ORIGINAL INVESTIGATIONS

Peripheral arterial disease in rheumatology

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Objective: *to assess the frequency of thromboangiitis obliterans (TAO) vascular lesions and its association with clinical and laboratory manifestations in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS).*

Material and methods. *The study included 172 patients (30 men and 142 women): 22 (13%) with isolated "primary" APS (pAPS), 66 (38%) with SLE, and 84 (49%) with SLE + APS. The median age was 36 [30; 46] years. Disease duration in the SLE + APS group was longer than in the pAPS and SLE groups (median 17 [9; 21], 5 [2; 13], and 7 [3; 12] years, respectively; $p<0.05$). All patients were hospitalized at the V.A. Nasonova Research Institute of Rheumatology due to exacerbation of the underlying disease and underwent a comprehensive examination.*

Results and discussion. *Vascular lesions of the TAO type were recorded in 17 (10%) of 172 patients: 1 with pAPS, 13 with SLE + APS, and 3 with SLE. The development of TAO in patients with SLE + APS was influenced by the following factors: dyslipidemia (odds ratio, OR 10.74; 95% confidence interval, CI 3.29–34.99; $p<0.01$), arterial hypertension (OR 7.19; 95% CI 1.98–26.07; $p<0.01$), and Raynaud's syndrome (OR 7.72; 95% CI 2.61–22.82; $p<0.01$). As a result of multivariate analysis, a prognostic model was obtained, according to which the number of aseptic bone necroses, the number of lower leg ulcers over the entire disease course, the type of thrombosis, APS duration, disease onset with APS manifestations, livedo reticularis, elevated levels of IgG antibodies to cardiolipin, to β_2-glycoprotein 1, total cholesterol, C-reactive protein (CRP), and an increase in leukocyte count are associated with a higher probability of TAO development in patients with SLE and/or APS.*

Conclusion. *Risk factors for the development of TAO in patients with SLE and APS are aseptic bone necroses, trophic ulcers of the lower legs, APS duration, livedo reticularis, elevated levels of IgG antibodies to cardiolipin, to β_2-glycoprotein 1, total cholesterol, CRP, and an increased leukocyte count.*

Keywords: *thromboangiitis obliterans; antiphospholipid antibodies; systemic lupus erythematosus; antiphospholipid syndrome.*

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Peripheral arterial disease (PAD) is one of the terms used to describe chronic occlusive disease of the arteries in the upper and lower extremities. Approximately 70% of patients with PAD over the age of 50 suffer from atherosclerotic occlusive disease, 20% patients suffer from thromboangiitis obliterans (TO), and the remaining 10% – have vasculopathy secondary to diabetes mellitus, autoimmune diseases, etc. [1]. TO – or Winiwarter–Buerger Disease – is a segmental thrombotic acute and chronic inflammatory process in small and medium arteries and veins, mainly in the upper and lower extremities, but in rare cases, cerebral, coronary, renal, and mesenteric vessels may be involved [2]. The disease affects young men and is characterized by pain in the legs, intermittent claudication, and ischemic changes ranging from cyanosis to ulcers or dry gangrene. In the 120 years since OT was first described, the concept of its diagnosis and mechanism of development has changed: a link between smoking and the progression and prognosis of the disease has been identified. A link has been found between TO and the major histocompatibility complex (HLA-A9, HLA-B54-MICA-1.4, HLA-DRB1, and HLA-DPB1 antigens), and a separate form of TO associated with antiphospholipid antibodies (aPL) has also been identified [3].

Classic aPLs include: antibodies to cardiolipin (aCL), antibodies to β2-glycoprotein 1 (aβ2GP1), and lupus anticoagulant (LA), which are included in the classification criteria for systemic lupus erythematosus (SLE) [4] and antiphospholipid syndrome (APS) [5].

SLE is a chronic multisystem disease that occurs predominantly in young women and girls in presence of genetically determined imperfections in immunoregulatory processes, leading to uncontrolled production of antibodies to the body's own cells and their components, with the development of autoimmune and immune complex chronic inflammation and damage of various organs and systems [6]. APS often accompanies SLE, belongs to acquired thrombophilia and is characterized by recurrent thrombosis and pregnancy morbidity associated with increased synthesis of antibodies to phospholipid determinants of cell membranes or phospholipid-binding proteins in the blood [7]. Since isolated "primary" APS (PAPS) can be a variant of SLE onset, a definite diagnosis can only be made through long-term observation of patients (≥5 years after the disease onset; this period is reduced to 3 years in the 2023 criteria) [5].

SLE and APS occur in young socially active men and fertile women, are progressive diseases, and, if left untreated, can lead to uncontrolled antibody production, damage of internal organs down to multiple organ failure and death [8]. On the other hand, the progressive course of TO in SLE and APS leads to the development of critical ischemia, the ineffectiveness of endovascular vascular repair (recurrent thrombosis of stents and/or vessels after surgical intervention), limb amputation, and disability. In light of this, early diagnosis of TO, identification and modification of risk factors, and timely treatment are becoming increasingly important.

The aim of the study was to evaluate the frequency of TO-type vascular damage and its relationship with clinical and laboratory manifestations in patients with SLE and APS.

Materials and methods. The study included 172 patients (30 men and 142 women): 22 (13%) with isolated PAPS, 66 (38%) with SLE, and 84 (49%) with SLE + APS. Patient characteristics are presented in Table 1. The median age was 36 [30; 46] years. The disease duration in the SLE + APS group was longer than in the PAPS and SLE groups (median is 17 [9; 21]; 5 [2; 13] and 7 [3; 12] years, respectively; $p<0.05$). All patients admitted to the V.A. Nasonova Research Institute of Rheumatology (V.A. Nasonova RIR) due to disease exacerbation.

All patients signed an informed consent form to participate in the study. The study was approved by the local ethics committee of the V.A. Nasonova RIR (protocol No. 25 dated December 19, 2019).

Patients underwent complete clinical, laboratory, and instrumental examinations, including peripheral vascular Doppler ultrasound, magnetic resonance imaging of the joints, and computed tomography of the chest organs, as indicated. Angiography was performed in the patients' local health facilities.

Statistical analysis was performed using the Medcalc. The median and interquartile range (Me [25th and 75th percentiles]) were used to describe quantitative variables. To describe the distribution of a qualitative characteristic, its absolute and relative (percentage) frequency was calculated. For quantitative variables, the Shapiro–Wilk and Kolmogorov–Smirnov tests were used to test for normality of distribution. For parameters whose distribution differed from normal when comparing two groups, the Mann–Whitney criterion was used. To analyze the difference in frequencies in two independent groups of research objects, Pearson's χ^2 criterion was used, and when the minimum expected number was <10, Fisher's exact criterion was used. Correlations were assessed using Spearman's method. A predictive model of the probability of a certain outcome was constructed using the logistic regression method. Nigelkerk's R2 coefficient served as a measure of certainty, indicating the part of the variance that can be explained by logistic regression. To analyze the diagnostic effectiveness of laboratory tests and constructed prognostic models, a characteristic curve was used – the ROC curve (receiver operating characteristic, "error curve"), reflecting the dependence of the frequency of true positive results (sensitivity) on the frequency of false positive results (1 – specificity). The clinical informativeness of a laboratory test was determined by how high its ROC curve lies: the closer to the diagonal, the lower the accuracy of the prognostic power. A universal method for evaluating ROC curves is to calculate the area under the curve (AUC), which varies from 0.5 (no predictive power) to 1.0 (maximum predictive power).

Results. TO-type vascular damage was recorded in 17 (10%) of 172 patients: 1 with PAPS, 13 with SLE + APS, and 3 with SLE. All patients were divided into two groups: the TO group (n=17) and the non-TO group (n=155; Table 2).

APS duration and the duration of observation were longer in the TO group, thrombosis in general and combined thrombosis in particular, as well as arterial hypertension (AH) were more common in TO patients, while venous thrombosis was more common in the non-TO group. In addition, TO patients had highly positive

Table 1. Clinical characteristics of the examined patients

Parameters	PAPS	SLE+APS	SLE	Total
Number of patients, n (%)	22 (13)	84 (49)	66 (38)	172
Female, n (%)	12 (55)	69 (82)	61 (92)	142 (83)
Male, n (%)	10 (45)	15 (18)	5 (8)	30 (27)
Age, years, Me [25; 75%]	38 [33; 43]	39 [32; 48]	35 [26; 45]	36 [30; 46]
Disease duration, years, Me [25; 75%]*	**5 [2; 13]**	**17 [9; 21]**	**7 [3; 12]**	11 [5; 19]
Duration of observation, years, Me [25; 75%]*	**0,5 [0,3; 5]**	**8 [1; 14]**	**1 [0,4; 5]**	3 [0,5; 10]
Thromboses, n (%):*	**18 (82)**	**67 (80)**	**11 (16)**	96 (56)
Arterial, n (%)*	**3 (14)**	**16 (19)**	**0**	19 (11)
Venous, n (%)*	**8 (36)**	**27 (32)**	**8 (12)**	43 (25)
Combined, n (%)*	**7 (32)**	**24 (29)**	**3 (5)**	34 (20)
PTE, n (%)*	**7 (32)**	**14 (17)**	**2 (3)**	23 (13)
Number of patients with FL, n (%)**	5/8 (63)	33/43 (77)	7/21 (33)	45/72 (63)
Positive aPL (one or more middle positive aPL subtypes), n (%)	22 (100)	80 (95)	4 (6)	106 (62)
Positive LA, n (%)***	14/16 (88)	52/64 (81)	3/66 (5)	69/146 (47)
SLE activity by SLEDAI score, points, Me [25; 75%]:	–	4 [2; 7]	6 [4; 12]	–
high degree, n (%)	–	10 (12)	17 (26)	–
moderate degree, n (%)	–	18 (22)	21 (32)	–
mild degree, n (%)	–	56 (67)	28 (42)	–
TO-type vascular damage, n (%)*	**1 (5)**	**13 (15)**	**3 (5)**	**17 (10)**

Note. * – $p < 0.05$, Me [25,75%] – median [interquartile range], PAPS – "primary" isolated antiphospholipid syndrome, SLE – systemic lupus erythematosus, PTE – pulmonary thromboembolism, FL – fetal loss, ** – numerator: number of episodes of pregnancy morbidity during the disease; denominator: number of pregnancies during the disease; aPL – antiphospholipid antibodies; LA – lupus anticoagulant, *** – in the numerator, the number of patients with positive LA; in the denominator, the number of patients who were tested for LA without anticoagulant therapy; TO – thromboangiitis obliterans.

Table 2. Characteristics of patients depending on vascular lesions

Parameters	the TO group n=17	the non-TO group n=155
Age, years Me [25; 75%]	46 [29; 52]	36 [30; 44]
Gender: female/male, n (%)	12 (71)/5 (29)	130 (84)/25 (26)
SLE , n (%)	3 (18)	63 (41)
SLE+APS, n (%)	13 (76)	71 (46)
PAPS, n (%)	1 (6)	21 (14)
SLE duration, years Me [25; 75%]	10 [1; 19]	6,8 [1,5; 17]
APS duration, years Me [25; 75%]*	**17 [10; 19,4]***	**1,7 [0,1; 12,2]***
Duration of observation, years Me [25; 75%]*	**10 [1,6; 16]***	**2,6 [0,4; 9]***
Disease onset with APS manifestations, n (%)	9 (53)	47 (30)
Thromboses, n (%):*: **Arterial, n (%)** **Venous, n (%)*** **Combined, n (%)***	**15 (88)*** 2 (13) **3 (20)*** **10 (67)***	**81 (52)*** 17 (21) **40 (49)*** **24 (29)***
PE, n (%)	4 (24)	19 (12)
Stroke, n (%)	5 (29)	27 (17)
MI, n (%)	1 (6)	4 (3)
Number of aseptic bone necroses, n (%)	7 (41)	14 (9)
The number of lower leg ulcers over the entire disease course, n (%)	14 (82)	9 (6)
Arterial hypertension, n (%)*	**14 (82)***	**61 (39)***
Raynaud's phenomenon, n (%)	6 (35)	13 (8)
Livedo reticularis, n (%)	8 (47)	29 (19)
Positive LA, n (%)	12 (75) of 16, without anticoagulants	57 (70) of 81, without anticoagulants
IgG- aCL (GPL), Me [25; 75%]*	**92,9 [41,8; 120,0]***	**13,9 [2,7; 89,8]***
IgM- aCL (GPL), Me [25; 75%]	6,9 [0,6; 17,9]	2,1 [0,7; 10,6]
IgG -aβ2GP1 (U/mL), Me [25; 75%]*	**100 [37,7; 100,0]***	**7,4 [2,5; 76,1]***
IgM- aβ2GP1 (U/mL), Me [25; 75%]	1,2 [0,1; 10,4]	1,7 [0,5; 6,1]
aDNA (U/mL), Me [25; 75%]	58,2 [20,0; 109,0]	29,7 [14,5; 76,9]
anti-Ro/SS-A (U/mL), Me [25; 75%]	0,1 [0,1; 0,1]	2,8 [1,2; 136,0]
anti-La/SS-B (U/mL), Me [25; 75%]*	0,1 [0,1; 0,4]	2,6 [1,1; 6,4]
C3-complement component (g/L), Me [25; 75%]	0,76 [0,68; 0,93]	0,89 [0,77; 1,08]
C4- complement component (g/L), Me [25; 75%]	0,13 [0,06; 0,17]	0,15 [0,11; 0,19]
Positive ANA, n (%)	16 (94)	147 (95)
SLE activity by SLEDAI score, points, Me [25; 75%]	6 [2; 8]	4 [2; 8]
C-reactive protein (mg/L), Me [25; 75%]*	2,8 [0,7; 6,5]	1,3 [0,5; 2,8]
Hemoglobin (r/L), Me [25; 75%]	122,5 [100,0; 138,0]	125,5 [114,0; 135,0]
Leukocytes ($\cdot 10^9$/L), Me [25; 75%]	7,7 [5,8; 10,1]	5,8 [4,4; 7,7]

Parameters	the TO group n=17	the non-TO group n=155
Platelets ($\cdot 10^9$/L), Me [25; 75%]	166,5 [107,0; 153,9]	223,0 [169,0; 275,0]
Total cholesterol (mmol/L), Me [25; 75%]	4,4 [4,1; 5,4]	4,8 [4,2; 5,5]

Note. Me [25; 75%] – median [interquartile range], TO – thromboangiitis obliterans, SLE – systemic lupus erythematosus, APS – antiphospholipid syndrome, ANA – antinuclear antibodies, SLEDAI – systemic lupus erythematosus activity index, aB2GP1 – antibodies to beta-2-glycoprotein 1, aCL – antibodies to cardiolipin, IgG – immunoglobulin G, IgM – immunoglobulin M, LA – lupus anticoagulant, MI – myocardial infarction, PTE – pulmonary thromboembolism, * – p<0.05 comparing 2 groups.

IgG-aCL and IgG-aβ2GP1 levels compared to patients without TO (see Table 2).

To assess the impact of various factors associated with SLE and APS on the prognosis of TO, the first step was to calculate the correlation coefficients of existing TO with various indicators, which are both clinical manifestations and risk factors for thrombosis in patients with SLE and APS (Table 3).

The most significant positive correlation of TO was found with distal necrosis, lower limb artery thrombosis, and dyslipidemia, while the most significant negative correlation was found with anti-Ro/SSA and anti-La/SSB levels.

Univariate regression analysis showed that the following factors influenced the development of TO in patients with SLE and APS: dyslipidemia (odds ratio, OR 10.74; 95% confidence interval, CI 3.29–34.99; p<0.01), AH (OR 7.19; 95% CI 1.98–26.07; p<0.01), and Raynaud's phenomenon (OR 7.72; 95% CI 2.61–22.82; p<0.01).

As a result of multifactorial analysis, a prognostic model was obtained, according to which the levels of IgG aCL, IgG α2GP1, the number of aseptic bone necroses, the number of leg ulcers over the entire disease course, the type of thrombosis, APS duration, disease onset with APS manifestations, livedo reticularis, an increase in leukocyte count, elevated total cholesterol and CRP levels are associated with a higher probability of developing TO. Based on a stepwise logistic regression model, a formula was calculated to assess the prognosis (P) of TO development in patients with SLE and APS:

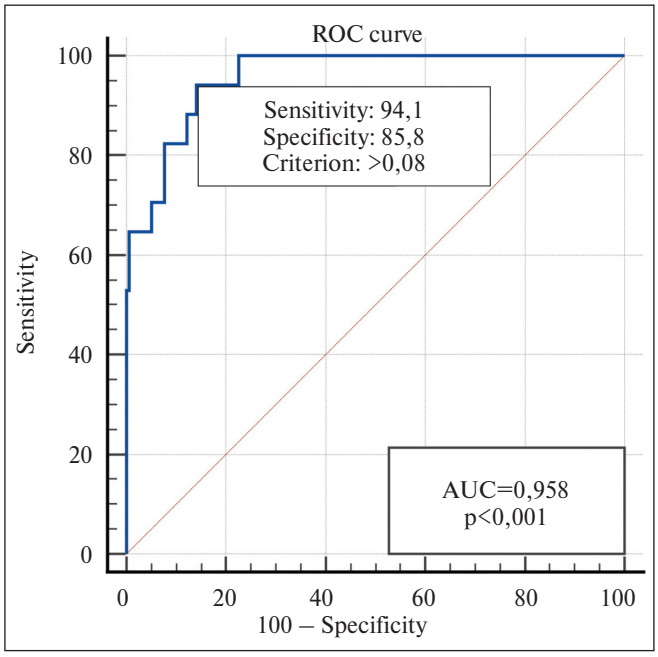
Y = -16,37 + 0,014*X1 + 0,019*X2 + 1,94*X3 + 1,407*X4 + 0,84*X5 + 0,069*X6 + 1,774*X7 + 0,470*X8 + 0,651*X9 - 1,449*X10 - 0,053*X11,

where
X1 is the IgG aCL level, absolute values, GPL;
X2 is the IgG α2GP1 level, absolute values, U/mL;
X3 – the number of aseptic bone necroses;
X4 – the number of lower leg ulcers over the entire disease course;
X5 – the type of thrombosis (0 – no thrombosis, 1 – arterial, 2 – venous, 3 – combined thrombosis);
X6 – the APS duration, years;
X7 – the disease onset with APS manifestations (0 – no, 1 – yes);
X8 – the number of leukocytes in peripheral blood, absolute values, $\cdot 10^9$/L;
X9 –total blood cholesterol level, absolute values, mmol/L;
X10 –livedo reticularis (0 – no, 1 – yes);
X11 – blood CRP level (in the absence of signs of infection), absolute values, mg/L.

With a value of P >0.5, patients with SLE and/or APS are classified as high risk for developing TO-type vascular damage.

ROC curve analysis was used to evaluate the effectiveness of the prognostic model. The significance level of this model is statistically significant (p<0.001). The area under the curve (AUC) was 0.958, 95% CI – 0.92–0.98, sensitivity – 94.1%, specificity – 85.8, positive predictive accuracy – 96% (see figure). Niggelkerke's R2 coefficient was 0.67, the predictive value of a positive result was 84.6%, the predictive value of a negative result was 96.2%, the likelihood ratio of a positive result was 6.63, the likelihood ratio of a negative result is 1.1, the false positive rate is 1%, and the Youden index is 0.799. All these indicators demonstrated the statistical significance of this model.

Discussion. To verify the diagnosis of TO, the current international diagnostic criteria for 2023 (Table 4) require that the patient, regardless of gender, age, clinical picture, laboratory and imaging test results, meet three mandatory criteria: active smoking in the past or present, typical histopathological and angiographic signs. Angiographic signs include normal structure of the proximal arteries, occlusion of the popliteal arteries, corkscrew-like collaterals and segmental lesions, absence of atherosclerotic plaques and microaneurysms [2]. Also important for diagnosis are the disease onset before the age of 45, signs of chronic ischemia of the lower and/or upper extremities, including Raynaud's phenomenon, migratory thrombophlebitis, and discoloration of the fingers and toes in patients with fair skin in the form of red to bluish hyperemia, which are minor classification criteria for probable TO and may occur to varying degrees in patients with obliterating atherosclerosis,



ROC curve for the integral predictor of TAO development

hypertension, diabetes mellitus, hyperlipidemia, trauma, systemic connective tissue diseases, myeloproliferative diseases associated with hypercoagulation, and the presence of a proximal source of embolism. At the same time, all of the conditions described may occur in patients with SLE and APS. [9, 10].

Indications for angiography arise only when clinical signs of arterial insufficiency appear, at the stage of ischemia, ulcers, and/or necrosis, which in the case of TO corresponds not to the early stage, but to the already pronounced stage of the disease. The diagnosis of Raynaud's phenomenon is based on the results of capillaroscopy, which is performed on the nail bed of the fingers and is not informative in terms of assessing obliteration/patency and thickening of the intima-media complex of peripheral arteries, but can confirm existing tissue ischemia and its degree [11]. At the same time, the development of peripheral ulcers and necrosis in patients with rheumatic diseases may be associated with microangiopathic APS and/or ongoing skin vasculitis in the context of SLE in the absence of occlusion of the distal arteries of the small and medium vessels, but pain in the affected area may affect limb function and mimic the clinical picture of intermittent claudication. In some cases, contrast-enhanced imaging is contraindicated in patients with SLE and APS with high disease activity, ongoing glomerulonephritis, and/or chronic kidney disease. All this dictates the need to search for alternative non-invasive methods for diagnosing vascular lesions.

Table 3. Correlation coefficients of TAO with various parameters of the SLE and APS patients (univariate correlation analysis)

Parameters	Spearman's correlation coefficient (r)	p
Distal necroses (yes/no)	0,789	**<0,0001**
Lower limb artery thrombosis (yes/no)	0,622	**<0,0001**
Dyslipidemia (yes/no)	0,352	**<0,0001**
Arterial thrombosis (yes/no)	0,351	**<0,0001**
Total number of thromboses (n)	0,322	**<0,0001**
IgG-aβ2GP1 (U/mL)	0,318	**<0,0001**
Raynaud's phenomenon (yes/no)	0,316	**<0,0001**
The number of aseptic bone necroses (n)	0,310	**<0,0001**
IgG-aCL (GPL)	0,275	**0,0003**
The number of lower leg ulcers over the entire disease course (n)	0,268	**0,0004**
Arterial hypertension (yes/no)	0,259	**0,0006**
Venous thrombosis (yes/no)	0,249	**0,0010**
APS duration (years)	0,240	**0,0015**
Disease onset with APS manifestations (yes/no)	0,239	**0,0016**
Livedo reticularis (yes/no)	0,204	**0,0074**
Leukocytes ($\cdot 10^9$ /L)	0,201	**0,0083**
Total cholesterol (mmol/L)	0,193	**0,0113**
C-reactive protein (mg/L)	0,178	**0,0196**
Positive ANA (yes/no)	-0,231	**0,0023**
C3 complement component (g/L)	-0,279	**0,0002**
Anti-Ro/SS-A (U/mL)	-0,350	**0,0002**
Anti-La/SS-B (U/mL)	-0,378	**0,0001**

The modern concept of preventive, predictive, and personalized medicine involves prevention (or assessment of the likelihood of development) and diagnosis of disease at an early stage. Predicting the onset of a particular condition is difficult, but analysis of existing clinical and laboratory manifestations allows us to identify correlations and thus predict the outcome of the disease. Previously proposed prognostic models for patients with SLE and APS are based on the assessment of kidney damage [12, 13], headache intensity [14], and the course of pregnancy and childbirth [15]. To date, there are no publications devoted to assessing the risk of TO development in patients with SLE and APS.

The search for ways to prevent critical limb ischemia in patients with non-rheumatic diseases has been conducted previously. An interesting study was conducted by A.V. Kazantsev and E.A. Korymasov [16], who proposed a method for predicting progressive arterial obliteration in atherosclerosis leading to critical limb ischemia. The authors developed a multifactorial system that takes into account indicators such as blood lipid profile, local tests of the hemostasis system, apolipoprotein A1, apolipoprotein B, interleukins 1β, 6, 8, tumor necrosis factor α, endothelin 1, homocysteine, von Willebrand factor, CRP, ankle-brachial index, and arterial resistance index based on data from duplex ultrasound scanning of the lower limb arteries. Each parameter was assigned a score. A total score of ≥13 corresponded to progressive peripheral arterial disease. The undoubted advantage of this model is that it does not require angiography. Its disadvantages include the costly and rarely used method of examining patients (testing for cytokine levels, markers of inflammation, and endothelial dysfunction), as well as the fact that clinical manifestations and immunological disorders are not taken into account; the system is designed for patients without rheumatic diseases.

The mathematical model proposed in our study is an accessible and rapid method for predicting TO in patients with SLE and APS, based on clinical data taking into account indicators studied in all patients at both the outpatient and inpatient stages, regardless of the degree of rheumatic disease activity. In addition, our results confirmed that the presence of APS determines a specific subtype of SLE and affects the likelihood of developing TO. The differences between patients in the TO and non-TO groups were in the APS

Table 4. Diagnostic criteria of thrombangiitis obliterans [2]

The 'definitive' diagnosis of TO can be made in a person (regardless of age, gender, clinical signs and symptoms, laboratory and imaging tests) with all of three mandatory features:
1) history of tobacco smoking (current or past smoker but not the second-hand smoker);
2) typical angiographic features (normal proximal arterial structure, absence of atherosclerotic plaque, lack of microaneurysm, infra-popliteal arterial occlusion, corkscrew collaterals and skip lesions);
3) typical histopathological features (particularly, intact internal elastic lamina, Infiltration of polymorphonuclear inflammatory cells in all small and medium-sized vessels' wall layers).

'Suspected' diagnosis of TO can be confirmed in the presence of one major criterion plus four or more minor criteria:
Major criteria
History of active tobacco smoking (current or past smoker but not the second-hand smoker)

Minor criteria
1. Disease onset at age less than 45 years
2. Ischemic involvement of both of the lower limbs, such as:
   – absence of any distal pulses (aa. dorsalis pedis и tibialis posterior) of both limbs, or
   – ankle brachial index less than 0.9 of both limbs, or
   – diminished Toe Brachial Index of both limbs (TBI <0,75), or
   – chronic sign of ischemia of either lower legs or feet (including hair loss, nail thickness and, skin atrophy) in addition to the absence of any distal pulses of at least one limb
3. Ischemic involvement of any of the upper limbs, such as:
   – positive Allen's test, or
   – absence of radial pulse, or
   – Raynaud's phenomenon
4. Thrombophlebitis migrans (history or in the physical examination)
5. Discoloration of the toes or fingers in patients with lighter skin tones as a peculiar blush ranging from a red to a red-blue shade of purple on edematous toes, in which the toes on a limb sometimes might not be affected to the same degree. It can extend to the ankle in dependent position of the limb.

duration and, as a result, in the duration of observation. Thrombosis in general and thrombosis of combined localization in particular, as well as AH, were more common in the TO group, while in the group without TO, venous thrombosis developed in most cases. In addition, IgG aCL and IgG α2GP1 levels were statistically significantly higher in patients with TO than in patients without TO.

Conclusion. The frequency of TO detection in the group of patients with SLE and APS was 10% (in 17 out of 172 patients). OT in SLE was significantly associated with APS: 76% of patients with TO had significant APS compared to 18% of patients with SLE without APS. Risk factors for the development of TO in patients with SLE and APS include the presence of aseptic bone necrosis, lower leg ulcers over the entire disease course, long APS duration, livedo reticularis, increased white blood cell count, elevated levels of IgG aCL and aβ2GP1, total cholesterol, and CRP.

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