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– ORIGINAL PAPERS –

Antiphospholipid Antibodies in Non-Hodgkin's Lymphoma

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Abstract

Introduction: *Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of malignant lymphoid tumors. Anticardiolipin (aCL), anti-β2 glycoprotein I (antiβ2GPI), lupus anticoagulant (LA) antibodies are found as NHL-associated acquired thrombophilic factors. Seropositivity of these antibodies in malignancies could remain asymptomatic. Despite these findings, the utility of routine testing for aCL, antiβ2GPI, LA antibodies in patients with NHL remains uncertain.*

Objective: *This study aims to assess the prevalence of aCL, antiβ2GPI, LA antibodies in patients with non-Hodgkin's lymphomas depending on age, gender, type of NHL, stage, B symptoms, onset of the disease.*

Material and methods: *A total of 161 patients diagnosed with NHL at the Oncology Institute of the Republic of Moldova were evaluated. Antibodies aCL IgM and IgG, antiβ2GP I IgM and IgG were estimated by enzyme-linked immunosorbent assay (ELISA), and LA by the turbidimetry.*

Results: *The prospective descriptive cross-sectional study included 161 de novo patients 48% women and 52% men, aged between 24 and 82 years, with aggressive (56.5%) and indolent (43.5%) NHL, with higher prevalence of generalized stages (III and IV) in 65.8%. aCL, antiβ2GPI and LA antibodies were recorded in 16.2% with increased incidence in aggressive, B-cell and gender-specific NHL. During the treatment, a tendency towards antibody negativity was observed.*

Conclusions: *The prevalence of aCL, antiβ2GPI and LA antibodies in patients with NHL is higher than in the general population (16.2%), being expressed by single positivity in 14.3%, double positivity in 1.3%, and triple positivity in 0.6% isolated in B cell NHL. A statistically significant difference in antibody positivity was observed based on age and NHL type. Statistically insignificant was the distribution of patients with NHL associated with antibody synthesis according to gender, the degree of dissemination, B symptoms and the location of the primary tumor focus. During the treatment, a tendency of antibody negativity was observed.*

Keywords: *Non-Hodgkin lymphoma, antibodies, thrombosis*

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Introduction

Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of malignant lymphoid tumors [1, 2] and is one of the most common malignant lymphoproliferative disorders [3]. According to the result of the GLOBOCAN 2020 study globally the incidence of primary NHL to increase from approximately 544,000 in 2020 to 778,000 by 2040, representing an estimated increase of 43% over two decades [4]. The results of current research have established that patients with lymphoproliferative diseases are prone to developing venous thromboembolism (VTE), which is the second cause of mortality [5]. The risk of thromboembolic events is four times higher in patients with malignancy than in the general population and this risk is further increased in patients undergoing chemotherapy [6]. The hypercoagulable state is induced by multiple factors through the complex and synergistic interaction of various factors, including tissue, platelet activation and endothelial injury, coagulation abnormalities, procoagulants secreted by tumor cells, abnormal flow, and abnormal tumor angiogenesis [7, 8, 9]. In the last decade, it has been demonstrated that some venous and arterial thrombosis, diagnosed during the evolution of NHL, were associated with an increased level of antibodies, which recognize as non-self antigens plasma proteins capable of binding to anionic phospholipids expressed or coupled by vascular endothelial cells, platelets, monocytes [10, 11]. It is difficult, but absolutely necessary, to predict the risk of thrombosis in asymptomatic carriers of aCL, LA, antiβ2GP I and risk stratification is the fundamental element of current medical research, including in patients with NHL [12]. Seropositivity of these antibodies in malignancies could remain asymptomatic. The pathogenic role of these antibodies in malignant hemopathies is still a matter of debate [9]. Although their positivity can help assess the thromboembolic risk, currently, there is no solid evidence to recommend their screening in patients with oncologic diseases. Despite these findings, the utility of routine testing for aCL, antiβ2GPI, LA antibodies in patients with NHL remains uncertain [13].

Material and methods

The prospective cross-sectional descriptive study included 161 de novo patients with aggressive and indolent NHL treated between 2020 and 2024 in the Hematology Department of the Oncology Institute of the Republic of Moldova. The inclusion criteria were age over 18 years, immunohistochemically confirmed diagnosis of NHL, patient's consent to participate in the study and the possibility of dynamic monitoring. The respondents included in the study were complexly investigated by clinical, paraclinical and imaging methods to assess the stage of the disease, and the primary tumor focus. Antibodies aCL IgM and IgG, antiβ2GP I IgM and IgG were estimated by enzyme-linked immunosorbent assay (ELISA), and LA by the turbidimetry method. The incidence of these antibodies was evaluated according to age, gender, NHL type, degree of dissemination, B symptoms, and onset of the disease.

To achieve the proposed goal, the collected data were statistically processed using Microsoft Excel, Graphpad Prism ver. 9.3.0., Epi Info – 7.2, EpiMax Table, and IBM SPSS Statistics version 26.0.

The research protocol, information and acceptance forms were approved by the Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy (No. 32 of 28.01.2020). The scientific research was developed with the support of the National Agency for Research and Development, within the Postdoctoral Programs, project number no. 24.00208.8007.02/PD.

Results

According to the eligibility criteria, 161 patients with NHL were included in the study, 77 (48%) (95% CI, 40-56) women and 84 (52%) (95% CI, 44-60) men, aged between 24 and 82 years, whose average age was median-59, average-56 years. The age distribution of NHL patients showed a prevalence of cases aged between 51 and 70 years - 96 (59.6%) (95% CI, 52-67), with a decrease of cases in the age category 41-50 years in 24 (14.9%) (CI 95%, 10-21). NHL was less often in patients over 71 years and in those aged 31–40 years, with 19 (11.8%) cases (95% CI, 7-18) and 17 (10.6%) cases (95% CI, 6-16), respectively.

Aggressive NHLs were represented by DLBCL in 65 (40.1%) (95% CI, 33-48) cases, lymphoblastic NHL in 10 (6.2%) (95% CI, 3-11) cases, grade III follicular NHL in 4 (2.5%) (95% CI, 0.7-6.2) cases, mantle cell NHL in 7 (4.6%) (95% CI, 1.8-8.8) cases, PMBCL in 3 (1.9%) (95% CI, 0.4-5.4) cases and 1 (0.6%) (95% CI, 0.02-3.4) case of gray zone NHL and anaplastic type. Indolent NHL were represented by SLL in 50 (31.8%) (95% CI, 24-39) cases, marginal zone NHL in 13 (7.3%) (95% CI, 4.4-13) cases, grade I and II follicular NHL in 7 (4.4%) (95% CI, 1.8-8.8) cases.

The distribution of patients according to NHL stage and B symptoms shows a higher prevalence of generalized stages (III and IV) in 106 (65.8%) (CI 95%, 58-73) cases, predominantly due to stage IV in 96 (59.6 %) (CI 95%, 52-67) of patients (p <0.001), with an even distribution of patients with or without B symptoms (49.7% and 50.3%, respectively) (95% CI, 42–58) (p = 0.5). Localized stages (I and II) were established in 55 (34.2%) (CI 95%, 27-42) cases.

The parameters	**Patients n, %, 95% CI**
Age range (years)	24-82
Gender	
Women	77 (48%) (95% CI, 40-56)
Men	84 (52%) (95% CI, 44-60)
Types of NHL	
Aggressive	91 (56.5%) (95% CI, 48-64)
Indolent	70 (43.5%) (95% CI, 36-52)
The cell substrate	
B	157 (97.5%) (95% CI, 93-99)
T	4 (2.5%) (95% CI, 0.80-6.6)
NHL stage	
Localized (I_II)	55 (34.2%) (95% CI, 27-42)
Advanced (III-IV)	106 (65.8%) (95% CI, 58-73)
Symptoms	
A	80 (49.7%), (95% CI, 42-58)
B	81 (50.3%), (95% CI, 42-58)
Onset of the disease	
Nodal	91 (56.5%) (95% CI, 49-64)
Extranodal	70 (43.5%) (95% CI, 36-52)

Table 1. *Characteristics of the research group*

Nodal onset predominated versus extranodal in 91 (56.5%) (95% CI, 49-64) and 70 (43.5%) (95% CI, 36-52) cases with predominance of nodal onset in aggressive NHL in 58 (36%) (CI 95%, 29-44) of cases versus 33 (20.5%) (CI 95%, 15-28) of cases in indolent NHL. A statistically insignificant difference is seen in the case of extranodal onset in patients with aggressive NHL in 33 (20.5%) (95% CI, 15-28) cases versus 37 (23%) (95% CI, 17-30) cases in indolent NHL (p=0.035).

The positivity of aCL IgG, aCL IgM, antiβ2GPI IgG, antiβ2GPI IgM and AL antibodies at the time of test collection was recorded in 26 patients with NHL, representing 16.2% (CI 95%, 10.8-23) of them. The distribution of these findings was totally inhomogeneous, with single positivity in 23 (14.3%) (95% CI, 9.3-21) cases, double positivity in 2 (1.3%) (95% CI, 0.2-4.4) cases, and triple antibody positivity in only 1 (0.6%) (95% CI, 0.02-3.4) case. Double positivity was represented by the association of aCL IgM + AL and aCL IgM + antiβ2GPI IgM. Triple positivity was characterized by the association between aCL IgM + AL+ antiβ2GPI IgG.

aCL IgG, aCL IgM, antiβ2GPI IgG, antiβ2GPI IgM or AL antibodies were assessed as seropositive only in B-cell NHL.

ANTIBODY	**TESTING**	**N(ABS), %, 95% CI,**
LA	positive	21 (13.1) (8.3-19.2)
	negative	140 (86.9) (81-92)
ACL IGM	positive	4 (2.5) (0.7-6.2)
	negative	157 (97.5) (94-99)
ACL IGG	positive	-

	negative	161 (100) (97.7-100)
ANTIß2GPI IGM	positive	4 (2.5) (0.7-6.2)
	negative	157 (97.5) (94-99)
ANTIß2GPI IGG	positive	1 (0.6) (0.02-3.4)
	negative	160 (99.4) (96.6-99.9)

Table 2. *Distribution of specific antibodies tested*

Note: LA - lupus anticoagulant; ß 2GPI IgM - ß 2 glicoprotein I Immunoglobulin M; ß 2GPI IgG - ß 2 glicoprotein I immunoglobulin G; aCL IgM – anticardiolipinine immunoglobulin M.

According to Table 2, we observe an inhomogeneous distribution of antibodies tested positive, with the obvious prevalence of AL being estimated in 21 (13.1%) (CI 95%, 8.3-19.2) cases, followed by antiβ2GPI IgM and aCL IgM in 4 (2.5%) (CI 95%, 0.7-6.2) cases. Only in 1 (0.6%) (CI 95%, 0.02-3.4) patient tested positive for anti-β2GPI IgG. IgM-type aCL and anti-β2GPI antibodies clearly prevailed over IgG-type aCL and anti-β2GPI antibodies in a ratio of 8:1.

Among the patients included in the study and tested with positive antibodies were those aged 24 - 71 years, with a median age of 50.5 years (value assessed using the Mann Whitney test p=0.0054, statistically significant), unlike the group of NHL patients with negative antibodies 135 (83.8%) (95% CI, 77-89) with a median age of 59.5 years.

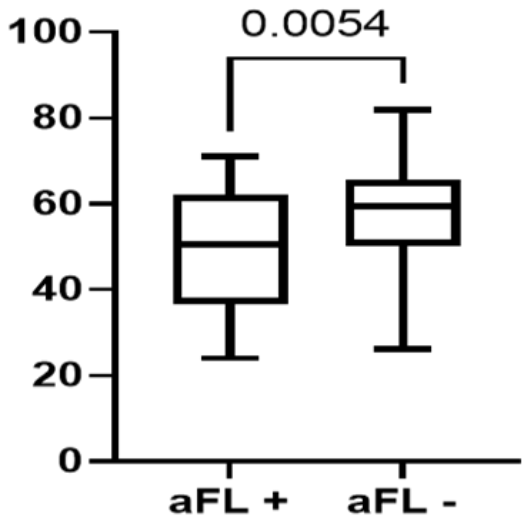

Figure 1*. Distribution of NHL patients according to age and antibody positivity.*

Statistically insignificant was the distribution of patients with NHL associated with antibody synthesis according to gender: 14 (8.7%) (95% CI, 4.8-14) men and 12 (7.5%) (95% CI, 3.9-12.6) women. LA, aCL, antiβ2GPI antibodies were detected in 20 (12.5%) (95% CI, 10.8-22.7) patients with aggressive NHL and only 6 (3.7%) (95% CI, 1.4-8) cases were tested positive in indolent NHL (p = 0.0297). The estimated relative risk (RR) of the association of aCL, antiβ2GP-1, LA antibodies synthesis is 1.463 with 95% CI, 1.066-1.854, and the Odds Ratio (OR) is 3.005 with 95% CI, 1.166-7.71.

Positive testing of one of aCL, antiβ2GPI, and LA was considered statistically insignificant depending on the degree of tumor spread: 13 (8%) (95% CI, 4.4-13.4) cases each among localized stages I-II and generalized III-IV (p=0.0733). The relative risk (RR) of the estimated association of aCL, antiβ2GPI, AL antibody synthesis is 0.6222 (95% CI, 0.4101-1.028), and the Odds Ratio (OR) is 0.4516 (95% CI, 0.1870-1.092).

The same statistical results were obtained in the case of the analysis of the frequency of erroneous antibody synthesis according to B symptoms (p=0.8317) with a relative risk (RR) of association of aCL, antiβ2GP-1 antibody synthesis, AL of 1.075 with 95% CI, 1.7290-1.771, and the Odds Ratio (OR) is 1.150 with CI 95%, 0.4956-2.621.

Positively tested antibodies were more frequently associated with nodal-onset NHL in 20 (12.5%) (95% CI, 11-22.7) cases, which constitutes 12.4% of 91 (56.5%) (95% CI, 48-64) of cases of NHL with nodal origin, regardless of the aggressive or indolent NHL subtype. From logical reasonings, we aimed to estimate the positivity of aCL, antiβ2GPI and LA antibodies over time, with collection over 3 months and over 6 months after initiation of first-line treatment.

I collection	II collection	III collection
aCL IgM+LA	aCL IgM+LA	-
LA	-	-
LA	LA	-
aCL IgM+LA+ ß2GPI IgG	acLIgM1+LA+ ß2GPI IgG	ß2GPI IgG
-	aCL IgM	-
LA	-	-
LA	-	-
ß2GPI IgM	ß 2GPI IgM	ß2GPI IgM
LA	-	-
-	ß 2GPI IgM	-
ß2GPI IgM	ß 2GPI IgM	-
LA	-	-
LA	-	-
aCL IgM + ß2GPI IgM	ß 2GPI IgM	-
LA	-	-
LA	-	-
LA	-	-
LA	-	-
LA	LA	-
LA	-	-
LA	-	-
LA	LA	-
LA	-	-
LA	LA	-
LA	-	-
LA	-	-

Table 3. *aCL, antiβ2GPI and LA antibody positivity over time*
Note: LA - lupus anticoagulant; ß 2GPI IgM - ß 2 glicoprotein I Immunoglobulin M; ß 2GPI IgG - ß 2 glicoprotein I immunoglobulin G; aCL IgM – anticardiolipinine immunoglobulin M.

During the evaluation of the results presented in table 3, we found that during the application of the first-line therapy, a trend of antibody negativity is appreciated. Only in 2 (1.2%) (95% CI, 0.2-4.4) patients out of 24 respondents with NHL tested positive until the initiation of treatment, at the distance of 6 months (estimated 24 weeks) the positivity was maintained.

Discussion

Antiphospholipid antibodies are a family of autoantibodies that target phospholipid-binding proteins and are associated with several clinical conditions [14]. There is increasing evidence that there are asymptomatic individuals in the general population who are positive for several types of aPL [15, 16]. According to Barreno-Rocha, phospholipid synthesis by tumor cells are targets for aCL, LA, antiβ2GPI [17]. Antibodies to aPL in the global population vary between 1-5% and increase with the association of chronic inflammatory, infectious pathologies, as well as with the development of oncological diseases [18]. The results of our study demonstrate a 16.2% incidence of aCL, AL, antiβ2GPI antibodies in primary NHL patients. A lower prevalence of autoantibodies 9 (41%) in patients with NHL was reported in 1995 by Sciarra et al. [19]. A percentage distribution of 22% of these antibodies in NHL was appreciated in the study of Indian origin [20]. About a third (35.7%) of NHL patients tested positive for aCL, AL, antiβ2GPI antibodies in the Thai study (2017 - 2018) [21]. Also in this study, AL and aβ2GPI-IgM were the most frequently recorded AL antibodies. In our cohort, the leading position was AL being positive in 21 (13.1%) (95% CI, 8.3-19.2) cases, followed by antiβ2GPI IgM and aCL IgM in 4 (2.5%) each (95% CI, 0.7-6.2). A higher prevalence of 40% of antiβ2GPI IgM was appreciated among 86 patients with NHL treated at the Institute of Hematology, Petah Tiqva, Israel [22].

Major risk for thrombosis is suspected when not only the positivity of an antibody is detected, but the association between 2-3 types regardless of their IgG or IgM isotype is estimated, called "aPL double profile" and "aPL triple profile", respectively [23]. Practically similar results to our study were recorded in the research of Kungwankiattichai et al determining unipositivity, double and triple in 29.9%, 5.2% and 0.6% of cases, respectively. [21].

The specialized literature mentions the risk of erroneous synthesis of antibodies in all age categories, but with a tendency to increase with advancing age. Due to the increased incidence of thrombotic events, aCL, antiβ2GPI, LA may be tested more frequently in the elderly population, thus creating bias in these findings [24]. Our research concludes the association of positive antibodies in people aged 24 - 71 years, with their median age of 50.5 years (p=0.0054, statistically significant), in contrast to the group of NHL patients with negative antibodies 135 (83.8%) (CI 95%, 77-89) with a median recorded age of 59.5 years. B lymphocytes (BL) are shown to be responsible for the physiological production of antibodies by modulating and activating the immune system [25]. There is a higher probability of the same BLs becoming tumorigenic to initiate antibody synthesis, but already erroneous and in a greater amount. This fact was also found in our study where NHLs associated with erroneous antibody synthesis had B cell substrate. We demonstrated that the incidence of aCL, antiβ2GPI, LA antibodies in patients with NHL depends on the immunohistochemical type with the predominance of 20 (12.5%) (95% CI, 10.8-22.7) patients with aggressive NHL versus 6 (3.7%) (95% CI %, 1.4-8) patients with indolent NHL (p = 0.0297).

Opposite results were obtained in the research of Rimesh and colleagues from India in which among 22.8% of NHL cases associated with seropositive antibodies no statistically significant association with histological subtype was appreciated [20].

Positively tested antibodies were more frequently associated in patients with nodal NHL in 20 (12.5%) (95% CI, 11-22.7) cases versus extranodal onset in 6 (3.7%) (95% CI, 1.4-8) cases. Erroneous aCL production has been described in both nodal [26] and extranodal NHL [27, 28].

The positivity of aCL, LA and antiβ2GPI antibodies can be of a transitory nature, mainly described during infectious, oncological diseases, etc. [29]. Consequently, repeated testing of these antibodies is welcome for early positivity and to demonstrate that the antibodies are related to a comorbidity, but not for monitoring classic APL. Taking into account the conclusions of several international studies published during the last 5 years, which evaluated the dynamics of antibody positivity in patients with various malignancies, such as after the completion of the chemotherapy program, the trend of negativity of antibodies previously tested positive is attested. According to Austrian research, which studied immune-mediated thrombophilia states associated with lymphoproliferative pathologies, especially associated with NHL, the conclusion was suggested that the detection of AL is categorically associated with the effectiveness of the applied therapy, demonstrated by the

negativity in more than a third of patients with complete remission [30].

The study focus of these antibodies could direct us to a better management of patients with NHL, aiming to predict the prognosis, which will improve the overall survival and improve the quality of life of these patients.

Conclusion

The prevalence of aCL, antiβ2GPI and LA antibodies in patients with NHL is higher than in the general population constituting 16.2% being expressed by unipositivity in 14.3%, double positivity in 1.3% and triple positivity in 0.6% isolated in B cell NHL. A statistically significant difference in antibody positivity was by age and NHL type. Statistically insignificant was the distribution of patients with NHL associated with antibody synthesis according to gender, the degree of dissemination, B symptoms and the location of the primary tumor focus. During the application of the first-line therapy, a tendency of antibody negativity is appreciated.

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Nil

Conflicts of interest

"This research did not receive any grant from agencies in the public, commercial, or not-for-profit sectors.
None of the authors has any conflict of interest.
The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Informed consent was obtained from all the patients included in the study."

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