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The Clinical Significance of Both IgM and IgG Anticardiolipin Antibodies in Non-Hodgkin's Lymphoma

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Abstract

Background: Anticardiolipin (ACL) antibodies are associated with a wide variety of disorders including malignancies. The aim of this study was to investigate the prevalence and prognostic implication of ACL antibodies in patients with Non-Hodgkin's lymphoma (NHL).

Methods: Sixty-four patients with NHL were included in this study. Enzyme-linked immunosorbent assay kits were used to measure the concentrations of all IgM and IgG antibodies.

Results: Antibodies (IgM, IgG) were found in 35.9% and 84.3% of patients respectively. The presence of elevated aCl IgM was correlated with relapse in NHL (P<0.001). Pretreatment serum levels of aCL IgG were significantly higher in patients with NHL (P<0.001), and significantly normalized in complete remission. Positive ACL IgG was also found in patients with relapse. A negative correlation was found between aCL antibodies (IgM, IgG) positivity and CD23 (P=0.037, P=0.003) respectively.

Conclusion: Anticardiolipin antibodies are associated with lymphomas. Their determination is useful to predict treatment outcome or disease prognosis.

Keywords: Anticardiolipin antibody; Non-Hodgkin's lymphoma

Introduction

Non-Hodgkin lymphoma (NHL) is a histologically, etiologically, and clinically heterogeneous group of malignant diseases of the lymphocytes [1]. Current classification systems include the Revised European-American Lymphoma (REAL) classification and the World Health Organization (WHO) classification of hematopoietic and lymphoid neoplasms [2]. The most common types of NHL are diffuse large B-cell lymphoma, which accounts for 30-40% of lymphomas, and follicular lymphoma, which accounts for approximately 20-30% [3]. The distribution of NHL types varies internationally [4]. Chronic lymphocytic leukaemia (CLL), contributes about 7% of B- and T/natural killer (NK) -cell lymphoma cases. Marginal zone B-cell, peripheral T-cell, mantle cell, and a variety of other B-, T- and NK-cell lymphomas constitute the remaining types, with distribution varying by geographic region. Subclinical immune dysfunction is the most consistent risk factor in NHL [5-8]. The disease accounts for approximately 3.4% of all cancer deaths [9].

Anticardiolipin (aCL) antibodies are a heterogeneous group of antibodies against phospholipid-binding proteins [10]. The isotype and the titres of aCL antibodies are important criteria for assessing the risk of antiphospholipid syndrome (APS), which is characterized by venous and arterial thrombosis, miscarriages [11]. Patients with malignancies have an increased incidence and prevalence of aCL [12-14]. Endler et al. [15] found in a large cohort of patients with positive anticardiolipin antibodies that the risk of cancer-related mortality was increased 2.6-fold. These antibodies are associated with many disorders, including autoimmune disease and malignancy [16-18].

The presence of aCL antibodies has been described in patients with NHL [19-22]. aCL antibodies are related to NHL, this is supported by the theory indicated that aCL antibodies are produced by the lymphoma cells [23]. An approximately 30% prevalence of anticardiolipin antibodies in patients suffering from non-Hodgkin's lymphomas has been reported [24]. Apparently, the presence of these antibodies at diagnosis and their persistence during follow-up was associated with resistance to treatment [25].

In this study, we measured the serum aCL IgM and IgG levels in patients with NHL and determined if these antibodies correlated with disease characteristics and final outcome.

Subjects and Methods

Patients and controls

Patients were chosen from the outpatient clinic of Minia Oncology Center, Minia University hospital. This group consists of 64 patients with NHL. They were separated into four groups according to the response to treatment: Group my including patients newly diagnosed with no treatment, Group II with complete remission (CR), group III with partial remission (PR) and group IV with relapse. The diagnosis of NHL was confirmed by immunophenotyping and histopathology.

CR was defined as the absence of clinical and radiographic evidence of disease, or disease-related symptoms. Partial remission was defined

as the decrease of 50% in tumour mass [26]. The controls were thirty, apparently healthy subjects. Their ages ranged from 21 to 70 years and this group included 15 males and 15 females.

Laboratory investigations

Lactate dehydrogenase (LDH), renal function tests (serum creatinine and blood urea), and liver enzymes: aspartate aminotransferase (AST), alanine aminotransferase (ALT) were determined by using Vitros 350 dry chemistry (Ortho clinical diagnostics, Johnson-Johnson company; USA) and ACE automated quantitative multistation chemistry Analyzer (Schiapparelli Biosystems. INC; USA). Complete blood count (CBC) was determined by automated cell counter Cell Dyn 1700 (USA).

Measurement of anticardiolipin antibodies

Anticardiolipin IgG and IgM antibodies were measured in all patients with a commercially available enzyme-linked immunosorbent assay kit (Sunred Biological Technology Co., Ltd, Shanghai). Results were expressed as GPL and MPL units, according to Harris et al. [27]. Values exceeding 18 GPL or MPL units were regarded as positive.

Statistical method and data analysis

The collected data were coded, tabulated, and statistically analysed using SPSS program (Statistical Package for Social Sciences) software version 20. Non-parametric quantitative data are transformed into the logarithm before analysis (WBCs, Platelets, ALT, AST). Analyses were done between more than two groups using one-way ANOVA test for quantitative data between groups, followed by post-HOC Tukey's correction between each two groups Analyses were done between the two groups using the independent sample t-test for quantitative data, Chi-square test was used for qualitative data between groups. The correlation between two quantitative variables was performed by using Pearson's correlation coefficient, and non-parametric Spearman's correlation coefficient.

Results

Patient characteristics

The clinical and pathological characteristics of the patients are shown in Table 1. The median age of the group was 46.64 ± 15.11 years (range 13-75 yr). 52 patients had B-cell lymphoma (10 follicular centre lymphoma, 23 diffuse large B-cell lymphoma, 14 chronic lymphocytic lymphomas, 1 patient with small cell lymphoma, 4 other lymphomas) and 12 patients with T-cell lymphoma.

Clinico-pathological features of NHL patients	Descriptive statistics
Age	
Range	(13-75)
Mean ± SD	46.64 ± 15.11
Sex	
Male	38 (59.4%)
Female	26 (40.6%)
Response to Treatment	
No treatment	23 (35.9%)
Complete remission	9 (14.1%)
Partial remission	10 (15.6%)
Relapse	22 (34.4%)
NHL histologic subtype	
B	52 (81.3%)
T	12 (18.8%)
B-NHL histologic subtype	
FCL	10 (19.2%)
DLCL	23 (44.2%)
CLL	14 (26.9%)
SCL	1 (1.9%)
others	4 (7.7%)
Hepatomegally	
No	28 (43.8%)
Yes	36 (56.2%)
Spleenomegally	
No	23 (35.9%)
Yes	41 (64.1%)
L.N. enlargement	
No	0 (0%)
Yes	64 (100%)

NHL: Non-Hodgkin's Lymphoma; FCL: Follicular Cell Lymphoma; DLCL: Diffuse Large B-cell Lymphoma; CLL: Chronic Lymphocytic Leukaemia; SCL: Small Lymphocytic Lymphoma; LN: Lymph Node

Table 1: Clinical characteristics of the patients.

For 23 patients (35.9%), blood samples were obtained at initial diagnosis of the lymphoma with no treatment. In the other patients, remission status of the disease at the time of blood sampling was noted (Table 1). 9 patients (14.1%) were in complete remission of the lymphoma at the time of blood sampling. 10 patients (15.6%) experienced a partial remission and 22 patients (34.4%) in relapse.

aCL IgM in NHL

Patients with NHL had significantly higher serum levels of aCL IgM than controls (P<0.001). The mean aCA IgM level was 13.65 ± 9.23 MPL in the patient group and 4 ± 1.44 MPL (1.6-6.4) in the control group (Figure 1A).

Serum aCA IgM levels were compared in different groups of patients. The newly diagnosed patients showed serum aCA IgM levels ranging from 3-30 MPL with a mean of 8.43 ± 5.15 MPL. Patients with CR had aCA IgM values ranging from 3 to 25 MPL with a mean of 8.11 ± 6.84 MPL. Patients with partial remission had Aca IgM levels

ranging from 4-27 MPL with a mean of 10.7 ± 7.84 MPL. Samples of patients who were in relapse were also analysed. Their aCA IgM values ranged from 8-45 MPL with a mean of 22.72 ± 7.09 MPL (Figure 1B).

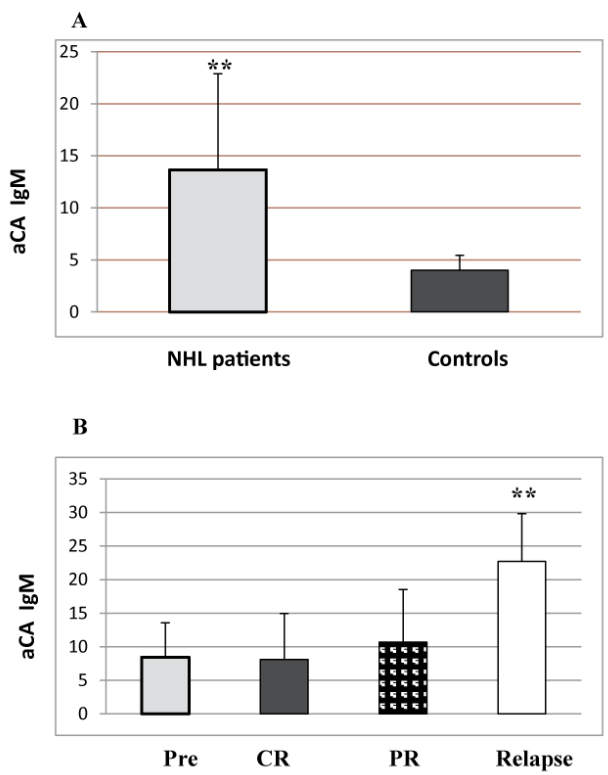

Figure 1: aCA IgM levels in NHL patients. **(A)** Serum aCA IgM level was measured and compared in NHL patients (n=64) and controls (n=30). Serum level of aCA IgM was significantly higher in NHL patients than in healthy controls (** P<0.001). **(B)** Serum aCA IgM levels in different groups of NHL patients. aCA IgM levels were significantly higher in the group with relapse compared to other groups (** P<0.001). NHL: Non-Hodgkin's Lymphoma; aCA: Anticardiolipin Antibodies; Pre: Pretreatment; CR: Complete Remission; PR: Partial Remission.

Taking 18 units as the cutoff for a positive ACA IgM. IgM Antibodies were found in 23 of 64 patients with NHL (35.9%). Among aCL antibody-positive patients, complete remission occurred in 1 of 23 patients (4.3%); 1 patient with no treatment (4.3%); and 2 patients with partial remission (8.7%). Relapse occurred in 19 of 23 patients with positive aCA IgM (82.6%). A significant positive correlation was found between relapse and aCA IgM antibodies (P<0.001). No correlation was found between aCL antibodies and clinical or laboratory parameters (Table 2).

	ACA IgM		P value
	Negative ACA (n=41)	Positive ACA (n=23)	
Age			
Range	(14-75)	(13-70)	0.588
Mean ± SD	47.41 ± 15.37	45.26 ± 14.88	
Sex			
Male	25 (61%)	13 (56.5%)	0.728
Female	16 (39%)	10 (43.5%)	
Treatment outcome			
No treatment	22 (53.7%)	1 (4.3%)	**<0.001****
complete remission	8 (19.5%)	1 (4.3%)	
partial remission	8 (19.5%)	2 (8.7%)	
relapse	3 (7.3%)	19 (82.6%)	
B-NHL histologic subtype			
FCL	4 (11.1%)	6 (37.5%)	0.127
DLCL	17 (47.2%)	6 (37.5%)	
CLL	12 (33.3%)	2 (12.5%)	
SCL	1 (2.8%)	0 (0%)	
others	2 (5.6%)	2 (12.5%)	
NHL histologic subtype			
B	36 (87.8%)	16 (69.6%)	0.073
T	5 (12.2%)	7 (30.4%)	
Hb			
Range	(7.4-14.1)	(7.4-15.8)	0.766
Mean ± SD	11.6 ± 1.82	11.75 ± 2.17	
WBCs			
Range	(1.5-20)	(2.1-11.1)	0.204
Mean ± SD	7.15 ± 4.36	5.65 ± 2.63	
Platelets			
Range	(50-651)	(62-541)	0.909
Mean ± SD	232.9 ± 128.77	226.47 ± 115.91	
AST			
Range	(13-566)	(14-241)	0.309
Mean ± SD	56.14 ± 89.41	55.95 ± 48.01	
ALT			
Range	(11-232)	(2.5-170)	0.787
Mean ± SD	51.46 ± 50.82	52.63 ± 38.69	
LDH			
Range	(268-1416)	(277-910)	0.055
Mean ± SD	633.04 ± 269.82	531.04 ± 147.05	
Urea			

Range	(14-65)	(18.7-62)	0.819
Mean ± SD	30.85 ± 11.11	31.51 ±10.77	
Creatinine			
Range	(0.5-2.7)	(0.5-1.2)	0.603
Mean ± SD	0.85 ± 0.38	0.81 ± 0.21	
Hepatomegally			
No	17 (41.5%)	11 (47.8%)	0.622
Yes	24 (58.5%)	12 (52.2%)	
Spleenomegally			
No	15 (36.6%)	8 (34.8%)	0.885
Yes	26 (63.4%)	15 (65.2%)	
LN. enlargement			
No	0 (0%)	0 (0%)	1
Yes	41 (100%)	23 (100%)	

Negative aCA IgM was <18 MPL; high, ≥ 18 MPL. Highly statistically significant differences (P<0.001) are indicated with asterisks (**). NHL: Non-Hodgkin's Lymphoma; N: Number; aCA: Anticardiolipin Antibodies; FCL: Follicular Cell Lymphoma; DLCL: Diffuse Large B-cell Lymphoma; CLL: Chronic Lymphocytic Leukaemia; SCL: Small Lymphocytic Lymphoma; Hb: Haemoglobin; WBCs: White Blood Cells; AST: Asparatate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; LN: Lymph Node.

Table 2: Correlation of positive aCA IgM level with features in NHL patients.

Significant negative correlation was found between CD23 and positive aCL IgM antibody titre (P=0.037) but not with other immunophenotyping markers (Table 3).

	ACA IgM		**P value**
	Negative ACA (n=41)	**Positive ACA (n=23)**	
CD 20			
-Ve	6 (14.6%)	6 (26.1%)	0.26
+Ve	35 (85.4%)	17 (73.9%)	
CD 5			
-Ve	24 (58.5%)	16 (69.6%)	0.382
+Ve	17 (41.5%)	7 (30.4%)	
CD 23			
-Ve	28 (68.3%)	21 (91.3%)	**0.037***
+Ve	13 (31.7%)	2 (8.7%)	
CD 10			
-Ve	24 (58.5%)	12 (52.2%)	0.622
+Ve	17 (41.5%)	11 (47.8%)	
CD 3			
-Ve	34 (82.9%)	17 (73.9%)	0.39
+Ve	7 (17.1%)	6 (26.1%)	
CD 15			
-Ve	41 (100%)	22 (95.7%)	0.178
+Ve	0 (0%)	1 (4.3%)	
TdT			
-Ve	40 (97.6%)	22 (95.7%)	0.674
+Ve	1 (2.4%)	1 (4.3%)	
LCA			
-Ve	39 (95.1%)	20 (87%)	0.243
+Ve	2 (4.9%)	3 (13%)	
c-myc			
-Ve	39 (95.1%)	21 (91.3%)	0.545
+Ve	2 (4.9%)	2 (8.7%)	
CD 99			
-Ve	40 (97.6%)	23 (100%)	0.45
+Ve	1 (2.4%)	0 (0%)	
CD 30			
-Ve	40 (97.6%)	22 (95.7%)	0.674
+Ve	1 (2.4%)	1 (4.3%)	
CD 68			
-Ve	40 (97.6%)	23 (100%)	0.45
+Ve	1 (2.4%)	0 (0%)	
CD79a			
-Ve	40 (97.6%)	21 (91.3%)	0.256
+Ve	1 (2.4%)	2 (8.7%)	
CD 22			
-Ve	28 (68.3%)	17 (73.9%)	0.637
+Ve	13 (31.7%)	6 (26.1%)	
CD 19			
-Ve	28 (68.3%)	17 (73.9%)	0.637
+Ve	13 (31.7%)	6 (26.1%)	
Bcl2			
-Ve	31 (75.6%)	16 (69.6%)	0.599
+Ve	10 (24.4%)	7 (30.4%)	
Bcl6			
-Ve	36 (87.8%)	17 (73.9%)	0.158
+Ve	5 (12.2%)	6 (26.1%)	

Negative aCA IgM was<18 MPL; high, ≥ 18 MPL. Statistically significant differences (P<0.05) are indicated with an asterisk (*). NHL: Non-Hodgkin's Lymphoma; N: Number; aCA: Anticardiolipin Antibodies

Table 3: Correlation of positive aCA IgM levels with immunophenotyping markers in NHL patients.

aCL IgG in NHL

Patients with NHL had significantly higher serum levels of aCL IgG than controls (P<0.001). The mean aCA IgG level was 28.91 ± 13.67 GPL (2-75) in the patient group and 3.41 ± 1.52 GPL (1.1- 6.0) in the control group (Figure 2A).

The newly diagnosed patients showed serum aCA IgG levels ranging from 7-55 GPL with a mean of 33.52 ± 10.62 GPL. Patients with CR had aCA IgG values ranging from 2 to 45 GPL with a mean of 11 ± 13.05 GPL. Patients with partial remission had aCA IgG levels ranging from 7-50 GPL with a mean of 26.2 ± 11.84 GPL. Patients in relapse had values ranged from 19–75 GPL with a mean of 32.63 ± 11.76 GPL (Figure 2B).

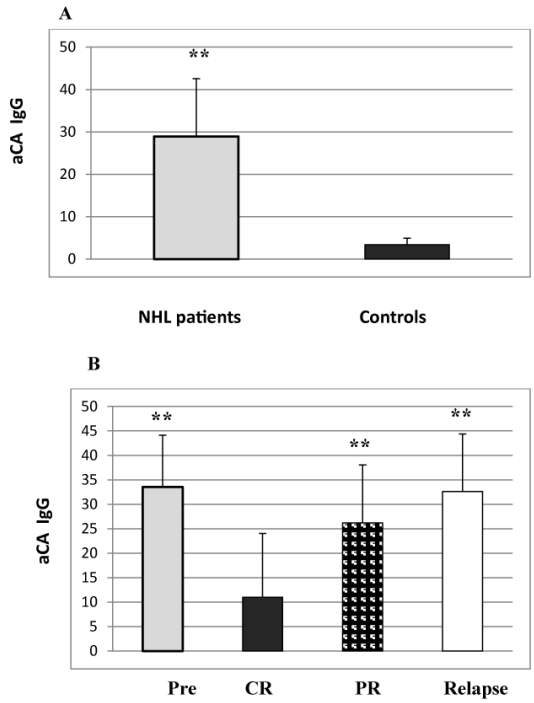

Figure 2: aCA IgG levels in NHL patients. (A): Serum aCA IgG level was measured and compared in NHL patients (n=64) and controls (n=30). Serum level of aCA IgG was significantly higher in NHL patients than in healthy controls (** P<0.001). (B): Serum aCA IgG levels in different groups of NHL patients. aCA IgG levels were significantly higher in patients with no treatment, in partial remission, relapse compared to complete remission (** P<0.001). NHL: Non-Hodgkin's lymphoma; aCA: Anticardiolipin Antibodies; Pre: Pretreatment; CR: Complete Remission; PR: Partial Remission.

IgG Antibodies were found in 54 of 64 patients with NHL (84.3%). Among aCL antibody-positive patients, complete remission occurred in 1 of 54 (1.9%); 22 patients with no treatment (40.7%); and 9 patients with partial remission (16.7%). Relapse occurred in 22 of 54 patients with positive aCA IgG (40.7%). Significant positive correlation was found between newly diagnosed patients with no treatment, patients in relapse and aCL IgG positivity (P <0.001). Significant negative correlation was found between aCL IgG antibodies and white blood cells (WBCs) (P=0.035). There was an association between the positivity of aCL IgG and histology of lymphoma (P=0.033) (Table 4).

	ACA IgG		**P value**
	Negative ACA (n=10)	**Positive ACA (n=54)**	
Age			
Range	(20-65)	(13-75)	0.384
Mean ± SD	50.5 ± 14.15	45.92 ± 15.3	
Sex			
Male	5 (50%)	33 (61.1%)	0.511
Female	5 (50%)	21 (38.9%)	
Treatment outcome			
No treatment	1 (10%)	22 (40.7%)	**<0.001****
complete remission	8 (80%)	1 (1.9%)	
partial remission	1 (10%)	9 (16.7%)	
relapse	0 (0%)	22 (40.7%)	
Diagnosis 1			
FCL	1 (11.1%)	9 (20.9%)	**0.033***
DLCL	2 (22.2%)	21 (48.8%)	
CLL	5 (55.6%)	9 (20.9%)	
SCL	1 (11.1%)	0 (0%)	
others	0 (0%)	4 (9.3%)	
Diagnosis 2			
B	9 (90%)	43 (79.6%)	0.44
T	1 (10%)	11 (20.4%)	
Hb			
Range	(2.8-20)	(1.5-18.9)	0.840*
Mean ± SD	9.16 ± 5.22	6.14±3.43	
WBCs			
Range	(2.8-20)	(1.5-18.9)	**0.035***
Mean ± SD	9.16 ± 5.22	6.14 ± 3.43	
Platelets			
Range	(60-347)	(50-651)	0.552
Mean ± SD	207.5 ± 103.81	234.87 ± 127.1	

AST			
Range	(17-163)	(13-566)	0.527
Mean ± SD	43.7 ± 43.38	58.37 ± 81.46	
ALT			
Range	(12-217)	(2.5-232)	0.585
Mean ± SD	49.3 ± 62.28	52.36 ± 43.71	
LDH			
Range	(300-648)	(268-1416)	0.066
Mean ± SD	469.8 ± 129.9	619.83 ± 245.69	
Urea			
Range	(22-38)	(14-65)	0.903
Mean ± SD	30.7 ± 5.79	31.16 ± 11.65	
Creatinine			
Range	(0.6-1.1)	(0.5-2.7)	0.381
Mean ± SD	0.75 ± 0.17	0.85 ± 0.35	
Hepatomegally			
No	6 (60%)	22 (40.7%)	0.259
Yes	4 (40%)	32 (59.3%)	
Spleenomegally			
No	4 (40%)	19 (35.2%)	0.771
Yes	6 (60%)	35 (64.8%)	
L.N. enlargement			
No	0 (0%)	0 (0%)	1
Yes	10 (100%)	54 (100%)	

Negative aCA IgG was <18 GPL; high, ≥ 18 GPL. Statistically significant differences (P<0.05) are indicated with an asterisk (*). Highly statistically significant differences (P<0.001) are indicated with asterisks (**). NHL: Non-Hodgkin's Lymphoma; N: Number; aCA: Anticardiolipin Antibodies; FCL: Follicular Cell Lymphoma; DLCL: Diffuse Large B - Cell Lymphoma; CLL: Chronic Lymphocytic Leukaemia; SCL: Small Lymphocytic Lymphoma ; Hb: Haemoglobin; WBCs: White Blood Cells; AST: Asparatate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; LN: Lymph Node.

Table 4: Correlation of positive aCA IgG level with features in NHL patients.

Significant negative correlation was found between CD23 and positive aCL IgG antibody titre (P=0.003) but not with other immunophenotyping markers (Table 5).

	ACA IgG		**P value**
	Negative ACA	**Positive ACA**	
	(n=10)	**(n=54)**	
CD 20			
-Ve	1 (10%)	11 (20.4%)	0.44
+Ve	9 (90%)	43 (79.6%)	
CD 5			
-Ve	4 (40%)	36 (66.7%)	0.11
+Ve	6 (60%)	18 (33.3%)	
CD 23			
-Ve	4 (40%)	45 (83.3%)	**0.003***
+Ve	6 (60%)	9 (16.7%)	
CD 10			
-Ve	7 (70%)	29 (53.7%)	0.34
+Ve	3 (30%)	25 (46.3%)	
CD 3			
-Ve	9 (90%)	42 (77.8%)	0.378
+Ve	1 (10%)	12 (22.2%)	
CD 15			
-Ve	10 (100%)	53 (98.1%)	0.664
+Ve	0 (0%)	1 (1.9%)	
TdT			
-Ve	10 (100%)	52 (96.3%)	0.536
+Ve	0 (0%)	2 (3.7%)	
LCA			
-Ve	10 (100%)	49 (90.7%)	0.316
+Ve	0 (0%)	5 (9.3%)	
c-myc			
-Ve	9 (90%)	51 (94.4%)	0.594
+Ve	1 (10%)	3 (5.6%)	
CD 99			
-Ve	10 (100%)	53 (98.1%)	0.664
+Ve	0 (0%)	1 (1.9%)	
CD 30			
-Ve	10 (100%)	52 (96.3%)	0.536
+Ve	0 (0%)	2 (3.7%)	
CD 68			
-Ve	10 (100%)	53 (98.1%)	0.664
+Ve	0 (0%)	1 (1.9%)	
CD 79a			
-Ve	9 (90%)	52 (96.3%)	0.387
+Ve	1 (10%)	2 (3.7%)	

CD 22			
-Ve	9 (90%)	36 (66.7%)	0.138
+Ve	1 (10%)	18 (33.3%)	
CD 19			
-Ve	9 (90%)	36 (66.7%)	0.138
+Ve	1 (10%)	18(33.3%)	
Bcl2			
-Ve	9 (90%)	38 (70.4%)	0.197
+Ve	1 (10%)	16 (29.6%)	
Bcl6			
-Ve	9 (90%)	44 (81.5%)	0.512
+Ve	1 (10%)	10 (18.5%)	
Negative aCA IgG was <18 GPL; high, ≥ 18 GPL. Statistically significant differences (P<0.05) are indicated with an asterisk (*). NHL: Non-Hodgkin's lymphoma; N: Number; ACA: Anticardiolipin Antibodies			

Table 5: Correlation of positive aCA IgG levels with immunophenotyping markers in NHL patients.

Discussion

A number of studies have focused on the association between anticardiolipin antibodies and hematological malignancies. These antibodies have been found in association with many malignancies, particularly hematological malignancies including lymphomas, acute myeloid leukaemia, chronic myelocytic leukemia and lymphoproliferative disorders [16,28].

This study showed elevated aCL antibodies, confirming that the prevalence of aCL antibodies in NHL patients is higher than in healthy subjects. In this study, aCl IgM and aCL IgG antibodies were detected in 35.9% and 84.3% respectively in NHL patients, which is higher to the previous reports. Stasi et al. [25] reported a prevalence of 35.7% aCL in NHL, whereas Genvresse et al. [29] and Zukerman et al. [17] reported a prevalence of 26.6% and 39% of aCL respectively.

The present study showed elevated serum levels of ACA IgM in (35.9%) of the patients with NHL. In previous reports, aCA IgM antibodies were found in only one patient [30]. In one study of 38 patients with NHL, aCA IgM could be detected in 5% of the patients [31]. This may be explained by detecting aCA IgM levels at the time of diagnosis of NHL.

When correlated with several other established clinical, laboratory and immunophenotyping markers, positive aCA (IgM, IgG) levels were negatively associated with CD23. CD23 antigen is expressed in low-grade NHL but is rarely present in high grade lesion [32,33]. Consequently, Anticardiolipin antibody-positive patients had more advanced disease in comparison with negative patients, thus high anticardiolipin antibody at advanced stage may support its use as a poor prognostic marker. This is supported by a study indicated that aCA levels are prognostic variables in aggressive NHL [34]. No studies analysed the serum levels aCA IgM with reference to the phenotypic characteristics.

Furthermore, positive aCA IgM levels showed a significant correlation with the failure of response to therapy. It would be of interest to determine whether serial monitoring of aCA IgM levels after remission could be useful for the early prediction of relapse. Various mechanisms have been suggested for the production of aCA IgM antibodies in relapse in the NHL including; production of ACL antibodies directly by malignant cells, production of autoantibodies by the immune system cells that activated against lymphoma cell phospholipid antigens and production of monoclonal antibodies with all antibody activities [35,36]. Normal levels of gamma globulins in patients ruled out the possibility of a nonspecific binding in the aCL-ELISA test as the main cause of the positivity for aCL IgM antibodies.

In the present study, serum levels of aCL IgG have been frequently elevated in patients with NHL at diagnosis, when compared with the levels in healthy controls, and after treatment, those levels decreased substantially. Their measurement, hence, was useful to predict treatment outcome and disease prognosis. It has been shown that anticardiolipin antibody-positive patients had the most advanced disease in comparison with negative patients [11,31].

Clinical and laboratory correlates of aCL IgG levels in NHL have been previously studied with some controversial results [37]. The present study verified a negative association between higher aCA IgG levels and white blood cells. This may be explained by the fact that cell recovery after treatment is affected. Additionally, patients with higher ACA IgG levels associated with lymphoma histology which may help in NHL diagnosis and treatment plan.

The patients were treated with CHOP chemotherapy [38] regimens in this study. While NHL is responsive to treatment, a continuous rate of relapse is usually seen in advanced stages. Previous studies have shown that histone methyltransferases G9a and GLP plays a key role in the regulation of embryonic stem cell differentiation [39] and maintenance of imprinted DNA methylation [40]. Since the enzymatic activity of G9a/GLP complex is also essential for the growth and differentiation of leukaemia cells, inhibition of G9a and its partner protein GLP has been found to prevent the deterioration of leukaemia [41]. In addition, since the inhibitor of EZH2, a component involved in PRC2 complex, also plays a role in the treatment of lymphoma [42], prevent the function of epigenetic modifiers might facilitate the treatment of lymphoma and generation the inhibitors of these enzymes might be the new strategies for the cure of human blood carcinomas. Therefore, it would be important to further evaluate whether the prognostic value of serum aCL levels in NHL patients receiving these new strategies.

In conclusion, anticardiolipin antibodies are associated with lymphomas. Their determination is useful to predict treatment outcome and disease prognosis.

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