

The Relationship between Antiphospholipid Antibodies and Silent Thrombosis Detected by Duplex in Patients with Lymphoproliferative Neoplasms

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ABSTRACT

Background: Numerous epidemiological research and investigations have been done discussing the connection between malignancies and antiphospholipid antibodies. Several investigations have shown that hematological malignancies may be related with the development of antiphospholipid antibodies but do not always enhance thrombotic risk in these patients.

Objective: The aim of the current work was to evaluate the association of lymphoproliferative disorders and thrombosis evident by duplex in clinically asymptomatic patients and how it relates to having antiphospholipid antibodies.

Patients and methods: Study was conducted on 46 patients with lymphoproliferative disorders diagnosed by either lymph node biopsy or bone marrow aspirate, biopsy and immunophenotyping. Patients were recruited from Kasr Alainy Clinical Hematology Department from July 2020 to May 2022. These patients performed duplex on mesenteric and lower limb vessels to detect recent thrombosis or evidence of old thrombotic events. The patients were also investigated for PTT, lupus anticoagulants (LA), antibodies of B2 glycoprotein I, anticardiolipin, complete blood picture (CBC), and kidney and liver function tests.

Results: Mean age of the studied group was 51.17±13.22 years with 52.2% males and 47.8% females. Twelve (26.1%) of patients showed evidence of thrombosis or remnant of thrombus and recanalization, all of them had no clinical symptoms while the rest of the patients; 34 (73.9%) revealed no signs of thrombosis. There was no relation between the positively found antiphospholipid antibodies and thrombosis in the studied population.

Conclusion: It could be concluded that there is evidence of increased thrombosis in patients with lymphoproliferative disorders, but no statistically significant correlation in relation to lymphoproliferative diseases and antiphospholipid antibodies.

Keywords: Duplex, Lymphoproliferative Neoplasms, Silent Thrombosis, Anti-Phospholipid antibodies.

INTRODUCTION

A diverse range of illnesses are included under lymphoproliferative disorders (LPD). They take place when the normal controls on lymphocyte proliferation fail, causing the lymphoid cells to proliferate unchecked and independently. This may result in extranodal areas involvement, such as the bone marrow, and occasionally can cause lymphocytosis and/or lymphadenopathy ⁽¹⁾.

Patients with cancer, particularly hematological cancers, can develop thrombosis, due to the malignancy itself or treatment-related ⁽²⁾. The synthesis of tissue factors and other pro-coagulant chemicals, which disrupt the endothelium balance between thrombosis and anti-coagulation, is a part of the pathophysiology of thrombosis associated with malignancy ⁽³⁾.

Antiphospholipid antibodies (APL) are autoantibodies directed towards complexes of anionic phospholipids and protein-phospholipid. It is associated with antiphospholipid syndrome ⁽⁴⁾.

Antiphospholipid syndrome (APS) characterized by thrombosis of veins or arteries, recurrent abortion in women, and persistent laboratory evidence of antiphospholipid antibodies. The most commonly identified APL antibodies are anticardiolipin (ACL), lupus anticoagulant (LA), and anti-2-glycoprotein I (anti-2GPI) ⁽⁴⁾.

Antiphospholipid antibodies have been found in a wide range of cancer patients. Numerous case reports and analysis have shown that a subset of people with cancer who have antiphospholipid antibodies also have thrombotic associations with APS ⁽⁵⁾.

The immune system's creation of autoantibodies in response to tumor antigens, or the synthesis of monoclonal immunoglobulins with LA and ACL activity, and tumor cell secretion of ACL have all been proposed as mechanisms explaining the link between aPL and cancer ⁽⁶⁾. APL antibody levels do not appear to reflect their pathogenicity, and the creation of APL does not always raise the risk of thrombosis in individuals with hematologic malignancies ⁽⁶⁾.

Patients suffering from cancer are already at a significant risk of thrombosis, and this risk is increased when the patients are APL carriers because cancer can act as the second hit that triggers thrombosis. However, the occurrence of APL-related complications is less frequent in patients suffering from hematological cancers and is even rare in patients with lymphoproliferative malignancies ⁽⁷⁾.

The study's goal was to look at the relationship between lymphoproliferative diseases, thrombosis, and antiphospholipid antibodies (LA, aCL IgG and IgM, and anti-2GPI IgG and IgM).

PATIENTS AND METHODS

This study included a total of 46 Egyptian adults with lymphoproliferative disorders, attending at Department and clinic of Clinical Hematology, Kasr Alainy University Hospitals. This study was conducted between July 2020 and May 2022.

Inclusion Criteria: Any adult patient with lymphoproliferative disorders and ≥ 18 years.

Exclusion Criteria: Patients < 18 years with a past history of the thrombotic event, a family history of thrombosis, or having any other known risk factor of thrombosis (thrombophilic or known to have an autoimmune illness).

All patients were subjected to:

A thorough history is taken, as well as a thorough clinical examination. Laboratory testing included a complete blood picture (CBC), liver function tests, renal function tests, LDH, Hepatitis B surface antigen (HBsAg), Anti Hepatitis Antibody (HCVAb), as well as human immunodeficiency virus (HIV) Ag & Ab and coagulation profile (PT, PTT, INR). Radiological investigations were done in the form of CT abdomen, neck and chest, Abdomino-pelvic ultrasonography in addition to abdominal and lower limb duplex.

Normal radiological tests required no preparation, but if a supplemental investigation of abdominal veins was also required, the patient was advised to fast for 12 hours prior to examination.

Duplex was performed on deep veins of the lower limb using 7.5 MHz probes, whereas abdominal arteries were investigated using probes ranging from 2 to 5 MHz. In other words; three probes and a high-level scanner are required.

The probe was used in a transverse position for deep venous ultrasonography (perpendicular to axis of the vein). Anatomy of the portal vein (PV) was investigated by B-mode imaging, whereas the anatomy of the mesentery was evaluated using a combination of B-mode imaging and Doppler assessment of the visceral arteries. Doppler evaluation assessed disease severity and should include assessing the presence or absence of flow, as well as evaluating peak systolic velocity, end diastolic velocity, and waveform analysis when flow is present⁽⁸⁾.

Detection of LA was done by Lupus anticoagulant-sensitive APTT Reagent and the result was considered prolonged if the APTT is more than 44 seconds. Detection of ACL & anti- $\beta 2$ GPI IgG/IgM Antibodies were done by ELISA. In ACL (Normal: IgG: 0 - 120 GPL-U/ml), (Normal: IgM: 0 - 80 MPL-U/ml). The result considered Negative if IgG < 7 GPL-U/ml, IgM < 10 MPL-U/ml and The result considered Positive if IgG > 7 GPL-U/ml, IgM > 10 MPL-U/ml. In anti- $\beta 2$ GPI IgG/IgM Antibodies (Normal IgG: 0 - 100 U/ml, IgM: 0 - 100 U/ml), The result considered

Negative if IgM < 5 U/ml, IgG < 5 U/ml, Borderline if IgM 5-8 U/ml, IgG 5-8 U/ml, Positive if IgM > 8 U/ml, IgG > 8 U/ml.

Statistical Methods

The social sciences statistical package (SPSS) version 26 was used to code and enter the data (IBM Corp., Armonk, NY, USA). The mean, standard deviation, median, minimum, and maximum values were used to summarize quantitative data, and frequency (count) and relative frequency (%) were used to summarize categorical data. The non-parametric Mann-Whitney test was used to compare quantitative variables. The Chi-square (χ^2) test was used to compare categorical data. When the anticipated frequency was less than 5, the exact test was employed instead. P values < 0.05 were statistically significant.

Ethical Commite Approval

Research Ethics Committee of Cairo University's approved its clearance for the project (Code:MS-146-2020). Written informed consent of all the participants was obtained (After discussing the essence of the disease, the complications and possible benefits of the research and the procedure, each patient signed an informed written consent form) . The conduct of this work guided by Helsinki's Declaration & the World Medical Association's code of ethics for studies that involve humans.

RESULTS

This study included 46 patients with mean age of 51.17 ± 13.22 ranged from 23 to 73 years. Regarding sex distribution 24 (52.2%) were males and 22 (47.8%) were females.

Laboratory results of the lymphoproliferative cases: Basic laboratory workup of patients are shown in Table 1.

Table (1): Basic workup of the patients

	Mean	Standard Deviation
TLC ($\times 10^3$ /ul)	24.58	2.370
Hemoglobin (g/dl)	10.46	2.51
PLTs ($\times 10^3$ /ul)	205.91	14.94
Urea (mg/dl)	30.80	1.37
Creatinine (mg/dl)	0.87	0.23
ALT (U/L)	28.72	5.90
AST (U/L)	32.65	6.59
LDH (IU/L)	329.04	24.75
PT (seconds)	13.17	1.39
INR	1.04	0.11
PTT (seconds)	32.12	9.35

Reference values of lab results are TLC ($4-11 \times 10^3$), Hemoglobin (12-15 g/dL), Platelets (150-450

10³), Urea (17-43 mg/dL), creatinine (0.6-1mg/dL), ALT (up to 35 U/L), AST (up to 35 U/L), LDH (208-378U/L), PT (11-15 seconds), INR (up to 1.1), PTT (up to 44 seconds).

Viral screening of the patients showed that 8 cases (17.4%) were HCV positive (Treated) while only one case (2.2%) was HBV positive (On treatment). The rest of the 37 cases had a negative virology screening. All the patients were HIV-negative.

Radiological assessment of these patients showed that 34 (73.9%) patients had splenomegaly and 38 patients (82.6%) had lymphadenopathy.

Spleen is considered enlarged with measurements more than 13 cm, while lymph nodes are considered enlarged with lymph nodes measuring more than 1.5 cm.

In 39.1 % of cases Indolent non-Hodgkin lymphoma was found including Waldenstrom lymphoma, chronic lymphocytic leukemia , marginal zone lymphoma, and hairy cell leukemia while aggressive non-Hodgkin lymphoma cases were 34.8% including large B cell lymphoma, anaplastic T cell lymphoma and angioimmunoblastic lymphoma. Hodgkin lymphoma was found in 8.7% of the cases, with the remaining 17.4% being other different kinds of Non-Hodgkin lymphoma.

Twelve (26.1%) of patients showed evidence of thrombosis or remanent of thrombus and recanalization, all of which had no clinical symptoms while the rest of the patients 34 (73.9%) revealed no signs of thrombosis. Antiphospholipid antibodies results are illustrated in Table(2).

Table (2): Antiphospholipid antibodies results

		Count	%
LAC	Positive	1	2.2%
	Negative	45	97.8%
ACL IgG	Positive	0	0.0%
	Negative	46	100.0%
ACL IgM	Positive	2	4.3%
	Negative	44	95.7%
B2Gpt IgG	Positive	2	4.3%
	Negative	44	95.7%
B2GPT IgM	Positive	6	13.0%
	Negative	40	87.0%

Antiphospholipid antibody positivity did not correlate with thrombosis in patients; all of the patients with positive antibodies did not have symptoms of thrombosis at the evaluation time .

Table (3): Relation between the positivity of antiphospholipid antibodies and thrombosis

		DUPLEX				p-value
		Thrombosis		No Thrombosis		
		Count	Percentage	Count	Percentage	
LAC	Positive	0	0.0%	1	100.0%	1
	Negative	12	26.7%	33	73.3%	
ACL IgG	Positive	0	0.0%	0	0.0%	-----
	Negative	12	26.1%	34	73.9%	
ACL IgM	Positive	0	0.0%	2	100.0%	1
	Negative	12	27.3%	32	72.7%	
B2Gpt IgG	Positive	0	0.0%	2	100.0%	1
	Negative	12	27.3%	32	72.7%	
B2GPT IgM	Positive	0	0.0%	6	100.0%	0.317
	Negative	12	30.0%	28	70.0%	

The study showed that 29.2% of patients having thrombosis were males while 22.7% were females both values are not statistically significant.

Relation of thrombosis to virology revealed no statistical significance, 24.3 % who had negative virology screen had thrombosis while 25% of HCV-positive patients had thrombosis and the single HBV-positive patient had thrombosis.

Regarding splenomegaly (20.6%) 7 of the patients with splenomegaly had thrombosis however this was not statistically significant while 12 of the patients (31.6%) with lymphadenopathy had thrombosis with borderline statistical significance showing a p-value 0.09.

Regarding the relation of thrombosis to diagnosis 50% of the patients with Hodgkin lymphoma had thrombosis (2 of the 4 patients enrolled), 22.2% of cases with indolent lymphoma had thrombosis, 25% of cases with aggressive lymphoma had thrombosis and other non-Hodgkin lymphomas also showed the same result of 25%. Those are all unremarkable in terms of statistics. Regarding the relation of the lab results to thrombosis, also no significant relation could be drawn from our results.

DISCUSSION

The occurrence of malignant disease and its treatment raises the likelihood of venous thromboembolism (VTE). Malignancy may be apparent before the development of VTE, concurrent with the diagnosis, or after the diagnosis⁽⁹⁾.

A research based on a large population involving 3220 consecutive patients between the ages of 18 and 70, stated that patients with cancer had a 7-fold higher risk of developing thrombosis in veins than those with no cancer. This study utilized the Multiple Environmental and Genetic Assessment (MEGA) of risk variables for venous thrombosis. The greatest danger of venous thrombosis was seen in individuals with hematological malignancies when age and gender were taken into account, followed by those with lung and gastrointestinal cancers⁽²⁾.

Multiple studies showed that the occurrence of thromboembolic consequences in lymphoproliferative patients is increased with a rate ranging from (1.5% up to 59.5%)and the incidence of VTE is comparable with that in solid tumors⁽¹⁰⁾.

Various study types (prospective or retrospective, with inpatient or outpatient patients, disease kinds (indolent vs. aggressive), the illness stage, and various intensities and quality of the chemotherapeutic protocols) are mostly to blame for this broad variation. The greatest VTE incidence among all lymphoma types was found central nervous system lymphoma patients, with a rate of 59.5% and a fatality rate of 7%⁽¹¹⁾.

This high prevalence may be due to combined central nervous system involvement from tumor-causing hypomobility and intense chemotherapy

frequently associated with steroids injection to address edema of the brain. Similar to how almost all patients experienced thromboembolic issues in the first three months of treatment, this further supports the idea that chemotherapy plays a part in the development of VTE⁽¹²⁾.

In 1038 lymphoma patients who received therapy, a research found a 7.7% total thromboembolic event incidence, with a statistically significant higher incidence in high-grade lymphoma than in low-grade lymphoma⁽¹³⁾.

Ottinger et al. found comparable results in a clinical trial looking at thromboembolization in patients suffering from high-grade NHLs. The clinical investigation revealed a (6.6%) prevalence of VTE⁽¹⁴⁾.

Numerous important epidemiological studies have examined the link between antiphospholipid antibodies and malignancies. Unresolved is the question of whether the existence of APL is a "epiphenomenon" of the malignancy or whether it is pathologically significant and directly affects the occurrence of thrombosis in these patients⁽¹⁵⁾.

It is currently unclear how antiphospholipid antibodies link to NHL. The findings in a patient with splenic lymphoma, where cultured lymphoma cells released IgM that was capable of binding cardiolipin in the presence of IL-6, support the idea that aPL are produced by the lymphoma cells⁽¹⁶⁾.

Additionally, in patients who reacted well to treatment, APL titers were stabilized. Additionally, multiple myeloma and Waldenström's macroglobulinemia are well-documented cases⁽¹⁷⁾.

The immune system may potentially create the antibodies as autoantibodies in reaction to the release of tumor-associated antigens or as monoclonal immunoglobulins with APL activity. In these situations, the decrease in titres of APL following chemotherapy can be attributed to either decreased immunosuppression brought on by the medication or lower antigenic stimulation of the smaller lymphoma mass⁽¹⁸⁾.

Reports of higher APL titres in patients with cutaneous T cell lymphoma revealed that pathogenic pathways may involve cytokine release by malignant cells T cells, activating the B-cell compartment to produce APL, and this may be related to an increase in the production of cytokines like IL-6⁽¹⁹⁾.

The existence of a common etiology for both diseases, such as genetic factors favoring a shared genetic susceptibility, with immune system immunoregulatory disturbances or persistent stimulation of lymphocytes increasing the likelihood of initiating mutations, is another theory that has been put forth⁽¹⁸⁾.

The authors further stated that the presence of APL may be a risk factor for hematological neoplasms and that it is important to keep this potential in mind both during the initial examination and subsequent monitoring of these patients. Gomez-Puerta et al.

validated this conclusion by studying 120 cases of APL antibodies and malignancies and finding that 26% of cases of antiphospholipid and cancer were hematological malignancies^(20,21).

It is recommended that not all NHL patients should have routine APL screening, but those who have episodes of thrombosis and abnormal coagulation tests should. In asymptomatic APL-positive patients, APL antibody frequently fades after rituximab treatment for the underlying B-cell NHL. However, in high-risk patient populations, thromboprophylaxis should be taken into account (triple APL positivity)⁽⁵⁾.

Our study was conducted on 46 patients with variable lymphoproliferative disorders who performed mesenteric and lower limb duplex and antiphospholipid antibodies (LA, ACL, β 2GPI). The mean age of patients was 51.17 ± 13.22 ranged from 23 to 73 years. Regarding sex distribution 24 (52.2%) were males and 22 (47.8%) were females. Among patients, 82.6% had widespread lymphadenopathy and 72.9% had splenomegaly at presentation. In our study 12 out of the 46 patients (26%) had thrombosis in mesenteric and lower limb vessels evident by duplex, without overt manifestations of these thrombotic events.

The highest positivity in APL was with anti- β 2GPI-IgM which was positive in 6 patients (13%) followed by anti- β 2GPI IgG and ACL-IgM both positive in 2 patients (4.3%) LA was only positive in one patient (2.2%), while ACL- IgG was negative in all patients. Our study concluded that no correlation was detected between antiphospholipid antibody positivity and thrombosis, as none of the patients with antibody positivity had thrombosis. Thrombosis might be correlated with lymphadenopathy with a borderline p-value of 0.09.

Our results were nearly agreed with the study conducted in 2007 by **Miesbach et al** which included patients with NHL history who had elevated IgM-APL titers, for the clinical signs of the antiphospholipid syndrome, they were examined. The patients tested positive for lupus anticoagulants and exhibited higher levels of IgG- ACL and IgM- ACL. These patients had no thrombotic complications thus This study hypothesized that antiphospholipid antibodies can develop in patients with hematopoietic and lymphoproliferative cancers even in the absence of thromboembolic symptoms⁽²²⁾.

Several studies came in agreement with our study regarding thrombosis in aggressive and indolent lymphomas. Where 25% of patients with aggressive lymphoma had thrombosis compared to 22% with indolent lymphoma. Keeping in mind that all patients in our study showed no clinical symptoms and their thrombosis was only detected by duplex.

There were 1149 thrombotic events among NHL patients, based on the analysis of 29 distinct cohorts encompassing 18,018 lymphoma patients.

Compared to those with low-grade disease, those with high-grade disease had a higher risk of thrombosis (8.3% versus 6.3%)⁽²³⁾.

Our study concluded that the most prevalent anti-phospholipid antibody among LPD patients was anti- β 2GPI- IgM, showing positivity in 13% of the patients.

Bairey, et al prospective's cohort study which included 86 patients with NHL who were tested for antiphospholipid antibodies, The most common serotypes were discovered to be anti-2GPI-IgM and anti-2GPI-IgA. Three out of 67 patients (4.5%) who took the lupus anticoagulant tested positive, while nine more patients had findings that were on the fence (13.4%)⁽¹⁶⁾.

These study results were similar to our results regarding anti- β 2GPI-IgM prevalence. in contrast, a 2004 research by **Pusterla et al** included 100 patients with various lymphomas who had their lupus anticoagulants and anticardiolipin antibodies measured at the time of diagnosis. Twenty-seven patients had lupus anticoagulants and/or anticardiolipin antibodies⁽⁷⁾. These patients when followed up showed a higher rate of thrombosis but were similar regarding relapse and death rates to antiphospholipid-negative patients. So this study showed that the determination of antiphospholipid antibodies may be helpful to identify patients who are at high risk for thrombotic problems. But, it cannot tell about therapy outcome or how long a patient will live.⁽⁷⁾.

Our study showed more prevalence of thrombosis in HL patients with a 50% (4/8) incidence of thrombosis compared to 23.8 % (10/42) in NHL. However, In a study of lymphoma patients, **Park et al** found that NHL patients had a greater global incidence of VTE than Hodgkin lymphoma (HL) patients (8% vs. 6.7%, respectively)⁽²⁴⁾.

Park et al showed the opposite result with a much lower prevalence of VTE (7.8%) in both HL and NHL patients compared to our 26 %. The diversity in the results between the previously conducted studies and this study is due to the heterogeneity of the cases with lymphoproliferative disorders included in this study and due to the small number of cases. It is advised to monitor a larger cohort of patients to determine whether or not thrombotic events or the emergence of APL will take place⁽²⁴⁾.

CONCLUSION:

It could be concluded that there is evidence of increased thrombosis in patients with lymphoproliferative disorders, but no statistically significant correlation in relation to lymphoproliferative diseases and antiphospholipid antibodies.

An important question that, if proven, will give us a quick and easy screening tool for determining the risk of thrombosis in malignancy patients generally and

patients with lymphoproliferative neoplasms in particular is the assessment of thrombotic risk in these patients and its association with an increased level of APL. In our study, there was no relationship between the positivity of APL and thrombosis in patients, and all the patients with positive antibodies showed no evidence of thrombosis till the time of examination.

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