;127(20):2375-2390. https://doi.org/10.1182/blood-2016-01-643569
9. Landsburg DJ, Nasta SD, Svoboda J, Morrissette JJD, Schuster SJ. 'Double-Hit' cytogenetic status may not be predicted by baseline clinicopathological characteristics and is highly associated with overall survival in B cell lymphoma patients. British Journal of Haematology. 2014 04 25;166(3):369-374. https://doi.org/10.1111/bjh.12901
10. Chisholm KM, Bangs CD, Bacchi CE, Kirsch HM, Cherry A, Natkunam Y. Expression Profiles of MYC Protein and MYC Gene Rearrangement in Lymphomas. The American Journal of Surgical Pathology. 2015 03;39(3):294-303. https://doi.org/10.1097/pas.0000000000000365
11. Zhang Y, Wang H, Ren C, Yu H, Fang W, Zhang N, Gao S, Hou Q. Correlation Between C-MYC, BCL-2, and BCL-6 Protein Expression and Gene Translocation as Biomarkers in Diagnosis and Prognosis of Diffuse Large B-cell Lymphoma. Frontiers in Pharmacology. 2019 01 07;9. https://doi.org/10.3389/fphar.2018.01497
12. Wang XJ, Medeiros LJ, Lin P, Yin CC, Hu S, Thompson MA, Li S. MYC Cytogenetic Status Correlates With Expression and Has Prognostic Significance in Patients With MYC/BCL2 Protein Double-positive Diffuse Large B-cell Lymphoma. The American Journal of Surgical Pathology. 2015 09;39(9):1250-1258. https://doi.org/10.1097/pas.0000000000000433
13. Salam DSDA, Thit EE, Teoh SH, Tan SY, Peh SC, Cheah S. C-MYC, BCL2 and BCL6 Translocation in B-cell Non-Hodgkin Lymphoma Cases. Journal of Cancer. 2020;11(1):190-198. https://doi.org/10.7150/jca.36954
14. Hoffman B, Liebermann DA. Apoptotic signaling by c-MYC. Oncogene. 2008 Oct;27(50):6462-6472. https://doi.org/10.1038/onc.2008.312
15. He X, Chen Z, Fu T, Jin X, Yu T, Liang Y, Zhao X, Huang L. Ki-67 is a valuable prognostic predictor of lymphoma but its utility varies in lymphoma subtypes: evidence from a systematic meta-analysis. BMC Cancer. 2014 03 05;14(1). https://doi.org/10.1186/1471-2407-14-153
16. Song M, Chung J, Lee J, Yang D, Kim I, Shin D, Shin H. High Ki-67 expression in involved bone marrow predicts worse clinical outcome in diffuse large B cell lymphoma patients treated with R-CHOP therapy. International Journal of Hematology. 2014 Dec 12;101(2):140-147. https://doi.org/10.1007/s12185-014-1719-3
17. Broyde A, Boycov O, Strenov Y, Okon E, Shpilberg O, Bairey O. Role and prognostic significance of the Ki-67 index in non-Hodgkin's lymphoma. American Journal of Hematology. 2009 06;84(6):338-343. https://doi.org/10.1002/ajh.21406
18. Alizadeh AA, Eisen MB, Davis RE, Ma C, Lossos IS, Rosenwald A, Boldrick JC, Sabet H, Tran T, Yu X, Powell JI, Yang L, Marti GE, Moore T, Hudson J, Lu L, Lewis DB, Tibshirani R, Sherlock G, Chan WC, Greiner TC, Weisenburger DD, Armitage JO, Warnke R, Levy R, Wilson W, Grever MR, Byrd JC, Botstein D, Brown PO, Staudt LM. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature. 2000 02;403(6769):503-511. https://doi.org/10.1038/35000501
19. Moussa M, Mostafa N, Helmy M, ElAzzazi M, Hegab H, Allah H, Elafifi A. Treatment outcome in Egyptian lymphoma patients, 2-year results, single-center experience. The Egyptian Journal of Haematology. 2014;39(4):209. https://doi.org/10.4103/1110-1067.153957
20. Cho HJ, Lee J, Yoon SR, Lee HG, Jung H. Regulation of Hematopoietic Stem Cell Fate and Malignancy. International Journal of Molecular Sciences. 2020 07 06;21(13):4780. https://doi.org/10.3390/ijms21134780
21. Valera A, Balagué O, Colomo L, Martínez A, Delabie J, Taddesse-Heath L, Jaffe ES, Campo E. IG/MYC Rearrangements are the Main Cytogenetic Alteration in Plasmablastic Lymphomas. The American Journal of Surgical Pathology. 2010 Oct;:1. https://doi.org/10.1097/pas.0b013e3181f3e29f
22. Kawasaki C, Ohshima K, Suzumtya J, Kanda M, Tsuchiya T, Tamura K, Kikuchi M. Rearrangements of Bcl-1, Bcl-2, Bcl-6, and C-Myc in Diffuse Large B-Cell Lymphomas. Leukemia & Lymphoma. 2001 01;42(5):1099-1106. https://doi.org/10.3109/10428190109097730
23. Nwanze J, Siddiqui MT, Stevens KA, Saxe D, Cohen C. MYC Immunohistochemistry Predicts MYC Rearrangements by FISH. Frontiers in Oncology. 2017 09 21;7. https://doi.org/10.3389/fonc.2017.00209
24. Maria A, Rotaru I, Olar L, Patrascu S. The prognostic role of Bcl-2, Ki67, c-MYC and p53 in diffuse large B-cell lymphoma. Romanian journal of morphology and embryology. 2017;58(3):837-43.
25. Hyun Yoon D, Ro Choi D, June Ahn H, Kim S, Ho Lee D, Kim S, Hee Park B, Yoon SO, Huh J, Lee S, Suh C. Ki-67 expression as a prognostic factor in diffuse large B-cell lymphoma patients treated with rituximab plus CHOP. European Journal of Haematology. 2010 04;:no-no. https://doi.org/10.1111/j.1600-0609.2010.01467.x