ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

ОРИГІНАЛЬНІ ДОСЛІДЖЕННЯ:

DOI: 10.21802/artm.2020.2.14.6.
UDC 616.5-002.525.2-031.81:616.1]-06

PATHOGENETIC ASSOCIATION OF VASCULAR AND CARDIAC LESIONS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: CHARASTERISTICS AND PREVALENCE

U.O. Abrahamovych[1], O.O. Abrahamovych[2], M.L. Farmaha[2], O.T. Romanyuk[2], L.O. Kobak[2]

[1]*Danylo Halytsky Lviv National Medical University, Department of Internal Medicine No. 2, Lviv, Ukraine, ORCID ID: 0000-0003-4762-3857, email: doculyana@i.ua;*
[2] *Danylo Halytsky National Medical University, Department of Internal Medicine No. 1, Lviv, Ukraine, ORCID ID: 0000-0001-6862-6809, email: docorest@gmail.com, ORCID ID: 0000-0003-1298-4644, email: martafarmaha@gmail.com, ORCID ID: 0000-0003-2922-7797, email: kovalolya8@gmail.com, ORCID ID: 0000-0002-2700-4007, email: k_liubov@ukr.net*

Abstract. Vascular and cardiac lesions are the most common lesions in patients with systemic lupus erythematosus. They also top the list of mortality reasons in patients with systemic lupus erythematosus and yet have to be addressed individually.

Objective. To characterize and clarify the prevalence of vascular and cardiac lesions that are pathogenetically associated with systemic lupus erythematosus.

Materials and methods. 370 patients (331 women and 39 men) were included in the study with a prior stratification by age, systemic lupus erythematosus duration and its degree of severity. The patients were comprehensively examined and diagnosed according to the requirements of modern medicine. In particular, the patients were subjected to electrocardiography, echocardiography, ultrasonography of lower limb veins and aortic arch branches, blood pressure monitoring, Holter monitoring, capillaroscopy, as well as ophthalmoscopy. The obtained data was processed in Microsoft Excel by means of descriptive statistics, $\chi 2$ test and z-test for comparing two proportions; the relationship was considered to be statistically significant when $p < 0.05$.

Results and discussion. 350 patients (94.60%) with systemic lupus erythematosus had vascular and cardiac lesions, especially Raynaud syndrome, atherosclerosis, retinal angiopathy, livedo reticularis, hemorrhagic vasculitis, capillaritis, varicose veins, venous thrombosis, post-thrombotic syndrome, lymphedema, venous ulcers, thrombophlebitis, secondary hypertension, primary hypertension, pulmonary hypertension, myocarditis, mitral insufficiency, aortic insufficiency, tricuspid insufficiency, atherosclerotic heart disease, ischemic heart diseases: stable angina, old myocardial infarction, cardiomyopathy. Of these lesions, Raynaud syndrome, capillaritis, hemorrhagic vasculitis, stable angina, retinal angiopathy, livedo reticularis, atherosclerosis, venous thrombosis, pulmonary hypertension, secondary hypertension, myocarditis were pathogenetically associated with systemic lupus erythematosus. Other lesions were induced by co-occurring circulatory system diseases, since there were no relationship between their prevalence and the severity degree of the underlying disease (systemic lupus erythematosus). The patients with systemic lupus erythematosus were predominantly diagnosed with stage II Reynaud syndrome, and it affected mostly hand fingers. The intima-media thickness ranged from 8.0 mm to 14.9 mm. The retinal angiopathy was of the first degree of severity, livedo reticularis predominantly affected lower limbs (legs). All patients had cutaneous form of hemorrhagic vasculitis (first degree of severity), and capillaritis affected hands. The venous thrombosis was observed at tibia and popliteal vein segments. The secondary hypertension was of first degree of severity, pulmonary hypertension was asymptomatic (first degree of severity), myocarditis was mild, and stable angina was of functional class II. The lesions that were pathogenetically associated with systemic lupus erythematosus had their own factors of prevalence: Raynaud syndrome was significantly more prevalent in women and patients aged 18 to 24, retinal angiopathy, livedo reticularis and secondary hypertension were significantly more prevalent in women and patients with the disease duration of more than 10 years. The venous thrombosis and stable angina were significantly more prevalent in elderly patients and patients with the disease duration of more than 10 years. Myocarditis was significantly more prevalent in men; atherosclerosis and pulmonary hypertension were significantly more prevalent in elderly patients.

Keywords: systemic lupus erythematosus, cardiac lesions, vascular lesions, characteristics, prevalence.

Introduction. Systemic lupus erythematosus (SLE) is a connective tissue disease occurring based on genetically induced imperfection of immunoregulatory processes that leads to the formation of multiple autoantibodies and the emergence of immunocomplex inflammation. The latter produces lesions in almost all human organs [8]. In particular, vascular and cardiac lesions are the most prevalent lesions in patients with SLE. They also top the list of mortality reasons in patients with SLE [10].

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Topicality. The specific vascular and cardiac lesions that are directly induced by systemic lupus erythematosus – autoimmune inflammation, activation of atherosclerotic process, antiphospholipid syndrome, etc. – have not been identified in previous studies yet [13, 16, 18]. The relationships between age, sex of patients, duration of the underlying disease and the spectrum of SLE-induced cardiac and vascular lesions have also not been studied enough.

Objective. To characterize and clarify the prevalence of vascular and cardiac lesions that are pathogenetically associated with systemic lupus erythematosus.

Materials and methods. Having obtained written consents to participate in comprehensive examinations in accordance with the principles of Helsinki Human Rights Declaration, Council of Europe Convention on Human Rights and Biomedicine, the relevant laws of Ukraine and other international instruments, after stratification by SLE diagnosis, we randomly chose 370 patients (331 women (89.46%) and 39 men (10.54%). All enrolled patients were diagnosed with SLE in accordance with the Order of the Ministry for Health of Ukraine No. 676 of October 12, 2006 "On the Approval of Protocols for the Provision of Medical Care under the Rheumatology Specialty" (as amended by Orders No. 263 of April 11, 2014, No. 762 of November 20, 2015), recommendations of the European League against Rheumatism (2019) and American College of Rheumatology (2010, 2012). They received treatment in 2010-2018 at the Rheumatology Department of Lviv Regional Clinical Hospital, the clinical base of the Departments of Internal Medicine No. 1 and No. 2 of Danylo Halytsky National Medical University.

SLE patients were stratified into groups by: 1) age, in accordance with the World Health Organization classification (2015) – young age group (aged 18-44, 204 patients), middle age group (aged 45-59, 153 patients), and old age group (aged 60-75, 13 patients); 2) duration of the disease – less than a year (21 patients), 1-5 years (133 patients), 5-10 years (78 patients) and more than 10 years (138 patients).

Comprehensive clinical, laboratory and instrumental examinations of the circulatory system lesions were held in accordance with the Order of the Ministry for Health of Ukraine of July 3, 2006 No. 436 "On the Approval of Protocols for the Provision of Medical Care under Cardiology Specialty" (as amended by Orders No. 384 of May 24, 2012, No. 455 of July 2, 2014). We considered passport information, patients' complaints, anamneses of the disease and their lives obtained through a comprehensive objective examination, as well as the results of additional laboratory and instrumental examinations. The latter included electrocardiography (ELI 230 Resting ECG, Mortara Instrument, USA), echocardiography (standard procedure on Samsung H-60 ultrasound scanner (South Korea) with a cardiovascular transducer in one-dimensional, two-dimensional and Doppler echocardiography modes (with pulsed-wave spectral Doppler, as well as color Doppler blood flow detection)), ultrasonography of the lower limb veins and the aortic arch branches (Samsung H-60 ultrasound scanner with LF 5-13 linear transducer), bicycle ergometer test according to the well-known method at the Seca bicycle ergometer (Germany) in sitting position with electrocardiogram registration on 6-channel 6-NEK-4-01 ECG (Germany), daily blood pressure monitoring according to standard protocol (ABPM-04 monitor (Meditech, Hungary)), Holter monitoring according to standard protocol (BI6600-12 Holter ECG monitor (Heaco, United Kingdom)), nailfold capillaroscopy test (carried out at the *fourth digit* of the *left hand using* M-70 capillaroscope), as well as ophthalmoscopy (using Model 2B Slit Lamp (Ukraine), after administering atropine sulfate 1.0%, 5.0 ml).

All patients with SLE were stratified into five groups based on the evaluation of SLE activity (SLEDAI scores): seven patients with inactive SLE (SLEDAI = 0), 61 patients with the mild activity of SLE (SLEDAI = 1 to 5), 158 patients with the moderate activity of SLE (SLEDAI = 6 to 10), 104 patients with the high activity of SLE (SLEDAI = 11 to 19), and 40 patients with the very high activity of SLE (SLEDAI ≥ 20).

The research was conducted in *three phases.* At the *first step* of the *first phase,* all patients with SLE were diagnosed with specific cardiac and vascular lesions to identify their nature and prevalence. At the *second step* of the *first phase,* we identified those lesions that were pathogenetically associated with SLE. In the *second phase,* we characterized vascular and cardiac lesions that were pathogenetically associated with SLE. In the *third phase,* we clarified relationships between their prevalence and sex (*first step*), age (*second step)* and duration of the disease (*third step*).

The obtained data were processed in Microsoft Excel by means of descriptive statistics, $\chi 2$ test, and z-test for comparisons of two proportions; the relationships were considered to be statistically significant when $p < 0.05$.

Results. *The first phase* consisted of *two consecutive steps*, where the *first step* was to determine the prevalence of all the circulatory system lesions in patients with SLE, and the *second step* was to determine relationships between disease activity and the prevalence of lesions with a view to identifying lesions that were pathogenetically associated with SLE.

Having examined complaints, anamneses, the results of clinical, laboratory, and instrumental examinations, we detected multiple vascular and cardiac lesions in patients with SLE. According to the results obtained in the *first step*, vascular and cardiac lesions were detected in 350 patients with SLE (94.60%). The most prevalent type of vascular lesions was Raynaud syndrome since it was detected in 201 patients (54.32%). Other vascular lesions occurred with the following prevalence: atherosclerotic vascular lesions were detected in 32 patients with SLE (41.03%), retinal angiopathy – in 131 patients (35.41%), livedo reticularis – in 99 patients (26.76%), hemorrhagic vasculitis – in eight patients (2.16%), capillaritis – in twelve patients (3,24%). Varicose veins of the lower extremities were diagnosed in 45 patients (12.16%), peripheral venous thrombosis – in 24 patients (6.49%), post-thrombotic syndrome – in 21 patients (5.67%), lymphedema – in eleven patients (2.97%), venous ulcers – in two patients (0.54%), and thrombophle-

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

bitis – in one patient with SLE (0.27%).

Secondary hypertension was detected in 124 patients with SLE (33.51%), and primary hypertension – in 36 patients (9.73%). Pulmonary hypertension was detected in 62 patients with SLE (22.55%).

Myocarditis (133 patients, 35.95%) was the most prevalent diagnosed type of cardiac lesions. Acquired heart defects, especially mitral insufficiency, were detected in 159 patients with SLE (42.97%). Tricuspid insufficiency was detected in 27 patients (7.30%). and aortic insufficiency was detected in 20 patients (5.42%). Atherosclerotic heart disease was detected in 34 patients with SLE (9.19%). Stable angina, a form of ischemic heart disease, was detected in five patients (1.35%), old myocardial infarction – in two patients (0.54%), and cardiomyopathy – in three patients (0.81%).

According to our data, cardiac and vascular lesions were detected in almost every patient with SLE (94.60%). The most prevalent type of lesions was Raynaud syndrome. More than a third of patients had atherosclerosis, myocarditis, retinal angiopathy, and secondary hypertension. The least prevalent lesions were cardiomyopathy, venous ulcers, and thrombophlebitis (≤ 1.00%).

The *second step of* this phase dealt with the relationships between the prevalence of the circulatory system lesions and SLE activity. In order to identify those relationships, we studied the prevalence of each vascular and heart lesion in combination with SLE activity. Thus, we performed statistical analysis to determine $\chi 2$ and test the null hypothesis that the observed random value obeys a certain theoretical law of distribution. The results are presented in Table 1.

Table 1

Prevalence of Vascular and Cardiac Lesions in Patients with Systemic Lupus Erythematosus and Their Relationship with SLE activity

No.	Vascular and cardiac lesions	SLE patients, no activity according to SLEDAI, n = 7		SLE patients, mild activity according to SLEDAI, n = 61		SLE patients, moderate activity according to SLEDAI, n = 158		SLE patients, high activity according to SLEDAI, n = 104		SLE patients, very high activity according to SLEDAI, n = 40	
		n	%	n	%	n	%	n	%	n	%
1	Raynaud syndrome	4	57.14	23	37.71	70	44.30	71	68.27	33	82.50
2	Atherosclerosis	n = 2		n = 1		n = 33		n = 36		n = 6	
		0	0.00	0	0.00	15	45.46	11	30.56	6	100.00
3	Retinal angiopathy	2	28.57	12	19.67	47	29.75	47	45.19	23	57.50
4	Livedo reticularis	2	28.57	10	16.39	31	19.62	36	34.61	20	50.00
5	Hemorrhagic vasculitis	0	0.00	0	0.00	0	0.00	2	1.92	6	15.00
6	Capillaritis	0	0.00	0	0.00	1	0.63	1	0.96	10	25.00
7	Varicose veins of the lower extremities	0	0.00	12	19.67	15	9.49	15	14.42	3	7.50
8	Venous thrombosis	0	0.00	2	3.28	9	5.70	4	3.85	9	22.50
9	Post-thrombotic syndrome	0	0.00	1	1.64	9	5.70	10	9.61	1	2.50
10	Lymphedema	0	0.00	0	0.00	3	1.90	7	6.73	1	2.50
11	Venous ulcers	0	0.00	0	0.00	1	0.63	0	0.00	1	2.50
12	Thrombophlebitis	0	0.00	0	0.00	0	0.00	0	0.00	1	2.50
13	Secondary hypertension	0	0.00	9	14.75	58	36.71	37	35.58	18	45.00
14	Primary hypertension	1	14.29	7	11.48	14	8.86	8	7.69	6	15.00
15	Pulmonary hypertension	n = 3		n = 41		n = 115		n = 78		n = 38	
		0	0.00	6	14.63	29	25.28	12	15.39	15	39.47
16	Myocarditis	2	28.57	13	21.31	53	33.54	44	42.31	21	52.50
17	Mitral insufficiency	2	28.57	27	44.26	71	44.94	41	39.42	18	45.00
18	Tricuspid insufficiency	0	0.00	5	8.20	13	8.23	6	5.77	3	7.50
19	Aortic insufficiency	0	0.00	2	3.28	9	5.70	5	4.85	3	7.50
20	Atherosclerotic heart disease	0	0.00	1	1.64	17	10.76	9	8.65	7	17.50
21	IHD: stable angina	0	0.00	0	0.00	1	0.63	0	0.00	4	10.00
22	IHD: old myocardial infarction	0	0.00	0	0.00	1	0.63	1	0.96	0	0.00
23	Cardiomyopathy	0	0.00	2	3.28	1	0.63	0	0.00	0	0.00

As shown in Table 1, there was a statistically significant relationship between the activity of SLE and the prevalence of Raynaud syndrome ($\chi 2 = 34.15$, $p = 0.00$), between the prevalence of atherosclerosis and the activity of SLE ($\chi 2 = 12.61$, $p = 0.01$), between the prevalence of retinal angiopathy and the activity of SLE ($\chi 2 = 21.85$, $p = 0.00$). The prevalence of livedo reticularis depended on the activity of SLE (the relationship was statistically significant: $\chi 2 = 21.77$; $p = 0.00$). We found a statistically significant relationship between SLE activity

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

and the prevalence of hemorrhagic vasculitis ($\chi2 = 36.19$, $p = 0.00$), between SLE activity and the prevalence of capillaritis ($\chi2 = 67.77$, $p = 0.00$). There was no statistically significant relationship between the prevalence of varicose veins of the lower extremities and the activity of SLE ($\chi2 = 6.55$, $p = 0.16$). The $\chi2$ coefficient indicated statistically significant relationship between the prevalence of peripheral venous thrombosis and the activity of SLE ($\chi2 = 19.79$, $p = 0.00$). There were no statistically significant relationships between the prevalence of post-thrombotic syndrome and the activity of SLE ($\chi2 = 6.05$, $p = 0.20$), the prevalence of lymphedema and the activity of SLE ($\chi2 = 7.84$, $p = 0.10$), the prevalence of venous ulcers and the activity of SLE ($\chi2 = 3.82$, $p = 0.43$), the prevalence of thrombophlebitis and the activity of SLE ($\chi2 = 8.27$, $p = 0.08$). There was a statistically significant relationship between the prevalence of secondary hypertension and SLE activity ($\chi2 = 13.00$, $p = 0.01$). There was no statistically significant relationship between the prevalence of primary hypertension and SLE activity ($\chi2 = 2.27$, $p = 0.69$) and was a statistically significant relationship between the prevalence of pulmonary hypertension and SLE activity ($\chi2 = 11.34$, $p = 0.02$). We found the relationship between the prevalence of myocarditis and SLE activity to be statistically significant ($\chi2 = 12.82$, $p = 0.01$). However, there were no statistically significant relationships between the prevalence of mitral insufficiency and the activity of SLE ($\chi2 = 1.48$, $p = 0.83$), the prevalence of tricuspid insufficiency and the activity of SLE ($\chi2 = 1.19$, $p = 0.88$), the prevalence of aortic insufficiency and the activity of SLE ($\chi2 = 2.04$, $p = 0.73$). There was no statistically significant relationship between the prevalence of atherosclerotic heart disease and SLE activity ($\chi2 = 8.69$, $p = 0.07$). However, we found the relationship between the prevalence of stable angina and the activity of SLE to be statistically significant ($\chi2 = 25.41$, $p = 0.00$). There were no statistically significant relationships between the prevalence of old myocardial infarction and the activity of SLE ($\chi2 = 0.95$, $p = 0.92$), the prevalence of cardiomyopathy and the activity of SLE ($\chi2 = 5.92$, $p = 0.21$).

Based on these results, we concluded that the Raynaud syndrome, capillaritis, hemorrhagic vasculitis, stable angina, retinal angiopathy, livedo reticularis, atherosclerosis, venous thrombosis, pulmonary hypertension, secondary hypertension, and myocarditis were pathogenetically associated with SLE. The other lesions were co-occurring circulatory system diseases, since there were no relationships between rise in their prevalence and the progression of the underlying disease (SLE).

The results obtained at the first phase of the study indicated that vascular and cardiac lesions occurred in 350 (94.60%) patients with SLE. The prevalence of Raynaud syndrome, capillaritis, hemorrhagic vasculitis, stable angina, retinal angiopathy, livedo reticularis, atherosclerosis, venous thrombosis, pulmonary hypertension, secondary hypertension, and myocarditis rose with SLE progression, so we concluded they could be considered to be pathogenetically associated with SLE.

The revealed fact highlighted the need for an additional general characterization of vascular and cardiac lesions that were pathogenetically associated with SLE. The *second phase* of the study was dedicated to this characterization. The *third phase* was dedicated to the identification of prevalence characteristics in combination with sex (*first step*), age (*second step*) of patients and the duration of SLE (*third step*).

The second phase. Raynaud syndrome was detected in 149 out of 201 cases on the second – fifth digits (74.13%), and in 52 out of 201 cases on the first – third digits (25.87%). 55 patients with Raynaud syndrome (27.36%) were diagnosed with the first (angiospastic) stage of the lesion. 146 patients with Raynaud syndrome (72.64%) were diagnosed with the second (angioparalytic) stage. There were no patients with the third (digital ulcers) stage.

Atherosclerosis was characterized by the thickness of the intima-media, where half of patients (50.0%) had this measure within 10.0-11.0 mm, 20.0% of patients had this measure within 8.0-10.0 mm, other 20.0% patients had this measure within 11.0-14.9 mm, in 5.0% of patients this measure was 8.0 mm, in other 5.0% of patients it was greater than 14.9 mm. Initial manifestations of retinal angiopathy (stage I) were detected in 94 patients (71.76%). The moderate activity of retinal angiopathy (stage II) was detected in 33 patients (25.19%). The most severe activity of retinal angiopathy (stage III) was detected in four patients (3.05%). In the vast majority of cases, livedo reticularis was detected on the legs (70 patients, 70.71%), in some cases – on the hands (15 patients, 15.15%), as well as on the hips and forearms (14 patients, 14.14 %). All (100.0%) cases of hemorrhagic vasculitis belonged to the cutaneous form of the disease and were of mild severity. Capillaritis was detected in 12 patients with SLE, and it affected in nine cases their hands (75.00%), in two cases – torso (16.67%) and in one case – forearms (8.33 %). We found 7 cases of superficial venous thrombosis (in tibia muscles, 29.17%) and 17 cases of deep venous thrombosis (in 14 patients with popliteal segment (58.33%), in three patients with iliac-femoral segment (12.50 %)). Out of all patients, eight patients had obstructive lesions (33.33%), and 16 patients had parietal lesions (66.67%).

Secondary hypertension was characterized by blood pressure measures. In particular, stage I hypertension was detected in 86 patients with SLE (69.35%), stage II hypertension was detected in 36 patients (29.03%), and stage III hypertension was detected in two patients (1.61%). Stage I asymptomatic pulmonary hypertension was detected in 52 patients with SLE (83.87%). Nine patients (17.31%) were diagnosed with stage II pulmonary hypertension, and one patient (1.92%) was diagnosed with stage III pulmonary hypertension.

Mild mmyocarditis with the stages 0-I cardiac insufficiency was detected in 80 patients (60.15%). Moderate myocarditis with stages I-IIA cardiac insufficiency occurred in 49 patients with SLE (36.84%). Severe myocarditis with manifestations of stage II A-B cardiac insufficiency and/or cardiac arrhythmias and conduction disturbances was detected in four patients (3.01%). Patients with stage III cardiac insufficiency were not detected. Stable angina in all five patients was graded as moderate (functional class II).

Summarizing the results, we concluded that

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

most patients had stage II Raynaud syndrome. It affected hand digits; the thickness of the intima-media ranged from 8.0 mm to 14.9 mm. Most patients had stage I retinal angiopathy with initial manifestations. Livedo reticularis affected mostly legs. The mild cutaneous form of hemorrhagic vasculitis prevailed. Capillaritis affected mostly hands. Thrombosis of the popliteal vein prevailed. Most patients had stage I secondary hypertension. Pulmonary hypertension was predominantly asymptomatic (stage I). Mmyocarditis was predominantly graded as mild, and stable angina was graded as moderate (functional class II).

The third phase. The results of the *first step of* this phase are presented in Table 2. This step dealt with identification of prevalence characteristics (of the vascular and cardiac lesions that were pathogenetically associated with SLE) in combination with sex.

Table 2

Prevalence Characteristics of Vascular and Cardiac Lesions in Combination with the Sex of Patients with Systemic Lupus Erythematosus

No.	Cardiac and vascular lesions	Patients with systemic lupus erythematosus			
		Women, n = 331		Men, n = 39	
		n	%	n	%
1	Raynaud syndrome	185	55.89	16 *	41.03
2	Atherosclerosis	n = 77		n = 1	
		31	40.26	1	100.00
3	Retinal angiopathy	125	37.76	6 *	15.39
4	Livedo reticularis	94	28.40	5 *	12.82
5	Hemorrhagic vasculitis	7	2.11	1	2.56
6	Capillaritis	12	3.63	0	0.00
7	Venous thrombosis	21	6.34	3	7.69
8	Secondary hypertension	118	35.65	6 *	15.39
9	Pulmonary hypertension	n = 247		n = 28	
		58	23.48	4	14.29
10	Myocarditis	113	34.14	20 *	51.28
11	IHD: stable angina	4	1.21	1	2.56

Note: * - statistically significant difference in the number of cases in women and men ($p < 0.05$).

Raynaud syndrome prevalence was significantly higher in women than in men with SLE (185 cases (55.89%) versus 16 cases (41.03%), respectively). Atherosclerosis was detected in 31 women (40.26%) and one man (100.00%), with no statistically significant difference between groups. Retinal angiopathy prevalence was significantly higher in women than in men (125 cases (37.76%) versus six cases (15.39%), respectively, $p < 0.05$). Livedo reticularis prevalence was also higher in women than in men (94 women (28.40%) versus five men (12.82%), $p < 0.05$). The hemorrhagic vasculitis prevalence was almost the same in women and men (seven cases (2.11%) versus one case (2.56%), respectively). Capillaritis was detected in twelve women (3.63%), but it was not detected in any men at all. Venous thrombosis was detected in 21 women (6.34%) and three men (7.69%). There were no statistically significant differences between prevalence in women and men for hemorrhagic vasculitis, capillaritis, and venous thrombosis ($p > 0.05$).

Secondary hypertension prevalence was significantly higher in women (118 women (35.65%) versus six men (15.49%), $p < 0.05$). Pulmonary hypertension was detected in 58 women (23.48%) and four men (14.29%), with no statistically significant difference ($p > 0.05$).

On the contrary, myocarditis prevalence was significantly higher in men that in women (113 women (35.65%) versus 20 men (51.28%), $p < 0.05$). Stable angina prevalence was equal in women and men (four women (1.21%) versus one man (2.56%), $p > 0.05$).

The findings indicated that Raynaud syndrome, retinal angiopathy, livedo reticularis, and secondary hypertension were more prevalent in women than in men, and myocarditis was more prevalent in men than in women.

The results of the *second step of* this phase of the study are presented in Table 3. This step dealt with identification of prevalence characteristics (of the vascular and cardiac lesions that were pathogenetically associated with SLE) in combination with patients' age. The young age group was subdivided into two subgroups: young age subgroup I (18 to 24 years, 42 patients) and young age subgroup II (25 to 44 years, 162 patients).

The obtained data indicated that Raynaud syndrome prevailed in the young age subgroup I (27 cases, 64.29%). The Raynaud syndrome prevalence was lower in the young age subgroup II (90 cases, 55.56%) and the middle age group (79 cases, 51.63%). The lowest prevalence of Raynaud syndrome was detected in the old age group (five cases, 38.46%), but the difference was statistically significant only for the young age subgroup II. Atherosclerotic vascular lesions were detected in the young age subgroup II (19 cases, 42.22%), the middle age group (11 cases, 52.38%), and in two patients of the old age group (2 cases, 100.00%), but the differences were not statistically significant. Retinal angiopathy was detected in the young age subgroup I (seven cases, 16.67%), the young age subgroup II (59 cases, 36.42%), the middle age group (59 cases, 38.56%), and the old age group (six cases, 38.46%).

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Table 3

Prevalence Characteristics of Vascular and Cardiac Lesions in Combination with the Age of Patients with Systemic Lupus Erythematosus

No.	Cardiac and vascular lesions	Patients with systemic lupus erythematosus							
		Young age group, n = 204				Middle age group, n = 153		Old age group, n = 13	
		Young age subgroup I, n = 42		Young age subgroup II, n = 162					
		n	%	n	%	n	%	N	%
1	Raynaud syndrome	27	64.29	90	55.56	79	51.63	5 *	38.46
2	Atherosclerosis	n = 10		n = 45		n = 21		n = 2	
		0	0.00	19 *	42.22	11 *	52.38	2 *	100.00
3	Retinal angiopathy	7	16.67	59	36.42	59	38.56	6	46.15
4	Livedo reticularis	9	21.43	53	32.72	33 #	21.60	4	30.77
5	Hemorrhagic vasculitis	1	2.38	4	2.50	3	1.96	0	0.00
6	Capillaritis	3	7.14	4	2.50	5	3.27	0	0.00
7	Venous thrombosis	1	2.38	5	3.09	16 #	10.46	2 * #	15.39
8	Secondary hypertension	12	28.57	57	35.19	51	33.33	4	30.77
9	Pulmonary hypertension	n = 33		n = 120		n = 114		n = 8	
		5	15.15	16	13.33	34 #	29.83	7 ^ * #	87.50
10	Myocarditis	16	38.10	61	37.65	50	32.68	6	46.15
11	IHD: stable angina	0	0.00	0	0.00	0	0.00	5 ^ * #	38.46

Notes:

* - statistically significant difference in the number of cases in the young age subgroup I and others ($p < 0,05$);

- statistically significant difference in the number of cases in the young age subgroup II and others ($p < 0,05$);

^ - statistically significant difference in the number of cases in the middle age group and others ($p < 0,05$).

No statistically significant differences were found between these groups. There were isolated cases of hemorrhagic vasculitis (one patient in the young age subgroup I (2.38%), four patients in the young age subgroup II (2.50%), three patients in the middle age group (1.96%)) and capillaritis (three patients in the young age subgroup I (7.14%), four patients in the young age subgroup II (2.50%), five patients in the middle age group (3.27%)) in all age groups. There were no cases of hemorrhagic vasculitis and capillaritis in the old age group. Peripheral venous thrombosis was significantly more prevalent in the old age group (2 cases, 15.39%) than in the young age subgroup I (2.38%), the young age subgroup II (3.09%) or the middle age group (10.46%).

Secondary hypertension was almost equally prevalent in each age group (12 cases in the young age subgroup I (28.57%), 57 cases in the young age subgroup II (35.19%), 51 cases in the middle age group (33.33%), and 4 patients in the old age group (30.77%)). Pulmonary hypertension was more prevalent in elderly patients: five cases (15.16%) were detected in the young age subgroup I, 16 cases (13.33%) were detected in the young age subgroup II, 34 cases were detected in the middle age group (29.83%), and seven cases (87,50%) were detected in the old age group.

Myocarditis was also equally prevalent in each age group (16 patients in the young age subgroup I (38.10%), 61 patients in the young age subgroup II (37.65%), 50 patients in the middle age group (32.68%) and 6 patients in the old age group (46.15%)). Stable angina was significantly prevalent only in elderly patients (five patients of the old age group (38.46%); it was not detected in other age groups.

Summarizing the results, we concluded that Raynaud syndrome was more prevalent in patients aged 18 to 24. Other pathogenetically associated with SLE types of lesions; especially atherosclerosis, venous thrombosis, pulmonary hypertension and stable angina were more prevalent in elderly patients with SLE.

The results of the *third step of* this phase of the study are presented in Table 4. This step dealt with identification of prevalence characteristics (of the vascular and cardiac lesions that were pathogenetically associated with SLE) in combination with the duration of the underlying disease. The obtained data indicated that Raynaud syndrome was significantly less prevalent in patients with the SLE duration of less than one year (seven cases, 33.33%) than in patients with the SLE duration of 1-5 years (72 cases, 54.14%), the SLE duration of 6-10 years (46 cases, 58.97%), and the SLE duration of more than 10 years (76 cases, 55.07%), Atherosclerosis was detected in one patient (100%) with the SLE duration of less than 1 year. This type of lesions was also detected in eight patients with the SLE duration of 1-5 years (44.44%), in 7 patients with the SLE duration of 6-10 years (22.58%), and in 16 patients with the SLE duration of more than 10 years (57.14%). Retinal angiopathy was more prevalent in patients with the SLE duration of more than 10 years (58 cases, 42.03%). It was less prevalent in patients with the SLE duration of less than 1 year (two cases, 9.52%). This type of lesions was detected in 43 patients (32.33%) with the SLE duration of 1-5 years, and in 28 patients (35.90%) with the SLE duration of 6-10 years.

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Table 4

Prevalence Characteristics of Vascular and Cardiac Lesions in Combination with the Duration of Systemic Lupus Erythematosus

No. for	Vascular and cardiac lesions	Duration of systemic lupus erythematosus							
		Less than 1 year, n = 21		1-5 years, n = 133		6-10 years, n = 78		More than 10 years, n = 138	
		N	%	N	%	N	%	N	%
1	Raynaud syndrome	7	33.33	72 *	54.14	46 *	58.97	76 *	55.07
2	Atherosclerosis	n = 1		n = 18		n = 31		n = 28	
		1	100.00	8	44.44	7 *	22.58	16 ^	57.14
3	Retinal angiopathy	2	9.52	43 *	32.33	28 *	35.90	58 * #	42.03
4	Livedo reticularis	2	9.52	33	24.81	11 #	14.10	53 * # ^	38.41
5	Hemorrhagic vasculitis	1	4.76	0 *	0.00	3 #	3.85	4 #	2.90
6	Capillaritis	2	9.52	9	6.77	0 #	0.00	1 * #	0.72
7	Venous thrombosis	0	0.00	7	5.26	3	3.85	14 ^	10.15
8	Secondary hypertension	4	19.05	29	21.81	34 # *	43.59	57 # *	41.30
9	Pulmonary hypertension	n = 9		n = 102		n = 66		n = 98	
		3	33.33	22	21.57	11	16.67	26	26.53
10	Myocarditis	8	38.10	47	35.34	29 *	37.18	49 *	35.51
11	IHD: stable angina	0	0.00	0	0.00	0	0.00	5 # ^	3.62

Notes:

* - statistically significant difference in the number of cases in patients with the SLE duration of less than 1 year ($p < 0.05$);

- statistically significant difference in the number of cases in patients with the SLE duration of 1-5 years ($p < 0,05$);

^ - statistically significant difference in the number of cases in patients with the SLE duration of 6-10 years ($p < 0,05$).

The prevalence of livedo reticularis was similar: it was more prevalent in patients with the SLE duration of more than 10 years (53 cases, 38.41%), and less prevalent in patients with the SLE duration of less than one year (two cases, 9.52%). Livedo reticularis was detected in 33 patients (24.81%) with the SLE duration of 1-5 years, and in 11 patients (14.10%) with the SLE duration of 6-10 years. Isolated cases of hemorrhagic vasculitis occurred in each group: one case (4.76%) in patients with the SLE duration of less than one year, three cases (3.85%) in patients with the SLE duration of 6-10 years, and four cases (2.90%) in patients with the SLE duration of more than 10 years. Capillaritis was more prevalent in patients with the SLE duration of less than one year (two cases, 9.52%) and 1-5 years (nine cases, 6.77%). It was less prevalent in patients with the SLE duration of 6-10 years (0.00%) and more than 10 years (one case, 0.72%). Peripheral venous thrombosis occurred mainly in patients with the SLE duration of more than 10 years (14 cases, 10.15%). It was also detected in seven patients (5.26%) with the SLE duration of 1-5 years and in three patients (3.85%) with the SLE duration of 6-10 years.

Secondary hypertension was significantly more prevalent in patients with the SLE duration of 6-10 years (34 cases, 43.59%) and more than 10 years (57 cases, 41.30%) than in patients with the SLE duration of less than one year (four cases, 19.05%) or 1-5 years (29 cases, 21.81%). Pulmonary hypertension was detected in three patients (33.33%) with the SLE duration of less than one year, in 22 patients (21.57%) with the SLE duration of 1-5 years, in 11 patients (16.67%) with the SLE duration of 6-10 years, and in 26 patients (26.53%) with the SLE duration of more than 10 years.

We detected eight cases (38.10%) of myocarditis in patients with the SLE duration of less than one year, 47 cases (35.34%) of myocarditis in patients with the SLE duration of 1-5 years, 29 cases (37.18%) of myocarditis in patients with the SLE duration of 6-10 years, and 49 cases (35.51%) of myocarditis in patients with the SLE duration of more than 10 years. The majority of cases of stable angina were observed in patients with the SLE duration of more than 10 years (five cases, 3.62%); no cases of stable angina were detected in other groups of patients.

Summarizing the results, we concluded that there were specific, pathogenetically associated with SLE, vascular and cardiac lesions and their prevalence rose or fell with the duration of the disease. In particular, capillaritis was more prevalent in patients with the lowest duration of SLE, and livedo reticularis, retinal angiopathy, venous thrombosis, secondary hypertension, and stable angina were more prevalent in patients with the longest disease duration (more than 10 years).

The findings indicated that there were certain prevalence characteristics of the pathogenetically associated with SLE vascular and cardiac lesions. In particular, Raynaud syndrome was significantly more prevalent in women and patients aged 18 to 24. Retinal angiopathy, livedo reticularis and secondary hypertension were significantly more prevalent in women and patients with the SLE duration of more than 10 years. Venous thrombosis and stable angina were more prevalent in patients with the SLE duration of more than 10 years. Myocarditis was more prevalent in men. Atherosclerosis and pulmonary hypertension were more prevalent in elderly patients with SLE.

Discussion of results. The prevalence rate of the circulatory system lesions in patients with SLE was as

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

high as 94.60%. This rate is consistent with the results of other studies where the prevalence rate of the circulatory system lesions in patients with SLE was somewhat lower, though (it ranged from 52.00% to 89.00%) [18]. The spectrum of the detected lesions includes: Raynaud syndrome, atherosclerosis, retinal angiopathy, livedo reticularis, hemorrhagic vasculitis, capillaritis, varicose veins of the lower extremities, venous thrombosis, post-thrombotic syndrome, lymphedema, venous ulcers, thrombophlebitis, secondary hypertension, primary hypertension, pulmonary hypertension, myocarditis, mitral insufficiency, tricuspid insufficiency, aortic insufficiency, atherosclerotic heart disease, stable angina, old myocardial infarction, cardiomyopathy. The determined prevalence rates for a number of lesions, especially Raynaud syndrome [5, 6], atherosclerosis [12], hemorrhagic vasculitis [4], retinal angiopathy [1, 7], primary hypertension [2, 6], pulmonary hypertension [15, 17], myocarditis [3, 6], valve insufficiencies [6], and ischemic heart disease [9], corresponded with the rates mentioned in contemporary literature. The review of available literature did not reveal any studies that mentioned prevalence rates for such conditions as livedo reticularis, capillaritis, varicose veins of the lower extremities, peripheral venous thrombosis, post-thrombotic syndrome, lymphedema, venous ulcers, thrombophlebitis and cardiomyopathy. We also did not find studies that analyzed relationships between the circulatory system lesions and the activity of SLE (according to SLEDAI) or tried to distinguish co-occurring diseases from those that were pathogenetically associated with SLE. We found that Raynaud syndrome, capillaritis, hemorrhagic vasculitis, stable angina, retinal angiopathy, livedo reticularis, atherosclerosis, venous thrombosis, pulmonary hypertension, secondary hypertension, myocarditis were closely related to SLE, i.e. they were pathogenetically associated with it.

In the second phase, we identified general characteristics of the circulatory system lesions that were pathogenetically associated with SLE. We found that most patients with Raynaud syndrome had lesions that were graded as angioparalytic (stage II), and it affected mostly hand digits. In 90.00% of patients with atherosclerosis, the thickness of the intima-media ranged from 8.0 mm to 14.9 mm. In three-quarters of patients with retinal angiopathy, lesions of the retinal vessels were graded as mild (stage I). In three-quarters of patients with livedo reticularis, it affected tibial vessels. All patients with hemorrhagic vasculitis were diagnosed with a cutaneous form of disease graded as mild (stage I). The capillaritis was limited mainly to hands. Deep venous thrombosis was more prevalent than superficial venous thrombosis. The former mostly affected popliteal vein. Having evaluated blood pressure measures, we found that the secondary hypertension in most patients was graded as mild (stage I). Pulmonary hypertension was asymptomatic in most patients. More than half of SLE patients, who were also diagnosed with myocarditis, had mild cardiac lesions. Stable angina in all patients with this diagnosis was graded as moderate (functional class II). The review of literature produced several references to the clinical characteristics of some lesions – namely, primary hypertension, atherosclerosis, retinal angiopathy, and myocarditis [6, 11, 14, 18]. We did not find descriptions of other lesions.

Having analyzed the prevalence of the pathogenetically associated with SLE vascular and cardiac lesions, we found certain characteristics that should be taken into account when screening patients with SLE for the lesions of the circulatory system. In particular, Raynaud syndrome, retinal angiopathy, livedo reticularis, and secondary hypertension were more prevalent in women with SLE, and myocarditis was more prevalent in men with SLE. Raynaud syndrome was also more prevalent in patients aged 18 to 24. Other pathogenetically associated with SLE lesions – atherosclerosis, venous thrombosis, pulmonary hypertension, and stable angina – were more prevalent in elderly patients. Capillaritis was more prevalent in patients with the lowest duration of SLE, while livedo reticularis, retinal angiopathy, venous thrombosis, secondary hypertension, and stable angina were more prevalent in patients with the longest duration of SLE (more than 10 years). The review of literature did not produce information about the prevalence of vascular and cardiac lesions that were pathogenetically associated with SLE.

Conclusions. Vascular and cardiac lesions were detected in 94.60% of patients with systemic lupus erythematosus. The prevalence of Raynaud syndrome, atherosclerosis, retinal angiopathy, livedo reticularis, hemorrhagic vasculitis, capillaritis, venous thrombosis, secondary hypertension, pulmonary hypertension, myocarditis, and stable angina rose with the progression of SLE. Therefore, these lesions are pathogenetically associated with SLE. They were also graded as mild or moderate and had certain prevalence characteristics: Raynaud syndrome, retinal angiopathy, livedo reticularis levedo, and secondary hypertension were more prevalent in women with SLE, and myocarditis was more prevalent in men. Raynaud syndrome was more prevalent in patients with SLE aged 18 to 24. On the contrary, atherosclerosis, venous thrombosis, pulmonary hypertension, and stable angina were more prevalent in elderly patients. Capillaritis was more prevalent in patients with the lowest duration of SLE. In contrast, retinal angiopathy, livedo reticularis, venous thrombosis, secondary hypertension, and stable angina were more prevalent in patients with the SLE duration of more than 10 years.

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УДК 616.5-002.525.2-031.81:616.1]-06

ПАТОГЕНЕТИЧЕСКИ АССОЦИИРОВАННЫЕ С СИСТЕМНОЙ КРАСНОЙ ВОЛЧАНКОЙ ПОРАЖЕНИЯ СОСУДОВ И СЕРДЦА: ХАРАКТЕРИСТИКА И ОСОБЕННОСТИ РАСПРОСТРАНЕНИЯ

У.О. Абрагамович[1], О.О. Абрагамович[2], М.Л. Фармага[2], О.Т. Романюк[2], Л.О. Кобак[2]

[1]Львовский национальный медицинский университет имени Данила Галицкого, кафедра внутренней медицины №2, г. Львов, Украина, ORCID ID: 0000-0003-4762-3857, e-mail: doculyana@i.ua;
[2]Львовский национальный медицинский университет имени Данила Галицкого, кафедра внутренней медицины №1, г. Львов, Украина, ORCID ID: 0000-0001-6862-6809, email: docorest@gmail.com, ORCID ID: 0000-0003-1298-4644, email: martafarmaha@gmail.com, ORCID ID: 0000-0003-2922-7797, email: kovalolya8@gmail.com, ORCID ID: 0000-0002-2700-4007, email: k_liubov@ukr.net

Резюме. Поражение сосудов и сердца не только одни из самых распространенных, но и занимают первые позиции в структуре причин смертности больных системной красной волчанкой, которые до сих четко не выделены.

Цель исследования. Охарактеризовать и выяснить особенности распространения патогенетически ассоциированных с системной красной волчанкой поражений сосудов и сердца.

Материалы и методы. Привлечено 370 больных (331 женщин и 39 мужчин), которых стратифицировано по возрасту, продолжительности и активности СКВ, которых комплексно обследовано. Результаты обработаны в программе «Excel» с помощью описательной статистики, $\chi 2$-критерия, z-критерия для сравнения двух частей; статистически достоверным считали связь, когда $p < 0,05$.

Результаты исследования. Поражение сосудов и сердца встречаются в 350 (94,60%) больных системной красной волчанкой, из которых синдром А.Г.М. Рейно, капилярит, геморагический васкулит, стабильная стенокардия, ангиопатия сетчатки, ретикулярного ливедо, атеросклероз, тромбоз вен, легочноя гипертензия, симптоматическая артериальная гипертензия, миокардит являются патогенетически ассоциированные с системной красной волчанкой. Эти поражения являются преимущественно легкой и средней степеней тяжести. А также имеют особенности распространения: синдром А.Г.М. Рейно достоверно чаще встречается у женщин и лиц в возрасте от 18 до 24 лет, ангиопатия сетчатки, ретикулярное ливедо и симптоматическая артериальная гипертензия – у женщин и тех больных, системная красная волчанка которых длится более 10 лет, тромбоз вен и стабильная стенокардия – у больных пожилого возраста и больных системной красной волчанкой более 10 лет,

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

миокардит – у мужчин, а атеросклероз и легочная гипертензия – наиболее характерны для больных пожилого возраста.

Ключевые слова: системная красная волчанка, поражения сердца, поражения сосудов, характеристика, распространение.

УДК 616.5-002.525.2-031.81:616.1]-06

ПАТОГЕНЕТИЧНО АСОЦІЙОВАНІ ІЗ СИСТЕМНИМ ЧЕРВОНИМ ВОВЧАКОМ УРАЖЕННЯ СУДИН ТА СЕРЦЯ: ХАРАКТЕРИСТИКА ТА ОСОБЛИВОСТІ ПОШИРЕННЯ

У.О. Абрагамович[1], О.О. Абрагамович[2], М.Л. Фармага[2], О.Т. Романюк[2], Л.О. Кобак[2]

[1]*Львівський національний медичний університет імені Данила Галицького, кафедра внутрішньої медицини №2, м. Львів, Україна,*
ORCID ID: 0000-0003-4762-3857,
e-mail: doculyana@i.ua;
[2]*Львівський національний медичний університет імені Данила Галицького, кафедра внутрішньої медицини №1, м. Львів, Україна,*
ORCID ID: 0000-0001-6862-6809,
email: docorest@gmail.com,
ORCID ID: 0000-0003-1298-4644,
email: martafarmaha@gmail.com,
ORCID ID: 0000-0003-2922-7797,
email: kovalolya8@gmail.com,
ORCID ID: 0000-0002-2700-4007,
email: k_liubov@ukr.net

Резюме. Ураження судин і серця є не лише одними з найбільш поширених, але й займають перші позиції у структурі причин смертності хворих на системний червоний вовчак, які до сьогодні чітко не виелімінувані.

Мета дослідження. Охарактеризувати та з'ясувати особливості поширення патогенетично асоційованих із системним червоним вовчаком уражень судин та серця.

Матеріали і методи. Залучено 370 хворих (331 жінок і 39 чоловіків), яких стратифіковано за віком, за тривалістю та активністю СЧВ, яких комплексно обстежено. Результати опрацьовано у програмі «Excel» за допомогою описової статистики, $\chi 2$-критерію, z-критерію для порівняння двох часток; статистично достовірним вважали зв'язок, коли $p < 0,05$.

Результати дослідження. Ураження судин і серця зустрічаються у 350 (94,60 %) хворих на системний червоний вовчак, з яких синдром А.Г.М. Рейно, капілярит, геморагійний васкуліт, стабільна стенокардія, ангіопатія сітківки, ретикулярного ліведо, атеросклерозу, тромбоз вен, легенева гіпертензія, симптоматична артеріальна гіпертензія, міокардит є патогенетично асоційовані з системним червоним вовчаком. Вказані ураження є, переважно, легкого та середнього ступенів тяжкості. А також мають особливості поширення: синдром А.Г.М. Рейно достовірно частіше зустрічається у жінок та осіб у віці від 18 до 24 років, ангіопатія сітківки, ретикулярне ліведо і симптоматична артеріальна гіпертензія – у жінок та тих хворих, системний червоний вовчак яких триває понад 10 років, тромбоз вен і стабільна стенокардія – у хворих похилого віку та хворих на системний червоний вовчак більше, ніж 10 років, міокардит – у чоловіків, а атеросклероз та легенева гіпертензія – найбільш характерні для хворих похилого віку.

Ключові слова: системний червоний вовчак, ураження серця, ураження судин, характеристика, поширення.

Стаття надійшла в редакцію 09.04.2020 р.