УДК 616.5-002.52-008.6:616.25-002]-06-071-097.3 DOI: http://doi.org/10.30978/TB2024-3-23

O.B. Iaremenko[1], D.I. Koliadenko[1], K.M. Iaremenko[2], N.D. Kozak[1], O.V. Dema[1]

[1] Bogomolets National Medical University, Kyiv, Ukraine

[2] Alexander Clinical Hospital, Kyiv, Ukraine

Pleuropulmonary Manifestations in Patients with Systemic Lupus Erythematosus

Objective — to assess the prevalence of non-infectious pleuropulmonary manifestations in patients with systemic lupus erythematosus (SLE), as well as the demographic, clinical and laboratory characteristics of such patients.

Materials and methods. A total of 435 patients with SLE (87.5 % female; median age 37 (26—49) years) were enrolled in a cross-sectional study, including 200 with pleuropulmonary manifestations and 235 without them. Patients were evaluated for demographic details, clinical SLE manifestations, SLE Disease Activity Index 2000 (SLEDAI-2K), SLICC/ACR Damage Index (DI). Laboratory evaluations included complete blood count with erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), interleukin-6 (IL-6), IL-10, complement C3 and C4 levels, specific autoantibodies. Procalcitonin and presepsin serum levels were measured to exclude infections.

Results and discussion. At least one pleuropulmonary manifestation occurred in 46 % of patients, with pleurisy being the most frequent (24 %). Respiratory involvement was associated with male sex, longer disease duration, and older age at disease onset. Patients with respiratory complications had higher SLEDAI-2K and SLICC/ACR DI scores than those without pleuropulmonary involvement. Patients with pleuropulmonary manifestations more frequently exhibited lymphadenopathy, nephritis, pericarditis, other cardiac manifestations, fever, weight loss, anemia, and thrombocytopenia; conversely, cutaneous manifestations occurred less frequently in patients with pleuropulmonary involvement. Patients with respiratory involvement were found to have higher levels of ESR, CRP, hs-CRP, and IL-6. A higher frequency of positive anti-La/SSB, antiphospholipid, and anti-chromatin antibodies was observed in patients with pleuropulmonary manifestations compared to those without them.

In multivariate logistic analysis, respiratory involvement was positively associated with older age (odds ratio (OR) 1.03 (95 % confidence interval (CI) 1.01—1.05), p = 0.004), higher SLEDAI-2K (OR 1.05 (95 % CI 1.01—1.09), p = 0.030) and SLICC/ACR DI scores (OR 11.34 (95 % CI 1.03—1.74), p = 0.027), presence of lymphadenopathy (OR 2.27 (95 % CI 1.33—3.88), p = 0.003), pericarditis (OR 4.40 (95 % CI 2.29—8.46), p < 0.001), other cardiac manifestations (OR 10.1 (95 % CI 5.65—17.9), p < 0.001), and systemic symptoms (OR 2.14 (95 % CI 1.24—3.70), p = 0.007). Cutaneous manifestations were, on the other hand, negatively associated with the occurrence of pleuropulmonary symptoms (OR 0.27 (95 % CI 0.15—0.50), p < 0.001).

Conclusions. Pleuropulmonary manifestations are frequent in SLE, particularly pleuritis. Respiratory involvement is associated with male sex, older age, longer disease duration, and occurs mainly in patients with active and severe lupus, often with previous or concomitant major organ involvement other than lungs. Patients with pleuropulmonary involvement have higher levels of inflammatory markers and higher frequency of positive anti-La/SSB, antiphospholipid, and anti-chromatin antibodies.

Keywords

Systemic lupus erythematosus, pleuropulmonary involvement, pleurisy, pneumonitis, risk factor, biomarkers, autoantibodies, interleukins.

Pleuropulmonary involvement in systemic lupus erythematosus (SLE) is not uncommon, as it has been reported to occur in 20—90 % of patients [1, 3, 4, 13, 18, 20, 21, 24, 27] and may be the presenting manifestation in 4—5 % of patients [10, 24]. All anatomical components of the respiratory system may be affected during the disease course, including airways, parenchyma, pleura, vessels, and respiratory muscles [26]. The severity of these respiratory complications is highly variable and ranges from subclinical or asymptomatic self-limiting disease to acute respiratory failure and potentially life-threatening conditions that significantly affect prognosis [10, 24]. The spectrum of pulmonary manifestations in SLE is diverse and includes pleural disease, upper and lower airway involvement, primary pulmonary hypertension, pulmonary thromboembolism, acute reversible hypoxemia, diffuse interstitial lung disease (ILD), acute lupus pneumonitis, diffuse alveolar hemorrhage, and shrinking lung syndrome. Some patients may experience more than one form of pleuropulmonary involvement during the course of their disease [21].

Pleuritis is the most common feature, affecting up to 60 % of SLE patients during the disease course [22, 27]. It is the only respiratory manifestation included in the 2019 EULAR/ACR criteria for SLE [5]. Lung parenchyma is affected in up to 13 % of lupus patients, most commonly in the forms of chronic ILD and acute lupus pneumonitis [27]. Chronic ILD in SLE seems to be less frequent compared to other connective tissue diseases and is rarely severe [6]. This manifestation may be observed in 3—13 % of SLE patients and is clinically manifested with exertional dyspnea, dry cough, end-inspiratory crackles and gas-exchange disorders. Various forms of ILD have been described in SLE including non-specific interstitial pneumonia, organizing pneumonia, lymphocytic interstitial pneumonia, follicular bronchitis, and usual interstitial pneumonia [1]. The exact prevalence is probably underestimated as in studies using high-resolution computed tomography, ILD was found in up to 70 % of cases, suggesting that the condition is frequently subclinical [23]. Acute lupus pneumonitis has been reported in up to 4 % of lupus patients. Diagnosis is challenging since clinical (fever, cough, dyspnea, hypoxia) and radiologic features (uni- or bilateral alveolar infiltrates) are non-specific and may resemble infection. Pulmonary thromboembolism develops in 1—5 % of SLE patients, usually in the context of positive antiphospholipid antibodies (APLA) and antiphospholipid syndrome [24]. The prevalence of pulmonary arterial hypertension in SLE patients has been reported to be about 4 to 5 % [6]. Diffuse alveolar hemorrhage is a rare (2 %) but severe respiratory manifestation of SLE associated with a high mortality rate of up to 90 % [4, 27]. Shrinking lung syndrome is an uncommon manifestation of SLE with an estimated prevalence of 0.5—2 %; it is caused by impaired phrenic nerve signaling and subsequent diaphragm dysfunction, leading to progressive reduction in lung volumes [4, 6, 20, 27]. Airway involvement is relatively infrequent in SLE patients, presenting with conditions such as paralysis of the vocal cords, ulcerative lesions, cricoarytenoid arthritis, necrotizing vasculitis with obstruction of the airways, bronchiectasis, and bronchiolitis obliterans [6].

Symptoms of acute pulmonary SLE manifestations can often mimic infections, thus making diagnosis a challenge. The risk of pulmonary infection is three times higher in patients with SLE than in the general population [2]; furthermore, immunosuppressive treatment could exacerbate the infection course. In this context, infections must be always ruled out in a SLE patient with respiratory complaints and/or the appearance of a new infiltrates prior to increasing the immunosuppressive therapy.

In general, primary respiratory involvement in SLE is not as well-known as other major organ involvement. Although some risk factors have been described (such as older age, late-onset SLE, disease duration > 1 year, and male gender [10]), associations of these complications are still unspecified and data on the characteristics and laboratory parameters of SLE patients with pulmonary involvement remain scarce. Moreover, exact diagnostic criteria for lung involvement in SLE remain elusive. The most commonly used tool for measuring disease activity, SLE Disease Activity Index 2000 (SLEDAI-2K) [12], only accounts for pleurisy as a scorable item of lupus activity involving the lungs. This may result in patients with respiratory complications of SLE being falsely considered in remission or a low disease activity state. There are also no specific guidelines for the management of these manifestations; the therapeutic approach remains empirical, based on evidence from other organ involvement in SLE, respiratory manifestations in other autoimmune diseases, or case reports. As pulmonary involvement is associated with higher mortality rate and negatively effects on patients' quality of life [10], understanding the factors associated with the occurrence and severity of respiratory manifestations is of great importance.

The **objective** of the study was to assess the prevalence of non-infectious pleuropulmonary manifestations in a large Ukrainian SLE cohort, as well as the demographic, clinical and laboratory characteristics of such patients.

Materials and methods

This cross-sectional study was conducted at the Department of Internal Medicine No. 3 of Bogomo-

lets National Medical University and included 446 patients 18 years and older who were diagnosed with SLE between 1994 and 2023. All patients initially monitored before 2019 were diagnosed according to American College of Rheumatology (ACR) criteria (1982, updated 1997) [14]. In 2019, the diagnosis of SLE in these patients was reviewed for compliance with the European League Against Rheumatism (EULAR)/ACR classification criteria 2019 [5]. According to the results of this review, 11 patients were excluded from the primary pool, and the data of 435 persons were included in the final analysis. The study protocol was approved by the Ethics Committee of Bogomolets National Medical University (protocol No. 127 dated 02.12.2019) and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

Patients were reviewed for demographic details (sex, age), age at SLE onset, clinical manifestations of SLE (current and in medical history), and drug therapy content (medications and current dosage). Disease activity was assessed using the SLEDAI-2K [12], and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) [11] was used to assess damage. Laboratory evaluations included complete blood count with erythrocyte sedimentation rate (ESR) measured by Westergren method, C-reactive protein (CRP) measured by latex turbidimetric method (Roche Diagnostics, Switzerland), high-sensitivity CRP (hs-CRP) measured by an enzyme-linked immunosorbent assay (ELISA) (DRG International Inc., USA), serum levels of interleukin-6 (IL-6) and IL-10 (ELISA, Demeditec Diagnostics GmbH, Germany), complement C3 and C4 levels (immunoturbidimetric method, Roche Diagnostics, Switzerland). Immunological markers, such as antinuclear antibodies detected by indirect immunofluorescence (EUROIMMUN, Germany; positive ≥ 1 : 80, in accordance with EULAR/ACR criteria 2019 [5]), anti-double-stranded DNA (anti-dsDNA), anti-Smith (anti-Sm) antibodies, anti-Ro/SSA, anti-La/SSB, anti-ribonucleoprotein (anti-RNP), anti-chromatin, APLA, including anticardiolipin and anti-β_2-glycoproteins antibodies (ELISA, EUROIMMUN, Germany), and lupus anticoagulant (coagulation assay, Siemens, Germany) were also documented. Procalcitonin (ELISA, Monobind Inc., USA) and presepsin (ELISA, Wuhan Fine Biotech Co., Ltd., China) serum levels were measured to exclude infections.

Respiratory involvement was considered primary when it was directly related to SLE activity, and infections, drug toxicity, chronic obstructive pulmonary disease, occupational exposure, and neoplasia had been excluded. Pleuropulmonary manifestations analyzed in this study included: 1) pleural disease according to the SLEDAI-2K definition [12]; 2) acute lupus pneumonitis (in accordance with the British Isles Lupus Assessment group (BILAG) 2004 [28] definition of interstitial alveolitis/pneumonitis); 3) chronic ILD (BILAG 2004 definition); 4) pulmonary fibrosis (SLICC/ACR DI definition) [11]; 5) pulmonary thromboembolism (SLICC/ACR DI definition) [11]. Upper and lower airway involvement, pulmonary hemorrhage, shrinking lung syndrome, and primary pulmonary hypertension were not analyzed in the study as these manifestations were not specifically recorded in our database.

For statistical analysis, EZR software (version 1.61) was used. Continuous variables were expressed as means (and standard deviations) if normally distributed, and medians (and interquartile ranges) if not. Categorical variables were presented by absolute numbers and percentage. Comparisons of numerical variables were conducted using Student's t-test or a Mann—Whitney U-test, according to normality adjustments, and categorical variables were compared using a chi-squared or Fisher's exact test as necessary. Odds ratio (OR) and 95 % confidence intervals (CI) were derived from univariable and stepwise multivariable logistic regressions. Statistical significance was assumed as a p-value of less than 0.05.

Results and discussion

Of the 435 patients included in the study, 87.5 % (n = 381) were female; the age at disease onset and study entry was 28 (20—40) years and 37 (26—49) years, respectively. All study cohort participants were of Caucasian ethnicity. The median disease duration was 60 (23—120) months. The median values of SLEDAI-2K and SLICC/ACR DI scores were 10 (6—16) and 1 (0—2), respectively. Hydroxychloroquine was used in 59.7 % of the patients, and glucocorticoids were used in 67.8 % of patients, with a daily dose approximately 10 (10—15) mg in prednisolone equivalent. Regarding immunosuppressants, cyclophosphamide, methotrexate, azathioprine, and mycophenolate mofetil were used in 6.1, 6.1, 5.4, and 2.2 % of the patients, respectively.

At least one pleuropulmonary manifestation at any time during the course of the disease was present in 46.0 % of patients (n = 200). The most common manifestation was pleural disease occurring in 104 (23.9 %) of patients, followed by pulmonary fibrosis (n = 38; 8.7 %), chronic ILD (n = 34; 7.8 %), acute lupus pneumonitis (n = 27; 6.2 %), and pulmonary thromboembolism (n = 5; 1.1 %). The majority of patients who developed pleuropulmonary

manifestations also had previous or concomitant involvement of other major organs.

Pleuropulmonary involvement in SLE was associated with longer disease duration and either older age of patients and older age at disease onset (Table 1). The proportion of male sex in patients with pleuropulmonary manifestations was higher than in patients without them (16.6 *vs* 8.9 %, p = 0.026). Patients with respiratory complications had higher SLEDAI-2K scores (12 (8—18) *vs* 8 (4—14) points, p < 0.001). As expected, the mean SLICC/ACR DI scores were also significantly higher in this group than in patients with no pleuropulmonary involvement (2 (1—2) *vs* 1 (0—1) points, p < 0.001). Patients with pleuropulmonary manifestations at any time during the disease course exhibited more frequently lymphadenopathy (64.5 *vs* 45.8 %, p < 0.001), nephritis (55.8 *vs* 35.8 %, p < 0.001), pericarditis (42.6 *vs* 12.5 %, p < 0.001), other cardiac manifestations (80.1 *vs* 33.9 %, p < 0.001), fever (38.6 *vs* 24.2 %, p = 0.002), and weight loss (23.5 *vs* 13.2 %, p = 0.014); cutaneous manifestations, on the other hand, occurred less frequently among patients with pleuropulmonary involvement (59.5 *vs* 73.4 %; p = 0.003). Anemia (66.7 *vs* 32.8 %, p < 0.001) and thrombocytopenia (37.9 *vs* 19.8 %, p = 0.013) were more common in patients with pleuropulmonary manifestations than in those without them. Patients with respiratory involvement were found to have higher levels of ESR (25 (12—48) *vs* 19 (10—35) mm/hr, p = 0.008), CRP (12 (0—48) *vs* 5 (0—12) mg/L, p = 0.026), hs-CRP (29 (7—34) *vs* 6 (2—11) mg/L, p < 0.001), and IL-6 (14.5 (2.9—38.1) *vs* 2.9 (2.3—6.1) pg/mL, p = 0.010). None of the examined patients had procalcitonin and presepsin values that exceeded the numbers indicating the presence of a bacterial infection (> 0.5 ng/ml for procalcitonin [7, 25], > 600 pg/mL for presepsin [17]). A higher frequency of positive anti-La/SSB (32.5 *vs* 14.6 %; p = 0.049), APLA (81.3 *vs* 50.9 %; p = 0.009), and anti-chromatin antibodies (87.5 *vs* 49.2 %, p = 0.009) was observed in patients with pleuropulmonary manifestations than in those without them. Patients with pleuropulmonary manifestations received significantly higher daily glucocorticoid dose (12.5 (10.0—22.5) *vs* 10.0 (7.5—15.0) mg, p = 0.025). No differences were found in regard to other medication use.

Based on the baseline comparisons above, the variables independently associated with the development of pleuropulmonary manifestation were estimated by logistic regression analysis (Table 2). In multivariate logistic analysis, respiratory involvement was found to be positively associated with older age of the patients (OR 1.03 (95 % CI 1.01—1.05), p = 0.004), higher SLEDAI—2K (OR 1.05 (95 % CI 1.01—1.09), p = 0.030) and SLICC/ACR DI scores (OR 11.34 (95 % CI 1.03—1.74), p = 0.027), presence of lymphadenopathy (OR 2.27 (95 % CI 1.33—3.88), p = 0.003), pericarditis (OR 4.40 (95 % CI 2.29—8.46), p < 0.001) and other cardiac manifestations (OR 10.1 (95 % CI 5.65—17.9), p < 0.001), systemic symptoms (OR 2.14 (95 % CI 1.24—3.70), p = 0.007). Conversely, cutaneous manifestations were negatively associated with the occurrence of pleuropulmonary symptoms (OR 0.27 (95 % CI 0.15—0.50), p < 0.001). An area under the curve (AUC) of 0.864 was obtained in the receiver operating characteristic (ROC) curve (Figure).

In this large cohort of Ukrainian SLE patients, pleuropulmonary manifestations were present in approximately half of the patients (46 %) during the course of the disease. This percentage lies within the reported range of 20 to 90 % from other studies, though it is higher than reported in the Latin American GLADEL cohort (28 %) [13], the Spanish RELESSER cohort (31 %) [21], and the Saudi Arabian cohort (33 %) [2]. This variability may be explained by different characteristics of the patients studied (most of our patients had an established disease), approaches taken to determine the presence of pulmonary involvement (we performed imaging and functional studies only if clinically indicated), diverse definitions, study designs, and known racial and ethnic phenotypic variability.

In our study, pleural involvement was the most frequent feature (23.9 %), consistent with observations from other registries reporting prevalence between 16 and 50 % [13, 20, 21, 24]. Among parenchymal manifestations, the most commonly observed were pulmonary fibrosis (8.7 %) and chronic ILD (7.8 %). Acute lupus pneumonitis and pulmonary thromboembolism were found in 6.2 and 1.1 % of cases, respectively. This is consistent with observations from other investigators [13, 16, 27], summarizing that non-pleural respiratory manifestations are uncommon, occurring in less than 4—13 % of cases.

Our findings align with other studies showing that respiratory involvement is more common in men than in women [26]. We also found the association of pleuropulmonary manifestations with longer disease duration confirming that respiratory manifestations may complicate SLE at any time, though they usually occur later in the course of the disease [9, 20, 26]. Studies from the LUMINA multiethnic cohort and RELESSER cohort documented the appearance of respiratory manifestations after a disease duration of 5.3 years and 5.8 years, respectively [8, 21]. In agreement with other reports [1, 13, 20, 21, 26], we also found older age of SLE onset in patients with respiratory involvement.

Table 1. **Demographic, clinical and laboratory characteristics of SLE patients depending on the presence of pleuropulmonary involvement at any time during the disease course**

Variables	SLE patients with pleuropulmonary involvement (n = 200)	SLE patients without pleuropulmonary involvement (n = 235)	p
Demographic data			
Male sex, n (%)	33 (16.5)	21 (8.9)	0.026
Age, years	40 (30—51)	36 (25—46)	0.003
Age at SLE onset, years	30 (21—43)	26 (19—38)	0.042
Disease duration, months	72 (24—144)	48 (20—108)	0.046
SLE-specific indices			
SLEDAI-2K score	12 (8—18)	8 (4—14)	< 0.001
SLICC/ACR DI	2 (1—2)	1 (0—1)	< 0.001
Clinical manifestations, n (%)			
Skin manifestations	119 (59.5)	168 (73.4)	0.003
Mucous membrane manifestations	76 (38.6)	78 (34.5)	0.436
Sjogren's syndrome	10 (5.6)	19 (9.0)	0.290
Musculoskeletal manifestations	178 (90.4)	204 (89.1)	0.787
Raynaud's syndrome	47 (24.0)	63 (28.1)	0.396
Lymphadenopathy	119 (60.4)	98 (43.2)	< 0.001
Nephritis	110 (55.8)	82 (35.8)	< 0.001
Cardiac manifestations	157 (80.1)	77 (33.9)	< 0.001
Pericarditis	84 (42.6)	28 (12.5)	< 0.001
Neuropsychiatric manifestations	52 (26.1)	64 (28.1)	0.734
Antiphospholipid syndrome	14 (7.4)	25 (11.9)	0.181
Fever	73 (38.6)	54 (24.2)	0.002
Weight loss	40 (23.5)	28 (13.2)	0.014
Laboratory data			
Anemia, n (%)	44 (66.7)	43 (32.8)	< 0.001
Leukopenia, n (%)	32 (50.8)	69 (51.9)	0.992
Thrombocytopenia, n (%)	25 (37.9)	26 (19.8)	0.013
Hypocomplementemia, n (%)	7 (41.2)	23 (59.0)	0.351
ESR, mm/hr	25 (12—48)	19 (10—35)	0.008
CRP, mg/L	12 (0—48)	5 (0—12)	0.026
hs-CRP, mg/L	29 (7—34)	6 (2—11)	< 0.001
IL-6, pg/ml	14.5 (2.9—38.1)	2.9 (2.3—6.1)	0.010
IL-10, pg/ml	8.9 (3.0—35.0)	9.3 (3.1—27.7)	0.995
Procalcitonin, ng/mL	0.22 (0.17—0.32)	0.21 (0.15—0.28)	0.744
Presepsin, pg/mL	134 (95—170)	138 (92—202)	0.785
Autoantibody positivity			
Anti-dsDNA, n (%)	72 (55.8)	142 (66.0)	0.078
Anti-Sm, n (%)	13 (27.1)	19 (19.0)	0.375
Anti-Ro/SSA, n (%)	31 (62.0)	50 (50.5)	0.248
Anti-La/SSB, n (%)	13 (32.5)	12 (14.6)	0.049
Anti-RNP, n (%)	13 (43.3)	30 (40.0)	0.928
APLA, n (%)	26 (81.3)	27 (50.9)	0.009
Anti-chromatin, n (%)	14 (87.5)	30 (49.2)	0.009
Medications			
Glucocorticoids, n (%)	137 (68.5)	158 (67.2)	0.857
Oral glucocorticoid dose, mg/d	12.5 (10—22.5)	10 (7.5—15)	0.025
Hydroxychloroquine, n (%)	112 (56.0)	147 (62.6)	0.198
Cyclophosphamide, n (%)	10 (7.5)	9 (5.0)	0.516
Mycophenolate mofetil, n (%)	2 (1.5)	5 (2.8)	0.697
Azathioprine, n (%)	4 (3.0)	13 (7.3)	0.145
Methotrexate, n (%)	5 (3.7)	14 (7.8)	0.195

Note. Values are expressed as a median (QI-QIII), mean (± standard deviations), or n (%). The percentage for each variable was calculated for only those patients in which the data were documented.
Abbreviations. SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; anti-dsDNA: anti-double-stranded DNA antibodies; anti-Sm: anti-Smith antibodies; anti-RNP: anti-ribonucleoprotein antibodies; APLA: antiphospholipid antibodies.

Table 2. **Logistic regression analysis of variables independently associated with the development of pleuropulmonary manifestations**

Variables	Univariate analysis			Multivariate analysis		
	Coefficient	Odds ratio (95 % CI)	p	Coefficient	Odds ratio (95 % CI)	p
Male sex	0.7 ± 0.3	2.01 (1.12—3.61)	0.019			
Age	0.02 ± 0.01	1.02 (1.01—1.03)	0.006	0.03 ± 0.01	1.03 (1.01—1.05)	0.004
Age at onset	0.02 ± 0.01	1.02 (1.01—1.03)	0.035			
Disease duration	0.002 ± 0.001	1.0 (1.0—1.0)	0.051			
SLEDAI-2K score	0.07 ± 0.01	1.07 (1.04—1.10)	< 0.001	0.04 ± 0.02	1.05 (1.01—1.09)	0.030
SLICC/ACR DI score	0.63 ± 0.10	1.88 (1.54—2.29)	< 0.001	0.29 ± 0.13	1.34 (1.03—1.74)	0.027
Skin rash	−0.58 ± 0.21	0.56 (0.37—0.85)	0.006	-1.31 ± 0.31	0.27 (0.15—0.50)	< 0,001
Lymphadenopathy	0.70 ± 0.20	2.01 (1.36—2.96)	< 0.001	0.82 ± 0.27	2.27 (1.33—3.88)	0.003
Nephritis	0.82 ± 0.20	2.27 (1.53—3.35)	< 0.001			
Cardiac manifestations	2.06 ± 0.23	7.84 (5.02—12.2)	< 0.001	2.31 ± 0.29	10.1 (5.65—17.9)	< 0.001
Pericarditis	1.65 ± 0.25	5.20 (3.20—8.46)	< 0.001	1.48 ± 0.33	4.40 (2.29—8.46)	< 0.001
Systemic manifestations	0.60 ± 0.21	1.77 (1.18—2.66)	0.006	0.76 ± 0.28	2.14 (1.24—3.70)	0.007
Anemia	1.41 ± 0.32	4.09 (2.18—7.67)	< 0.001			
Thrombocytopenia	0.90 ± 0.34	2.46 (1.28—4.75)	0.007			
Glucocorticoid dose	0.03 ± 0.02	1.03 (0.99—1.07)	0.081			
ESR	0.01 ± 0.005	1.01 (1.01—1.02)	0.007			
CRP	0.01 ± 0.004	1.01 (1.01—1.02)	< 0.001			
hs-CRP	0.07 ± 0.02	1.08 (1.03—1.12)	< 0.001			
IL-6	0.06 ± 0.02	1.06 (1.01—1.11)	0.010			
Anti-La/SSB	1.03 ± 0.46	2.81 (1.14—6.92)	0.025			
Anti-chromatin	2.05 ± 0.80	7.75 (1.63—36.8)	0.010			
APLA	1.43 ± 0.53	4.17 (1.48—11.8)	0.007			

Abbreviations. SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index-2000; SLICC/ACR DI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; APLA: antiphospholipid antibodies.

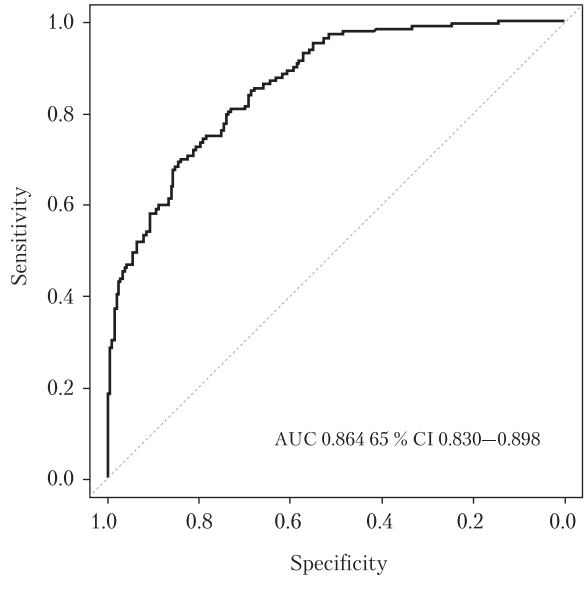

Figure. **ROC-curve for the multivariate logistic analysis of risk factors for pleuropulmonary involvement in patients with SLE**

Variables included in the model: age, SLEDAI-2K score, SLICC/ACR DI, skin manifestations, lymphadenopathy, pericarditis, cardiac manifestations (excluding pericarditis), systemic manifestations (fever, weight loss).

In agreement with previous reports [2, 13, 20, 21, 27], our SLE patients with active disease, higher SLICC/ACR DI scores, and the previous or concomitant presence of lupus nephritis, cardiac disease, hematological manifestations, lymphadenopathy, and systemic symptoms had significantly higher occurrence of pleuropulmonary manifestations. This data suggests that the development of respiratory complications occurs in patients with severe disease and accumulated damage. Conversely, cutaneous manifestations were negatively associated with pleuropulmonary involvement, consistent with previous studies [8, 13, 19].

In line with previously published data [10, 15, 24], our study corroborates that pleuropulmonary manifestations are associated with increased levels of inflammatory markers (ESR, CRP, hs-CRP) and proinflammatory cytokines (IL-6). We found an association of respiratory involvement in SLE with the presence of anti-La/SSB, APLA, and anti-chromatin antibodies, which is supported by previous investigations [3, 13]. As previously reported [27], the occurence of respiratory involvement did

not correlate with lupus-specific serologic markers, such as anti-dsDNA antibodies and complement components C3/C4. Some other authors have documented a relationship between anti-RNP [8, 9], anti-Ro/SSA [16, 27] and anti-Sm [20] antibodies with pleuropulmonary manifestations but we could not corroborate these associations.

In our study, SLE patients with pleuropulmonary involvement received higher doses of glucocorticoids compared to non-respiratory SLE. This finding aligns with the GLADEL cohort study shoing more frequent use of glucocorticoids in patients with pleuropulmonary manifestations [13].

Our study has some limitations. First, in most patients the baseline variables were collected many years into the disease course rather than at onset. Second, pleuropulmonary manifestations were not systematically evaluated but diagnosed based on suggestive clinical manifestations, potentially underestimating the frequency of some manifestations. Third, not all autoantibodies were available in all patients at the time pleuropulmonary manifestations occurred. Fourth, data on smoking habits were not collected, so the possible role of tobacco use in the occurrence of these manifestations could not be examined.

Conclusions

1. Pleuropulmonary manifestations are frequent in SLE, particularly pleuritis.

2. Respiratory involvement is associated with male sex, older age, longer disease duration, and occurs mainly in patients with active and severe lupus (with previous or concomitant nephritis, lymphadenopathy, pericarditis and other cardiac manifestations, fever, weight loss, anemia, thrombocytopenia).

3. Patients with pleuropulmonary involvement have higher levels of inflammatory markers (ESR, CRP, hs-CRP, IL-6) and higher frequency of positive anti-La/SSB, APLA and anti-chromatin antibodies.

No conflict of interests.
Authors participation: conceivement of study conception, acquisition of clinical data, manuscript final editing — O.B. Iaremenko; acquisition of clinical samples and data, analysis and interpretation of data, writing the manuscript — D.I. Koliadenko; laboratory measurement — K.M. Iaremenko; conceivement of study design, writing the manuscript — N.D. Kozak; statistical processing of data — O.V. Dema.

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О.Б. Яременко[1], Д.І. Коляденко[1], К.М. Яременко[2], Н.Д. Козак[1], О.В. Дема[1]

[1] Національний медичний університет імені О.О. Богомольця, Київ
[2] Олександрівська клінічна лікарня, Київ

Плевропульмональні ураження у хворих на системний червоний вовчак

Мета роботи — вивчити поширеність неінфекційних плевропульмональних уражень у хворих на системний червоний вовчак (СЧВ), демографічні, клінічні та лабораторні характеристики таких хворих.

Матеріали та методи. У крос-секційному дослідженні взяли участь 435 хворих на СЧВ (87,5 % жінок, середній вік — 37 (26—49) років), із них 200 із плевропульмональними виявами і 235 без них. Проаналізовано демографічні дані, клінічні вияви СЧВ, індекси активності захворювання (SLEDAI-2K) і пошкодження (SLICC/ACR DI). Лабораторні дослідження передбачали загальний аналіз крові з визначенням швидкості осідання еритроцитів (ШОЕ), вмісту С-реактивного білка (С-РБ), високочутливого С-РБ (вч-С-РБ), інтерлейкіну-6 (ІЛ-6), ІЛ-10, комплементу С3 і С4, специфічних автоантитіл. Для заперечення інфекцій визначали сироваткові рівні прокальцитоніну та пресепсину.

Результати та обговорення. Щонайменше один плевропульмональний вияв зареєстровано в 46 % пацієнтів із СЧВ, найчастіше — плеврит (24 %). Ураження дихальної системи асоціювалося з чоловічою статтю, більшою тривалістю захворювання та старшим віком на момент дебюту СЧВ. Пацієнти з респіраторними виявами мали вищі значення індексів SLEDAI-2K та SLICC/ACR DI, ніж пацієнти без плевропульмональних уражень. У пацієнтів із плевропульмональними виявами частіше фіксували лімфаденопатію, нефрит, перикардит, інші кардіальні вияви, лихоманку, втрату маси тіла, анемію та тромбоцитопенію, а шкірні вияви виникали рідше. У пацієнтів з ураженням органів дихання зареєстровано вищі рівні ШОЕ, С-РБ, вч-С-РБ та ІЛ-6, частіше виявляли антитіла до La/SSB, хроматину, антифосфоліпідні антитіла.

При проведенні багатофакторного аналізу виявлено, що ураження органів дихання прямо пропорційно корелювало зі старшим віком (відношення шансів (ВШ) — 1,03 (95 % довірчий інтервал (ДІ) — 1,01—1,05); p = 0,004), вищими значеннями індексів SLEDAI-2K (ВШ — 1,05 (95 % ДІ — 1,01—1,09); p = 0,030) та SLICC/ACR DI (ВШ — 11,34 (95 % ДІ — 1,03—1,74); p = 0,027), наявністю лімфаденопатії (ВШ —2,27 (95 % ДІ — 1,33—3,88); p = 0,003), перикардиту (ВШ — 4,40 (95 % ДІ — 2,29—8,46); p < 0,001), інших кардіальних виявів (ВШ — 10,1 (95 % ДІ — 5,65—17,9); p < 0,001) та конституційних симптомів (ВШ — 2,14 (95 % ДІ — 1,24—3,70); p = 0,007). Шкірні вияви були пов'язані зі зниженням ризику виникнення плевропульмональних симптомів (ВШ — 0,27 (95 % ДІ — 0,15—0,50); p < 0,001).

Висновки. Плевропульмональні ураження є частим виявом СЧВ, особливо плеврит. Ураження дихальної системи асоціюється з чоловічою статтю, старшим віком, більшою тривалістю захворювання та виникає переважно у хворих з активним і тяжким перебігом СЧВ. Пацієнти з плевропульмональним ураженням мають вищі рівні маркерів запалення та більшу частоту виявлення антитіл до La/SSB, хроматину, антифосфоліпідних антитіл.

Ключові слова: системний червоний вовчак, плевропульмональне ураження, плеврит, пневмоніт, фактор ризику, біомаркери, автоантитіла, інтерлейкіни.

Контактна інформація */ Corresponding author*

Яременко Олег Борисович, д. мед. н., проф., зав. кафедри внутрішньої медицини № 3
https://orcid.org/0000-0003-2095-5819
01601, м. Київ, бульв. Т. Шевченка, 13
E-mail: o.b.iaremenko@gmail.com

Стаття надійшла до редакції/Received 14.06.2024.
Стаття рекомендована до опублікування/Accepted 19.07.2024.

ДЛЯ ЦИТУВАННЯ

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