High Incidence of Antiphospholipid Antibodies in Newly Diagnosed Patients With Lymphoma and a Proposed aPL Predictive Score

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Abstract

Given that the presence of antiphospholipid (aPL) antibodies has been proposed to be associated with thrombosis in newly diagnosed patients with lymphoma, we conducted a prospective cohort study on these patients. In all, 154 patients were enrolled. More than half were advanced-stage diffuse large B-cell lymphoma. Approximately one-third (35.7%) of the patients had the presence of aPLs, with single-, double-, and triple-aPL positivities of 29.9%, 5.2%, and 0.6%, respectively. Of the 154 patients, 8 (5.19%) developed symptomatic thrombosis during follow-up. There were no significant differences in the incidences of thrombosis for the aPL-positive and aPL-negative groups (5.5% vs 5.1%; $P = 1.000$). In a multivariate analysis, patients with male sex and lymphoma stage IV were significant risk factors for aPL positivity, with odds ratio [OR] = 2.22 (95% CI: 1.11-4.45), $P = .025$, and OR: 2.34 (95% CI: 1.17-4.67), $P = .016$, respectively. An aPL predictive score of ≥ -1 was predictive of aPL positivity, with a sensitivity of 83.6% and specificity of 34.3%.

Introduction

Patients with cancer are more at risk of thrombosis than the general population, having a 5-fold higher risk than those without cancer. In fact, the incidence of thrombosis is as high as 10% to 15% during the course of their cancer.[1,2] This applies to both hematologic malignancies and solid cancers.[3-5] The incidence in large groups of patients with malignant lymphomas has varied between 1.5% and 59.5%, depending on the patients' lymphoma subtype, disease stage, chemotherapy regimen, and the intensity of the chemotherapy protocol.[3-5] The highest incidences have been found among patients with major risk factors for thrombosis, namely, high-grade non-Hodgkin lymphoma, a high international prognostic index score, and the presence of a mediastinal mass and/or central nervous system lymphoma. Minor thrombotic risk factors have been reported in those with old age, a higher stage of disease, immobilization, and/or the presence of a central venous catheter. Most thromboses occur upon the diagnosis of the cancer or early in the course of the cancer treatment (particularly during the first 3 months).[3-9]

Currently, the pathogenesis of thrombosis in patients with lymphoma is still not well understood. Venous stasis from tumor compression or immobilization is well-known risk factors that contribute to thrombosis, particularly in patients with lymphoma with a huge mass or with immobilization due to a neurological deficit found in central nervous system lymphoma (CNSL).[10] Nevertheless, thrombosis may occur in lymphomas that are not large or do not have any CNS involvement. This suggests that there might be other causes, such as a hypercoagulable state, that lead to thrombosis. Given that lymphomas have a tendency to produce antibodies to many proteins,[11]

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immune-mediated thrombophilia is a possible cause of thrombosis in some patients with lymphoma.

Recent research has revealed a correlation between a thrombophilic state and a higher incidence of thrombosis in many kinds of malignancy, including lymphoma. Thus, 27% of newly diagnosed patients with lymphoma were found by one study to have lupus anticoagulants (LAs) and/or anticardiolipin (aCL) antibodies, compared with the incidence of 8% for the general population.[12] Interestingly, during the follow-up period of that research, the rate of thrombosis in the series was significantly higher among the patients with antiphospholipid (aPL) antibodies than without aPLs (5.1% vs 0.75% patients per year, respectively).[12] Those data have since been corroborated by another study of 66 cases of immune-mediated thrombophilia in lymphoma: Thrombosis occurred in 22 of 48 evaluable cases. Given that, after completion of the chemotherapy course, the LA became negative in more than one-third of the patients, its presence was suggested to be associated with the malignant disorder.[13] Although a number of studies also supported this proposed hypothesis of correlation between the presence of aPLs and thrombosis in patients with lymphoma,[14,15] others have not.[16] The pathogenesis of thrombosis of lymphoma and the presence of aPLs, therefore, remains unclear.[17]

In addition, we are not aware of any study having been conducted on an Asian population. We conducted this study to determine the incidence of aPL positivity in newly diagnosed patients with lymphoma with the goal of developing a predictive score for the presence of aPLs in those patients.

Methods

Patients and Procedures

This prospective, cohort study enrolled newly diagnosed patients with lymphoma. The patients were aged 15 years or older, and they were followed up at Siriraj Hospital, Mahidol University, Bangkok, Thailand, October 16, 2017, to February 28, 2018. We excluded patients with a history of any of the following: (1) previous venous/arterial thrombosis, (2) an unexplained recurrent abortion, (3) familial thrombophilia, (4) an autoimmune disease, (5) anticoagulant use, and (6) a liver disease or elevated liver enzyme (> 3 times the upper normal limit). Before the patients received lymphoma treatment, blood samples were collected for aPLs, comprising LA, aCL-immunoglobulin M (IgM), aCL-IgG, anti-β2 glycoprotein I (aβ2GPI)-IgM, and aβ2GPI-IgG. Lupus anticoagulant was detected using the dilute Russell's viper venom time and activated partial thromboplastin time (aPTT) tests (actin FSL reagent, Siemens) which is different from aPTT testing in routine coagulogram workup (actin FS). The enzyme-linked immunosorbent assay method was used to measure aCL-IgM, aCL-IgG, aβ2GPI-IgM, and aβ2GPI-IgG. We utilized commercially available kits (Euroimmun) for all testing. Following the guidelines outlined in the Declaration of Helsinki and all of its subsequent amendments, the institutional review board of

the Siriraj approved our study. It was supported by the Faculty of Medicine Siriraj Hospital, Mahidol University.

Clinical manifestations were collected; these consisted of the symptoms and physical signs of all of the patients at their initial presentation. A hospital-based chart review was performed for every patient until the end of the first chemotherapy regimen. Details of the thrombotic events that occurred throughout the first course of chemotherapy were also collected.

Statistical Analysis

The clinical characteristics were presented as median with interquartile range and as mean with standard deviation or percentage. The paired t test or the Mann-Whitney U test was used to analyze continuous data. Categorical data for comparisons between the groups were analyzed by the χ^2 test or Fisher exact test. Parametric and nonparametric analyses were applied. Univariate and multivariate predictors of aPL positivity were evaluated using a binary logistic regression analysis (backward-stepwise method) and presented as odds ratios (ORs) and 95% CIs. For all tests performed, a 2-tailed P value of <.05 was considered to be statistically significant. The aPL predictive score was calculated using a multiple logistic regression model, and a nomogram was employed to estimate the probability of aPL positivity. A receiver operating characteristic curve was used to evaluate the most suitable cutoff point. Furthermore, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value of this cutoff point. A software package (IBM SPSS Statistics for Windows, version 24.0, IBM Corp) was used for all statistical analyses.

Results

Baseline Characteristics

A total of 154 newly diagnosed patients with lymphoma were enrolled. Their mean age was 58.7 ± 16.5 years, with equal proportions of males and females. The most common lymphoma subtype was diffuse large B-cell (DLBC) lymphoma (52.6%), followed by marginal zone lymphoma (MZL; 9.7%), follicular lymphoma (FL; 6.5%), and primary CNSL (5.2%). Nearly half of the patients had lymphoma stage IV. The initial complete blood counts demonstrated a mean hemoglobin of 11.0 ± 2.3 g/dL, a median white blood cell count of 8.0×10^9/L (range: $1.5\text{-}44.0 \times 10^9$/L), and a median platelet count of 268×10^9/L (range: $21\text{-}764 \times 10^9$/L). The coagulogram results were a mean prothrombin time of 11.5 ± 1.6 seconds, a mean aPPT of 24.7 ± 3.3 seconds, and a median fibrinogen level of 442.1 mg/dL (range: 56.2-1,396.9 mg/dL). Table 1 illustrates the baseline patient characteristics and initial laboratory findings.

Incidence of aPL Positivity and Thrombotic Events

Approximately one-third (35.7%) of the patients had the presence of aPLs, with single-, double-, and triple-positivities of 29.9%, 5.2%, and 0.6%, respectively. The following positive

Table 1. Baseline Patient Characteristics and Initial Laboratory Findings.

	Cases, N = 154
Age (years), mean ± SD	58.7 ± 16.5
Gender	
Female	77 (50%)
Lymphoma subtypes	
Diffuse large B-cell lymphoma	81 (52.6%)
Marginal zone B-cell lymphoma	15 (9.7%)
Follicular lymphoma	10 (6.5%)
Hodgkin lymphoma	9 (5.8%)
Peripheral T-cell lymphoma	8 (5.2%)
Burkitt lymphoma	5 (3.2%)
Mantle cell lymphoma	4 (2.6%)
Extranodal NK/T-cell lymphoma	4 (2.6%)
Others	18 (11.7%)
Laboratory findings	
Complete blood count	
Mean Hb level (g/dL)	11.0 ± 2.3
Median WBC count (×10^9 L)	8 (1.5-44)
Median platelet count (×10^9 L)	268 (21-764)
Coagulogram	
Mean PT (seconds)	11.5 ± 1.6
Mean aPTT (seconds)	24.7 ± 3.3
Median fibrinogen (mg/dL)	443.1 (56.2-1396.9)
Median D-dimer (μg/L)	1255.1 (100-10 000)

Abbreviations: aPTT, activated partial thromboplastin time; Hb, hemoglobin; NK, natural killer; PT, prothrombin time; WBC, white blood cell.

results were determined: LA, 17.5% which were positive by aPTT-based method using actin FSL reagent (14.3%), dilute russell viper venom time method (2.6%) and both methods (0.6%); aβ2GPI-IgM, 17.3%; aβ2GPI-IgG, 0.6%; aCL-IgM, 3.2%; and aCL-IgG, 3.9%. Overall, aPL positivity was found for 39.5% of the DLBC lymphoma cases, 33.3% of the Hodgkin lymphoma, 40% of the FL, and 40% of the MZL. Moreover, aPL positivity was found in 25% of angioimmunoblastic T-cell lymphoma cases, 25% of peripheral T-cell lymphoma, and 50% of natural killer/T-cell lymphoma. Of the 154 patients, 8 developed thrombotic events, with venous thrombosis in 7 and an arterial thrombosis in the 1. Interestingly, only 3 thrombotic cases were aPL positive. One patient had triple positivity for aPLs without developing clinical thrombosis. Table 2 details the thrombotic events.

Comparisons of Clinical Characteristics, Laboratory Results, and Outcomes

The clinical characteristics of the aPL-positive and aPL-negative patients (age, body mass index, comorbidities, and initial laboratory findings) were not significantly different. However, 2 factors—gender and lymphoma stage IV—were statistically significantly different. The incidences of thrombosis in the aPL-positive and aPL-negative groups was identical (5.5% vs 5.1%; $P = 1.000$).

In the univariate and multivariate analyses, male gender and lymphoma stage IV had higher likelihoods of aPL positivity in patients with lymphoma, as presented in Table 3.

Development of a Predictive Score for aPL Positivity

The aPL predictive score of aPL positivity was assessed using the following multiple logistic regression model:

$$\text{aPL predictive score} = -1.44 + (0.8 \times A) + (0.85 \times B),$$

where $A = 0$ (if female sex) or $A = 1$ (if male sex) and $B = 0$ (if stage ≤III) or $B = 1$ (if stage IV).

We used the receiver operating characteristic curve analysis of the aPL predictive score. The most suitable cutoff level for aPL positivity was obtained when the area under the curve was 0.64 (95% CI: 0.55-0.73). The sensitivity of the score was 83.5%, whereas the specificity was 34.3% (Table 4).

Discussion

The prevalence of aPLs in the normal population has been reported by several studies to range from 1% to 5.6%.[18-21] In the present study, we analyzed the prevalence in newly diagnosed patients with lymphoma; we noted a considerably higher level (37.5%) in this group of patients, consistent with reports on other patients.[12,13] Notably, LA and aβ2GPI-IgM were the first and second most common aPLs in the aPL-positive group of our cohort. This finding differs from an earlier study, in which aCL antibodies were predominant,[12] while another study by Bairey et al[22] reported that aβ2GPI-IgM was the most common aPL found in lymphoma, with a prevalence of 40%. The current research is thus the first to report on Asian patients with lymphoma; furthermore, it used a prospective cohort design and enrolled a large number of patients. Although a number of case reports have demonstrated an association between aPLs and lymphoma,[23-26] most of the lymphoma subtypes hitherto published have been MZL. This could be explained theoretically by its unique, plasmacytic-differentiation characteristic. Nonetheless, our data showed that aPLs can also be found not only in indolent lymphomas (such as FL or MZL) but also in DLBC and T-cell lymphomas. These findings support 2 aPL production mechanisms: direct synthesis by lymphoma cells (found in plasmacytic-differentiated lymphomas)[27] and immune system production of the antibodies against the protein expressed on lymphoma cells.[11] The explanation why advanced-stage lymphoma tends to have more aPL positivity might be that a higher tumor load can produce more antibodies. For primary antiphospholipid syndrome, female gender is well known to be predominant due to a close correlation with auto-immune diseases. This is similar to other immune-mediated cytopenia (eg, immune thrombocytopenia or autoimmune hemolytic anemia) in which a majority of patients are young female. Nonetheless, the proportion of males nearly equate to females in the elderly groups.[28] This might explain why our results demonstrate a higher possibility of aPL positivity for the male gender due to our high mean age of 58.4 years. In addition, it has been proposed that HIV infection might contribute to aPL positivity.[29] There were only 4 HIV patients included in this study. Two of them had DLBC lymphoma and the aPL results were both positive for LA. While the other 2 patients had Burkitt lymphoma

Table 2. Details of Thrombotic Events in 8 Patients.

Case number	Age (years), gender	aPL results	Lymphoma subtype, location, and size	Location of thrombosis
Related to local compression (n = 5)				
1.	45, male	Positive	DLBCL, anterior mediastinal mass 6.7 cm × 9.5 cm × 10.6 cm	Right internal jugular and bilateral subclavian vein thrombosis
2.	63, male	Negative	PCNSL, right cerebellopontine mass 3.9 cm × 4.6 cm × 5.5 cm	Right sigmoid venous sinus thrombosis
3.	60, female	Negative	DLBCL, left retroperitoneal mass 5 cm × 6.2 cm × 8.3 cm	Left common femoral vein thrombosis
4.	19, male	Negative	DLBCL, anterior mediastinal mass 9.4 cm × 11.4 cm × 14.1 cm	Right internal jugular vein and right subclavian vein thrombosis
5.	31, male	Positive	DLBCL, HIV infection, multiple dural mass at right frontal, right sphenoid, left frontobasal, left temperoparietal, and left sphenoid area with bone and venous sinus invasion	Right cavernous sinus and left transverse sinus and left sigmoid sinus thrombosis
Unrelated to local compression (n = 3)				
6.	63, female	Negative	DLBCL, left parotid mass 2.6 cm × 3.7 cm × 4.3 cm	Acute pulmonary embolism
7.	23, male	Positive	DLBCL, HIV infection, hepatosplenomegaly without CNS involvement	Cerebral venous sinus thrombosis
8.	80, male	Negative	DLBCL, bilateral adrenal mass without compressive symptoms	Bowel ischemia (hypoperfusion and atherosclerosis)

Abbreviations: aPL, antiphospholipid; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; PCNSL, primary central nervous system lymphoma.

Table 3. Univariate and Multivariate Analysis for Risk Factors of aPL Positivity.

	aPLs negative, N = 99	aPLs positive, N = 55	*P* value	OR (95% CI)
Univariate				
Age (years)	58 ± 16	60 ± 17	0.392	
Male sex	43 (43.4%)	34 (61.8%)	***0.029***	2.11 (1.08-4.14)
BMI (kg/m^2)	22 ± 3.1	21.6 ± 3.0	0.429	
Hb (g/dL)	11.0 ± 2.2	11.1 ± 2.3	0.839	
WBC (×10^9 L)	8.2 (1.8-33.9)	7.8 (1.5-44)	0.444	
Platelet (×10^9 L)	278 (21-764)	254 (46-693)	0.315	
PT (seconds)	11.4 ± 1.5	11.6 ± 1.9	0.470	
Actin FS aPTT (seconds)	24.4 ± 3.4	25.4 ± 3.0	0.091	
D-Dimer (µg/L)	1095.6 (100-10 000)	1362.9 (100-9061.1)	0.598	
Fibrinogen (mg/dL)	440.7 (56.2-1396.9)	479.6 (149.3-1261.4)	0.913	
Lymphoma stage IV	38 (38.4%)	32 (58.2%)	***0.018***	2.23 (1.14-4.37)
Clinical thrombosis	5 (5.1%)	3 (5.5%)	1.000	
Multivariate				
Male sex	43 (43.4%)	34 (61.8%)	0.025	2.22 (1.11-4.45)
Lymphoma stage IV	38 (38.4%)	32 (58.2%)	0.016	2.34 (1.17-4.67)

Abbreviations: aPL, antiphospholipid; BMI, body mass index; Hb, hemoglobin; OR, odds ratio; PT, prothrombin time; WBC, white blood cell.

Table 4. Sensitivity, Specificity, Positive, and Negative Predictive Values of aPL Predictive Score.

Laboratory findings	Cutoff value	AUC	Sensitivity	Specificity	PPV	NPV
aPL predictive score		0.64	83.5%	34.3%	41.4%	79.1%
	≤−1	(0.55-0.73)	(71.2-92.2)	(25.1-44.6)	(32.2-51.2)	(64.0-90.0)

Abbreviations: aPL, antiphospholipid; AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

with negative aPL results. However, due to limited number of HIV patients in this study, we cannot clearly define the association between HIV infection and aPLs.

A previous aPL score to predict diagnosis of aPL syndrome and thrombosis has been proposed to be utilized in systemic autoimmune patients.[30] The parameters used in this score mainly depend on aPL testing. However, we developed a predictive score with high sensitivity for aPL screening in newly diagnosed patients with lymphoma. Patients who score ≤−1 might not benefit from aPL screening. In other words, if a patient is either male or stage IV lymphoma, it is worthwhile performing an aPL test. Nevertheless, the high incidence of

aPL positivity did not affect the frequency of thrombotic events in this patient group. Our results revealed that the incidence of symptomatic thrombosis after lymphoma diagnosis was approximately 5% for both the aPL-positive and aPL-negative groups. This contrasts with a previous report which found a significant relationship between aPL positivity and thrombosis.[12] The reasons behind this might be explained by certain limitations to our study. First, 60% of our thrombosis cases accounted for the compression of the venous system by the large lymphoma mass at presentation. As such, the hypercoagulable state did not contribute to thrombosis in those patients. In addition, the number of patients with thrombosis in the current research might not have been high enough to demonstrate a correlation between aPLs and the thrombotic rate. Thus, it would be beneficial to undertake further studies that include more patients in order to detect a greater number of thrombosis cases. Furthermore, although the sensitivity of aPL predictive score was good, the specificity was 34.3%. The current study recommends that high specificity tests were required for the aPL syndrome diagnosis.[31] We, therefore, have ongoing research on validating this score. Of note, routine aPTT coagulogram workup (actin FS) failed to show significant difference between aPLs-negative and aPLs-positive patients in univariate analysis to identify predictive factors of APL positivity for developing aPL predictive score, as shown in Table 3, that can be explained by its lower sensitivity to detect LA. Actin FSL reagent (aPTT-based method for LA screening) is different from actin FS reagent because it is designed to have lower phospholipid content, which is why it provides increased sensitivity to detect LA.[32] However, actin FSL reagent is not recommended to be used as a routine aPTT coagulogram workup to avoid false prolongation especially in elderly population.[32,33] Lastly, false positives of aβ2GPI and aCL can be found with several conditions, such as infections and inflammation; hence, this may have led to a high incidence of aPL positivity in our study. Repeated aPL profiles are needed to confirm the persistence of those findings. Although our results are unable to demonstrate a correlation between aPL positivity and the development of thrombosis, the positivity of aPLs in indolent lymphoma will alter the management plan for selected patients from watchful waiting to specific treatment.

Conclusions

There was a high incidence of aPL positivity in newly diagnosed patients with lymphoma. Nevertheless, there was no clear association between aPL positivity and the incidence of symptomatic thrombosis. An aPL predictive score was proposed to assume APLA positivity in newly diagnosed patients with lymphoma. We recommend testing for aPLs in patients with an aPL score higher than −1 because the positivity of aPLs may alter the plan of management, especially in cases of indolent lymphoma.

Authors' Note

All procedures were conducted in accordance with the ethical standards of the responsible committee on human experimentation, and in accordance with the 1964 Declaration of Helsinki and all of its subsequent revisions. The local ethical commission approved the study. Written informed consent was included. All authors designed the study. SK collected and drafted the manuscript. WO and TR supervised the project and made critical revisions to the manuscript. YN performed all laboratory results. All authors read and approved the final manuscript. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Scates SM. Diagnosis and treatment of cancer-related thrombosis. *Semin Thromb Hemost*. 1992;18(4):373-379.
2. Rickles FR, Levine MN. Epidemiology of thrombosis in cancer. *Acta Haematol*. 2001;106(1-2):6-12.
3. Caruso V, Di Castelnuovo A, Meschengieser S, et al. Thrombotic complications in adult patients with lymphoma: a meta-analysis of 29 independent cohorts including 18 018 patients and 1149 events. *Blood*. 2010;115(26):5322-5328.
4. Zhou X, Teegala S, Huen A, et al. Incidence and risk factors of venous thromboembolic events in lymphoma. *Am J Med*. 2010; 123(10):935-941.
5. Elice F, Rodeghiero F. Hematologic malignancies and thrombosis. *Thrombosis Res*. 2012;129(3):360-366.
6. Yokoyama K, Murata M, Ikeda Y, Okamoto S. Incidence and risk factors for developing venous thromboembolism in Japanese with diffuse large B-cell lymphoma. *Thromb Res*. 2012;130(1):7-11.
7. Park LC, Woo SY, Kim S, et al. Incidence, risk factors and clinical features of venous thromboembolism in newly diagnosed lymphoma patients: results from a prospective cohort study with Asian population. *Thromb Res*. 2012;130(3):e6-e12.
8. Khorana AA, Francis CW, Culakova E, Lyman GH. Risk factors for chemotherapy-associated venous thromboembolism in a prospective observational study. *Cancer*. 2005;104(12):2822-2829.
9. Ottinger H, Belka C, Kozole G, et al. Deep venous thrombosis and pulmonary artery embolism in high-grade non-Hodgkin's

lymphoma: incidence, causes and prognostic relevance. *Eur J Haematol*. 1995;54(3):186-194.

10. Goldschmidt N, Linetsky E, Shalom E, Varon D, Siegal T. High incidence of thromboembolism in patients with central nervous system lymphoma. *Cancer*. 2003;98(6):1239-1242.

11. Sawamura M, Yamaguchi S, Murakami H, et al. Multiple antibody production in a patient with splenic lymphoma. *Ann Hematol*. 1994;68(5):251-254.

12. Pusterla S, Previtali S, Marziali S, et al. Antiphospholipid antibodies in lymphoma: prevalence and clinical significance. *Hematol J*. 2004;5(4):341-346.

13. Lechner K, Simonitsch I, Haselböck J, Jäger U, Pabinger I. Acquired immune-mediated thrombophilia in lymphoproliferative disorders. *Leuk Lymphoma*. 2011;52(10):1836-1843.

14. Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum*. 2002; 46(4):1019-1027.

15. Go mez JAP, Cervera R, Espinosa G, et al. Antiphospholipid antibodies associated with malignancies: clinical and pathological characteristics of 120 patients. *Semin Arthritis Rheum*. 2006; 35(5):322-332.

16. Genvresse I, Lüftner D, Späth-Schwalbe E, Buttgereit F. Prevalence and clinical significance of anticardiolipin and anti-beta2-glycoprotein-I antibodies in patients with non-Hodgkin's lymphoma. *Eur J Haematol*. 2002;68(2):84-90.

17. Tincani A, Taraborelli M, Cattaneo R. Antiphospholipid antibodies and malignancies. *Autoimmun Rev*. 2010;9(4):200-202.

18. El-Roeiy A, Gleicher N. Definition of normal autoantibody levels in an apparently healthy population. *Obstet Gynecol*. 1988;72(4): 596-602.

19. Fields RA, Toubbeh H, Searles RP, Bankhurst AD. The prevalence of anticardiolipin antibodies in a healthy elderly population and its association with antinuclear antibodies. *J Rheumatol*. 1989;16(5):623-625.

20. Infante-Rivard C, David M, Gauthier R, Rivard GE. Lupus anticoagulants, anticardiolipin antibodies, and fetal loss. A case-control study. *N Engl J Med*. 1991;325(15):1063-1066.

21. Shi W, Krilis SA, Chong BH, Gordon S, Chesterman CN. Prevalence of lupus anticoagulant and anticardiolipin antibodies in a healthy population. *Aust N Z J Med*. 1990;20(3):231-236.

22. Bairey O, Blickstein D, Monselise Y, et al. Antiphospholipid antibodies may be a new prognostic parameter in aggressive non-Hodgkin's lymphoma. *Eur J Haematol*. 2006;76(5): 38491.

23. Belančić A, Vranić L, Ševeljević I, Hadžisejdić I, Načinović AD, Jonjić N. Antiphospholipid antibodies associated with nodal marginal zone lymphoma and its progression to diffuse large B-cell lymphoma—a case report. *Pathol Res Pract*. 2019;215(1):222-228.

24. Oka S, Ono K, Nohgawa M. Successful treatment of catastrophic antiphospholipid antibody syndrome associated with MALT lymphoma by autologous hematopoietic stem cell transplantation. *Intern Med*. 2017;56(10):1207-1212.

25. Gebhart J, Lechner K, Skrabs C, et al. Lupus anticoagulant and thrombosis in splenic marginal zone lymphoma. *Thromb Res*. 2014;134(5):980-984.

26. Regunath H, Shortridge J, Raza S, et al. Occult pulmonary mucosa-associated lymphoid tissue lymphoma presenting as catastrophic antiphospholipid antibody syndrome. *Oncol Lett*. 2013; 6(5):1261-1264.

27. Thiagarajan P, Shapiro SS, De Marco L.Monoclonal immunoglobulin M lambda coagulation inhibitor with phospholipid specificity. Mechanism of a lupus anticoagulant. *J Clin Invest*. 1980; 66(3):397-405.

28. Moragues Martinez MC, Hurst K, Mingot Castellano ME, Heiniger Mazo AI. Primary immune thrombocytopenia in elderly patients: clinical profile, efficacy and safety of treatment protocols. *Blood*. 2014;124 (21):4196. doi:10.1182/blood.V124.21.4196.4196

29. Leder AN, Flansbaum B, Zandman-Goddard G, Asherson R, Shoenfeld Y. Antiphospholipid syndrome induced by HIV. *Lupus*. 2001;10(5):370-374.

30. Persijn L, Decavele AS, Schouwers S, Devreese K. Evaluation of a new set of automated chemiluminescense assays for anticardiolipin and anti-beta2-glycoprotein I antibodies in the laboratory diagnosis of the antiphospholipid syndrome. *Thromb Res*. 2011; 128(6):565-569.

31. Otomo K, Atsumi T, Amengual O, et al. Efficacy of the antiphospholipid score for the diagnosis of antiphospholipid syndrome and its predictive value for thrombotic events. *Arthritis Rheumatism*. 2012;64(2):504-512.

32. Kitchen S, Geisen U, Kappelmayer J, et al. Evaluating the analytical performance of five new coagulation assays for the measurement of prothrombin time and activated thromboplastin time. *Int J Lab Hematol*. 2018;40(6):645-654.

33. Pengo V. ISTH guidelines on lupus anticoagulant testing. *Thromb Res*. 2012;130:S76-S77.