DOI: https://doi.org/10.17816/mechnikov63358

Profile of immunological markers in skin biopsies from patients with probable and confirmed systemic lupus erythematosus

© Viktoria A. Lila, Vadim I. Mazurov

North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

The purpose of this study was to determine the profile of immunoreactants deposited in intact skin biopsies from the patients with confirmed and probable systemic lupus erythematosus. The study involved 94 patients who, along with a standard clinical and laboratory examination, underwent a biopsy of clinically healthy skin in the deltoid muscle area (lupus band test). The nature and combination of immune deposits in the skin, the strength of immunofluorescence, and the location were evaluated. In the patients with significant systemic lupus erythematosus (n = 56), lupus band test was positive in 60.7 % of the cases and correlated with disease activity according to SLEDAI 2K (p = 0.001). At the same time, the skin biopsy often revealed the immunoreactant IgM (85.3 %), the degree of fluorescence of which had direct correlations with the increased level of antibodies to dsDNA ($p < 0.05$). In the examined patients with probable systemic lupus erythematosus, positive lupus band test was detected in 47 % of cases, and IgM was detected in 72.2% of patients, which brought them closer to the group of patients with confirmed systemic lupus erythematosus. However, 33.3% of patients with probable systemic lupus erythematosus had isolated deposits of any one immunoreactant, while the association of immunoreactants (IgM+IgG) and (IgM+IgG+C3) characteristic of confirmed systemic lupus erythematosus occurred in only 27.7 and 5.5% of cases, respectively. It should be noted that the C1q immunoreactant was detected in the skin biopsies with both confirmed (38.2%) and probable systemic lupus erythematosus (39%). The data obtained suggest that lupus band test with the presence of a specific pattern of immunoreactants can be used as an additional diagnostic test for the diagnosis of systemic lupus erythematosus.

Keywords: systemic lupus erythematosus; probable systemic lupus erythematosus; lupus band test; direct immunofluorescence.

To cite this article:
Lila VA, Mazurov VI. Profile of immunological markers in skin biopsies from patients with probable and confirmed systemic lupus erythematosus. *Herald of North-Western State Medical University named after I.I. Mechnikov*. 2021;13(1):39–48. DOI: https://doi.org/10.17816/mechnikov63358

Received: 22.02.2021 **Accepted:** 15.03.2021 **Published:** 31.03.2021

DOI: https://doi.org/10.17816/mechnikov63358

Профиль иммунологических маркеров в биоптатах кожи у пациентов с вероятной и достоверной системной красной волчанкой

© В.А. Лила, В.И. Мазуров

Северо-Западный государственный медицинский университет имени И.И. Мечникова, Санкт-Петербург, Россия

Целью исследования явилось изучение профиля иммунореактантов в неповрежденной коже у пациентов с вероятной и достоверной системной красной волчанкой. В исследовании приняли участие 94 пациента, которым наряду со стандартным клинико-лабораторным обследованием выполняли биопсию кожи в области дельтовидной мышцы (тест волчаночной полосы). В группе пациентов с достоверной системной красной волчанкой (n = 56) тест волчаночной полосы был положительным в 60,7 % случаев и коррелировал с активностью заболевания по данным SLEDAI-2K (p = 0,001). При этом в биоптате кожи у них часто выявляли иммунореактант IgM (85,3 %), степень флюоресценции которого прямо коррелировала с повышенным уровнем антител к двухспиральной ДНК (p < 0,05). У обследованных с вероятной системной красной волчанкой положительный тест волчаночной полосы зарегистрирован в 47 % случаев, а IgM — у 72,2 % пациентов, что сближало их с группой больных достоверной системной красной волчанкой. Однако у 33,3 % пациентов с вероятной системной красной волчанкой встречались изолированные отложения какого-либо одного иммунореактанта, в то время как характерная для достоверной системной красной волчанки ассоциация иммунореактантов (IgM + IgG) и (IgM + IgG + C3) встречалась всего лишь в 27,7 и 5,5 % случаев соответственно. Следует отметить, что иммунореактант C1q определялся в биоптатах кожи как при достоверной (38,2 %), так и при вероятной системной красной волчанке (39 %). Полученные данные дают основание полагать, что тест волчаночной полосы с наличием специфического паттерна иммунореактантов может быть использован в качестве дополнительного теста для диагностики системной красной волчанки.

Ключевые слова: системная красная волчанка; вероятная системная красная волчанка; тест волчаночной полоски; прямая иммунофлюоресценция.

Как цитировать:
Лила В.А., Мазуров В.И. Профиль иммунологических маркеров в биоптатах кожи у пациентов с вероятной и достоверной системной красной волчанкой // Вестник Северо-Западного государственного медицинского университета им. И.И. Мечникова. 2021. Т. 13. № 1. С. 39–48. DOI: https://doi.org/10.17816/mechnikov63358

Рукопись получена: 22.02.2021 **Рукопись одобрена:** 15.03.2021 **Опубликована:** 31.03.2021

ЭКО • ВЕКТОР

INTRODUCTION

The detection of immunoreactants, including IgA, IgM, IgG, C3, and C1q, by direct immunofluorescence in skin biopsy specimens from patients with systemic lupus erythematosus (SLE), is known as the lupus band test (LBT) [1–3]. The test was originally used to differentiate skin lesions in SLE and discoid lupus erythematosus. As a rule, immunoreactants were not found in a biopsy specimen of an unaffected skin area in patients with discoid SLE [4, 5]. However, further studies revealed a high incidence of immunoreactants (50%–77%) in biopsies of unaffected skin in patients with SLE [6–8]. In addition, the authors established certain correlations between immunoreactants in the LBT and SLE activity and ongoing therapy [6, 8–11].

LBT assessment in patients with probable SLE when patients have specific immunological markers and some clinical symptoms similar to SLE, but they do not fully meet the classification criteria of the American Rheumatism Association or Systemic Lupus International Collaborating Clinics (SLICC 2012) is of particular interest [8, 12–14]. Probable SLE may develop over time into definitive SLE or other connective tissue diseases, such as Sjogren disease and rheumatoid arthritis. However, in some cases, it can remain at the immunological disorder stage for a long time and not transform into certain nosological forms [12, 14–16].

In the literature, only a few data are presented on LBT values of probable SLE. Determining an immunoreactant profile by assessing the nature, quantity, degree of immunofluorescence, and site of their detection in the skin biopsy are of both scientific and practical interest.

MATERIALS AND METHODS

This study included 94 patients with an elevated antinuclear factor titer. Of these, 56 patients were diagnosed with significant SLE since they had at least four SLICC 2012 classification criteria. The group with probable SLE included 38 patients who had less than four SLICC 2012 criteria.

The study did not include patients with SLE under 18 years, pregnant and breastfeeding women, and persons with severe concomitant pathology of the cardiovascular system, gastrointestinal tract, liver, kidneys, and malignant neoplasms. The study was approved by the local committee of the North–Western State Medical University named after I.I. Mechnikov.

At the next stage of the study, patients with significant SLE were divided into two subgroups. The first subgroup consisted of 25 patients with advanced SLE who received glucocorticoid and disease-modifying anti-rheumatic drugs, and the second subgroup included 31 patients with newly diagnosed (early) SLE.

All patients underwent clinical, laboratory, and instrumental examinations using routine diagnostic methods. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index modified 2K (SLEDAI–2K). Antibodies against double–stranded DNA were determined by enzyme immunoassay (reference values–0–25 U/ml). Along with this, a biopsy of intact skin in the outer surface area of the upper third of the shoulder (in the area of the deltoid muscle) was performed. Immunoglobulins IgA, IgM, and IgG, and complement components C3, C1q (LBT) were detected in skin biopsy using immunohistochemical methods in the laboratory of the Scientific and Methodological Center for Molecular Medicine of the First Pavlov Saint-Petersburg State Medical University. If immunoreactants were detected in the biopsy specimen, the LBT was considered positive. LBT was assessed based on the type of IgA/IgM/IgG/C1q–/C3–complement components deposits, the intensity of their luminescence (+ to +++), the nature of the luminescence (fine–granular, granular, linear), the site of immunoreactant deposition (small vessels of the dermis; papillary layer of the dermis; basement membrane zone–dermoepidermal junction).

Statistical processing of the results was performed using the statistical data analysis package Statistica 10.0 for Windows (Statsoft Inc., USA), including parametric and nonparametric analysis methods. Differences were considered statistically significant at $p < 0.05$.

STUDY RESULTS

In subjects with significant SLE (n = 56), 86% were women; their mean age was 37.3 years, and the disease duration was 2.5 years. The disease activity according to the SLEDAI–2K index corresponded on average to 9.2 ± 5.9 points. In addition, an increased level of antibodies against double–stranded DNA (dsDNA) was observed in 25 (73.5%) patients. In the subjects with probable SLE (n = 38), 92.1% were women with a mean disease duration of nine months, and the mean age was 38.1 years. The disease activity was significantly lower than in the group with significant SLE and corresponded to 4.3 ± 2.4 points. Also, increased antibody levels against dsDNA were observed in 10 (26.3%) patients.

The data analysis showed that positive LBT was detected in 34 (60.7%) patients with significant SLE and 18 (47%) patients with probable SLE. Analysis of the study results in the patient subgroups with confirmed SLE showed that LBT was positive in 23 (74%) patients with early SLE. In addition, only 11 (44%) patients had an advanced clinical and laboratory form of the disease (Fig. 1).

Thus, an LBT positive result was significantly more often recorded in the group with early SLE than the group with advanced SLE (p = 0.02) and probable SLE (p = 0.02).

DOI: https://doi.org/10.17816/mechnikov63358

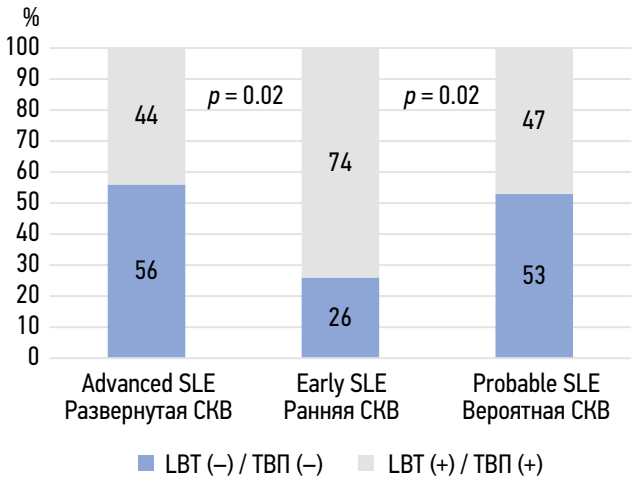

Fig. 1. Lupus band test (LBT) results in the studied patient groups. SLE — systemic lupus erythematosus

Рис. 1. Результаты теста волчаночной полоски (ТВП) у пациентов исследуемых групп. СКВ — системная красная волчанка

The lower detectability of immunoreactants in skin biopsies in patients with advanced SLE may be related to pathogenetic therapy in this group [84% of patients received oral glucocorticoids at low and moderate doses, 36% of subjects received combined pulse therapy with high doses of methylprednisolone and cyclophosphamide, 40% of subjects received cytostatic therapy (methotrexate, azathioprine, or mycophenolate mofetil), 64% of subjects received hydroxychloroquine (Plaquenil), 24% of subjects received non–steroidal anti–inflammatory drugs, and 8% of subjects received the genetically engineered biological drug rituximab].

The frequency, nature, and various combinations of specific immunoreactants detected in all groups are shown in Table 1. More than one immunoreactant (IgA, IgM, IgG, C3, C1q) was found in all groups, including 66.7% of cases with probable SLE. The most common immunoreactant was IgM, and various combinations (IgM + IgG) were recorded significantly more often in the group of significant (61.8%). Advanced SLE (72.7%) compared with probable SLE (27.7%) ($p = 0.02$ and $p = 0.018$, respectively). When comparing the groups of patients with early and probable SLE, no significant differences were obtained ($p = 0.066$). The combination of three immunoreactants (IgG + IgM + C3) was detected significantly more often in the groups of examined patients with significant, extensive, and early SLE compared with probable SLE, where such a combination was found in only 5.5% of cases ($p = 0.03$, $p = 0.03$, and $p = 0.046$, respectively). In the study of other combinations of immunoreactants in the compared groups, no significant differences were established.

Although positive LBT was more often recorded in patients with early SLE compared with advanced SLE (74% and 44%, respectively, $p = 0.02$) when assessing the nature and incidence of specific immunoreactants in the skin biopsy, the data of these two groups were comparable. In early SLE, IgG and IgM were determined more often (60.9% and 82.6%, respectively), and in probable SLE–IgM (72.2% of cases).

The data obtained served as the basis for studying the peculiarities of immunoreactant distribution in biopsy of unaffected skin in patients of the compared groups considering the localization, intensity, and nature of their distribution (Table 2). In advanced SLE, immunoreactants IgG

Table 1. The profile of immunoreactants deposited in the skin biopsy materials of patients with LBT (+)

Таблица 1. Профиль выявляемых иммунореактантов в кожных биоптатах у обследованных пациентов с положительным тестом волчаночной полосы

Immunohistochemical data	Systemic lupus erythematosus			
	expanded ($n = 11$)	early ($n = 23$)	significant ($n = 34$)	probable ($n = 18$)
IgG	8 (72.7)	14 (60.9)	22 (64.7)	8 (44.4)
IgM	10 (90.9)	19 (82.6)	29 (85.3)	13 (72.2)
IgA	3 (27.3)	3 (13)	6 (17.6)	7 (39)
C3	7 (63.6)	13 (56.5)	20 (58.8)	8 (44.4)
C1q	4 (36.4)	9 (39.1)	13 (38.2)	7 (39)
		One immunoreactant		
	1 (9.1)	5 (21.7)	6 (17.6)	6 (33.3)
		One immunoreactant		
	10 (90.9)	18 (78.3)	28 (82.4)	12 (66.7)
		Two immunoreactants		
IgG + IgM	8 (72.7)*	13 (56.5)	21 (61.8)*	5 (27.7)*
		Three immunoreactants		
IgG + IgM + C3	4 (36.4)*	7 (30.4)*	11 (32.4)*	1 (5.5)*

* $p < 0.05$.

Table 2. Character, location, and degree of fluorescence immunoreactants in the groups of patients with LBT (+), *n* (%)

Таблица 2. Характер, локализация и интенсивность свечения иммунореактантов в обследованных группах пациентов с положительным тестом волчаночной полосы, *n* (%)

Parameters	Systemic lupus erythematosus		
	expanded (*n* = 11)	early (*n* = 23)	probable (*n* = 18)
IgA, glow:			
weak (1+)	3 (27.3%)	1 (4.3%)	4 (22%)
moderate (2+)	0 (0)	1 (4.3%)	0 (0)
intense (3+)	0 (0)	1 (4.3%)	3 (16.7%)
IgG, glow:			
weak	4 (36.4%)	4 (17.4%)	6 (33.3%)
moderate	3 (27.3%)	9 (39.1%)*	1 (5.6%)*
intense	1 (9.1%)	1 (4.3%)	1 (5.6%)
IgM, glow:			
weak	3 (27.3%)	3 (13%)	6 (33.3%)
moderate	3 (27.3%)	14 (61%)*	3 (16.7%)*
intense	4 (36.4%)	2 (8.7%)	3 (16.7%)
C3 component of complement, glow:			
weak	3 (27.3%)	6 (26%)	5 (27.8%)
moderate	3 (27.3%)	7 (30.4%)	2 (11.1%)
intense	1 (9.1%)	0 (0)	1 (5.6%)
C1q component of complement, glow:			
weak	3 (27.3%)	7 (30.4%)	4 (22.2%)
moderate	1 (9.1%)	2 (8.7%)	3 (16.7%)
intense	0 (0)	0 (0)	0 (0)
The nature of the deposits:			
fine–grained	6 (54.5%)	17 (74%)	9 (50%)
granular	5 (45.5%)	6 (26%)	7 (39%)
linear	0 (0)	0 (0)	2 (11.1%)
Localization of immunoreactants:			
in small vessels of the dermis	2 (18.2%)	7 (30.4%)	5 (27.8%)
in the papillary layer of the dermis	1 (9.1%)	2 (8.7%)	1 (5.6%)
along the basement membrane of the epidermis	8 (73%)	14 (61%)	12 (66.7%)

* $p < 0.05$.

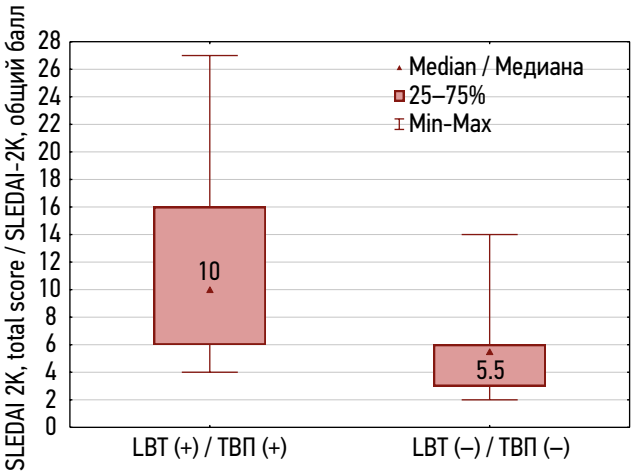

Fig. 2. SLEDAI 2K (Me [25%; 75%]) groups of LBT (+) and LBT (–) of the patients with systemic lupus erythematosus (*n* = 56)

Рис. 2. Активность системной красной волчанки по данным SLEDAI-2K (Me [25 %; 75 %]) в группах с положительным [ТВП (+)] и отрицательным [ТВП (–)] тестом волчаночной полосы у пациентов с достоверной системной красной волчанкой (*n* = 56)

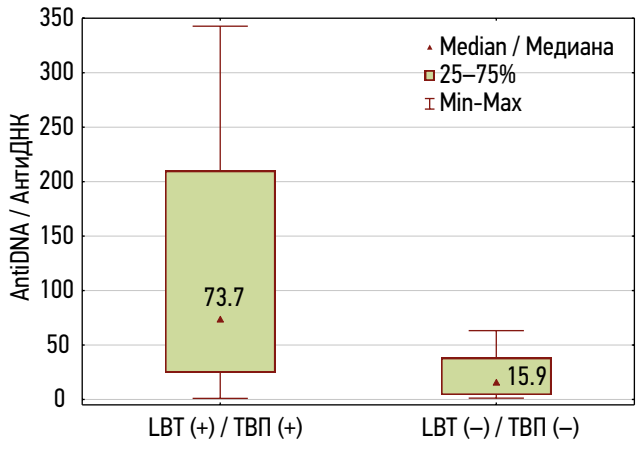

Fig. 3. Level of antiDNA (Me [25%; 75%]) in the groups of LBT (+) and LBT (–) of the patients with systemic lupus erythematosus (*n* = 56)

Рис. 3. Титр антител к дсДНК (Me [25 %; 75 %]) у пациентов с достоверной системной красной волчанкой (*n* = 56) в группах с положительным [ТВП (+)] и отрицательным [ТВП (–)] тестом волчаночной полосы

Table 3. The correlation between different combinations of immunoreactants and increased antiDNA in patients with systemic lupus erythematosus (n = 56)

Таблица 3. Корреляционные связи между различными сочетаниями иммунореактантов и повышением титра антиДНК у пациентов с достоверной системной красной волчанкой (n = 56)

Parameter	Lupus band test result, n (%)								
	LBT (–)	IgM + IgA	IgM + C3	IgM + C1q	IgM + IgG	IgM + IgG + C3	IgM	C1q	IgM + C3 + C1q
	n = 22	n = 6	n = 17	n = 10	n = 21	n = 11	n = 29	n = 13	n = 7
AntiDNA >25 U/ml	7 (31.8)	4 (66.7)	14 (82.4)*	9 (90)*	14 (66.7)*	8 (72.7)*	22 (75.9)*	11 (84.6)*	6 (85.7)*

Note. LBT (–) – negative lupus strip test. * p < 0.05 compared with the LBT group (–).

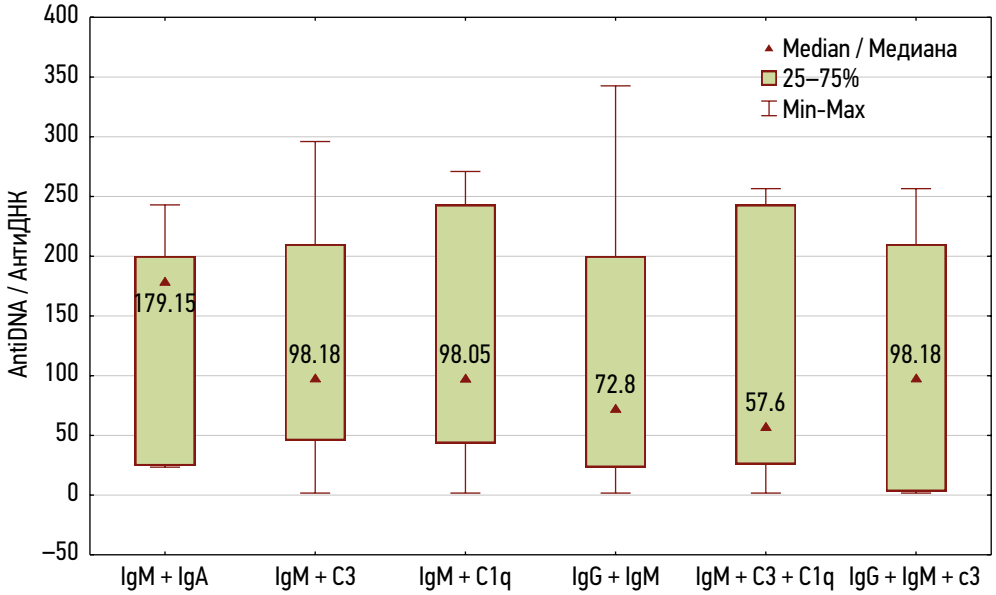

Fig. 4. The level of antiDNA (Me [25%; 75%]) depending on different associations of immunoreactants in the skin biopsy materials of the patients with systemic lupus erythematosus (n = 56)

Рис. 4. Уровень антител к дсДНК (Me [25 %; 75 %]) в зависимости от различных ассоциаций иммунореактантов в биоптате кожи у пациентов с достоверной системной красной волчанкой (n = 56)

Table 4. Relationship between the degree of IgM immunofluorescence and the increase in antiDNA of patients with systemic lupus erythematosus (n = 56)

Таблица 4. Взаимосвязь между степенью иммунофлюоресценции IgM и повышением антител к двухспиральной ДНК у пациентов с достоверной системной красной волчанкой (n = 56)

Parameter	Immunofluorescence IgM, n (%)			
	LBT (–) n = 22	1+ (weak) n = 6	2+ (moderate) n = 17	3+ (intense) n = 6
AntiDNA >25 U/ml	7 (31.8)	4 (66.7)	13 (76.5)*	5 (83.3)*

Note. LBT (–) – negative lupus strip test. * p < 0.05 compared with the LBT group (–).

(72.7%), IgM (90.9%), and C3 (63.6%) with varying degrees of luminescence intensity were mainly found. In contrast, in patients with early SLE luminescence of IgG (p = 0.01) and IgM (p = 0.004) of moderate intensity was detected significantly more often than in subjects with probable SLE. Also, deposits of immunoreactants were detected in small vessels of the dermis that may indirectly indicate the presence of immunocomplex vasculitis.

In the LBT results analysis, depending on the activity of SLE and the level of antibodies against dsDNA, a relationship between positive LBT, the activity of SLEDAI–2K disease, and the antibody titer to dsDNA were established. Thus, SLE activity in patients with LBT (+) was 10 points, and in patients with LBT (–), it was 5 points (p = 0.001) (Fig. 2). At the same time, the titer of antibodies to dsDNA in patients with SLE who had LBT (+) amounted to 73.7 [24.7; 210] U/ml, and with LBT (–)—only 15.9 [4.1; 38.2] U/ml (p = 0.001) (Fig. 3).

The most common immunoreactant in patients with significant SLE was IgM (29%–85.3%), whereas an increase in the level of antibodies against dsDNA was

noted in 25 (73.5%) patients. In the presence of IgM and its various combinations with other immunoglobulin classes and complement components, an increase in the titer of antibodies against dsDNA was significantly more often detected ($p < 0.05$) (Table 3). At the same time, a higher level of dsDNA was found in patients with IgM + IgA association (the median of antibodies against dsDNA was 179.15 U/ml) (Fig. 4). Along with this, a relationship between an increase in the level of antibodies to dsDNA and a moderate ($p < 0.05$) or high ($p < 0.05$) degree of IgM immunofluorescence was established (Table 4).

DISCUSSION

This study revealed a high incidence of immunoreactants (60.7%) in patients with SLE, confirmed by data from several authors. For example, Zecevic (2001) found immunoreactants in 23 (60.5%) of 38 patients with SLE [7], and Gangaram et al. (2004)–in 63% of patients with SLE on unaffected photo-exposed areas of the skin [6]. In patients with advanced SLE, the frequency of a positive test was lower and amounted to 44%, which could be explained by the effect of combined therapy on the studied immunoreactant expression. However, the possibility of the therapy effect on LBT parameters is still under discussion. Thus, according to Davis and Gilliam (1984), the initial LBT (+) or LBT (–) more often remained unchanged at repeated skin biopsy in patients with SLE during treatment with prednisolone (daily dose–40 mg) or cytostatic drugs [9]. According to other authors, there was a direct relationship between immunoreactant levels and SLE activity [10, 17]. Moreover, Provost et al. (1980) showed that immunoreactants might disappear, or their number may decrease. The intensity of their fluorescence may decrease with a decrease in SLE activity or achievement of remission [18].

In our study, a relationship between positive LBT and disease activity was established according to SLEDAI–2K data ($p = 0.001$) as well as an increased titer of antibodies against dsDNA ($p = 0.001$) compared with LBT (–). Furthermore, in the study performed by Gangaram and Kong (2004), a significant correlation was also noted between LBT (+) in the skin and antibodies against dsDNA ($p = 0.02$). However, the authors did not observe the relationship between LBT, disease activity, and the presence of kidney damage and skin lesions. This served as the basis for the assertion that LBT can be used to diagnose SLE but cannot assess disease activity [6].

The most frequently detected immunoreactant in patients with SLE with LBT is IgM (approximately 90% of cases), IgA is much less common [19, 20]. Our study also confirms these data since IgM in skin biopsies of patients with significant SLE was determined in 85.3% of cases, and IgA–only in 17.6%. Such a high detection rate of IgM can be associated with its larger size compared with other proteins. Therefore, it can remain in the dermoepidermal junction for a longer time than other immunoreactant representatives [5, 18]. The deposition of immunoglobulins and complement components in the skin of patients with SLE is a dynamic process. It can vary depending on various factors (environment, stress, infections, drugs, others) [5, 18].

Previously, most researchers noted that with a higher activity of SLE and in the presence of renal damage and high titers of antibodies against dsDNA, IgG was more often detected in skin biopsies. In contrast, IgM deposits were associated with a more favorable disease course without kidney damage [11, 18]. Detection of weak immunofluorescence of monoimmunoreactant IgM in skin biopsy is less specific for SLE, and weak intermittent immunofluorescence of IgM and C1q deposits in the dermoepidermal junction can be detected, including in healthy individuals, in almost 20% of cases [21, 22]. In contrast, Permin et al. (1979) showed that in skin biopsies of 500 patients with SLE and other diseases, LBT was positive in $^3/_4$ of patients with SLE, and the deposition of the C1q component of complement was observed mainly in SLE and never in patients with diabetes mellitus, allergic diseases. SLE-like drug-induced syndrome indicates the specificity of the C1q immunoreactant for SLE [23]. In a study performed by Leibowitch et al. (1981), C1q deposits were found in 90% of patients with SLE and only 29% of patients with discoid lupus erythematosus. This finding led the authors to conclude that C1q deposits in the skin may be a valuable SLE marker [24].

In the study performed by Minz et al. (2010) in SLE, the immunoreactant IgM was most often detected (85%), its combination with IgG was noted in 77% of cases, and IgM in combination with IgG and C3 was observed in 46% of patients [25]. On the other hand, Luo (2013) reported that in patients with SLE, IgM was detected in a skin biopsy in 86% of cases, and a combination of IgM with C3 was found in 28% of patients. At the same time, the presence of several immunoreactants simultaneously correlated with disease activity, whereas the detection of only one immunoreactant was not very informative for predicting SLE activity [11].

In our study, isolated immunoglobulins G and M in skin biopsies from patients with a confirmed diagnosis of SLE practically did not occur; IgG was combined with other classes of immunoglobulins and complement components. At the same time, the combination of IgG + IgM was detected in 61.8% of patients with a significant SLE diagnosis, and the combination of IgG + IgM + C3 was recorded in 31.4%. The incidence of C1q was 38.2%.

The assessment of LBT in patients with probable SLE is of particular interest. Several studies are presented in the literature. According to Ullman (1975), although patients had antinuclear antibodies in serum and symptoms similar

to SLE, they were not enough to confirm the diagnosis. However, immunoreactants in biopsies of unaffected skin were found in 1/3 of patients [26]. Akarsu et al. (2017) studied LBT in patients with borderline SLE (the presence of antinuclear antibodies and mucocutaneous manifestations) and SLE with discoid lesions. They found a similarity to SLE in deposits in skin biopsies of IgM and IgG. However, they were less likely to have deposits of multiple conjugates than SLE [27]. According to Goldstein et al. (1985), when examining 33 patients with undifferentiated connective tissue disease (including probable SLE), the LBT results did not differ significantly. However, 18% of patients from this group subsequently developed significant SLE, and 6% had rheumatoid arthritis [28]. The results of a prospective study performed by Leibowitch et al. (1981) showed that of 42 patients with discoid SLE, four (9.5%) patients who had C1q in the skin biopsy transformed into SLE. The authors suggested that the presence of C1q in the skin biopsy may be directly related to the risk of developing systemic autoimmune diseases [24].

In our study, the immunoreactant detection rate in biopsy of unaffected skin in patients with probable SLE was 47%. The most frequently detected immunoreactant was IgM (72.2%). However, in 16.6% of cases, it was found in isolation, its combination with IgG was observed in five (27.7%) patients, and the combination of IgM + IgG + C3 was observed in only one (5.5%) patient. Immunoreactants M and G in this group of subjects were characterized by weak immunofluorescence. In seven (39%) patients with probable SLE, C1q was detected in skin biopsies. How many of them will transfer to the group with significant SLE can be answered during follow-up.

CONCLUSION

The analysis of LBT results in patients with probable SLE showed some similarity with significant SLE (positive LBT in 47% of cases, IgM detection in 72.2% of patients). However, in 33.3% of patients with probable SLE, an isolated deposition of a single immunoreactant was found in the skin biopsy, whereas SLE is characterized by a combination of several immunoreactants (IgM + IgG; IgM + IgG + C3).

Thus, considering the detected immunoreactants, their associations, the degree of immunofluorescence, and the site of deposition in the skin biopsy, LBT can be deemed an additional test for verifying the diagnosis of probable and significant SLE.

REFERENCES

1. Reich A, Marcinow K, Bialynicki-Birula R. The lupus band test in systemic lupus erythematosus patients. *Ther Clin Risk Manag.* 2011;7:27–32. DOI: 10.2147/TCRM.S10145

2. Lapin SV, Totolyan AA. Immunologicheskaya laboratornaya diagnostika autoimmunnykh zabolevaniy. Saint Petersburg: Chelovek; 2010. (In Russ.)

3. Lila VA, Mazurov VI, Lapin SV, et al. Current possibilities for early diagnosis of systemic lupus erythematosus. *Modern Rheumatology Journal.* 2018;12(3):34–39. (In Russ.). DOI: 10.14412/1996-7012-2018-3-34-39

4. George R, Kurian S, Jacob M, Thomas K. Diagnostic evaluation of the lupus band test in discoid and systemic lupus erythematosus. *Int J Dermatol.* 1995;34(3):170–173. DOI: 10.1111/j.1365-4362.1995.tb01560.x

5. Makhneva NV. Cellular and humoral components of the immune system of the skin. *Russian Journal of Skin and Venereal Diseases*. 2016;19(1):12–17. (In Russ.). DOI: 10.18821/1560-9588-2016-19-1-12-17

6. Gangaram HB, Kong NC, Phang KS, Suraiya H. Lupus band test in systemic lupus erythematosus. *Med J Malaysia.* 2004;59(5):638–648.

7. Zecevic RD. Significance of deposits of immunoglobulins G, A, M and C3 complement component in the basal membrane zone of clinically unchanged skin for the diagnosis and evaluation of systemic lupus erythematosus activity. *Vojnosanit Pregl.* 2001;58(4):369–374. (In Serbian)

8. Lila VA. Clinical and laboratory relationships in patients with different variants of the course of systemic lupus erythematosus. *Modern Rheumatology Journal.* 2020;14(1):26–31. (In Russ.). DOI: 10.14412/1996-7012-2020-1-26-31

9. Davis BM, Gilliam JN. Prognostic significance of subepidermal immune deposits in uninvolved skin of patients with systemic lupus erythematosus: a 10-year longitudinal study. *J Invest Dermatol.* 1984;83(4):242–247. DOI: 10.1111/1523-1747.ep12340246

10. Zecević RD, Pavlović MD, Stefanović D. Lupus band test and disease activity in systemic lupus erythematosus: does it still matter? *Clin Exp Dermatol.* 2006;31(3):358–360. DOI: 10.1111/j.1365-2230.2006.02113.x

11. Luo YJ, Tan GZ, Yu M, et al. Correlation of cutaneous immunoreactants in lesional skin with the serological disorders and disease activity of systemic lupus erythematosus. *PLoS One.* 2013;8(8):e70983. DOI: 10.1371/journal.pone.0070983

12. Al Attia HM. Borderline systemic lupus erythematosus (SLE): a separate entity or a forerunner to SLE? *Int J Dermatol.* 2006;45(4):366–369. DOI: 10.1111/j.1365-4632.2006.02508.x

13. Bourn R, James JA. Preclinical lupus. *Curr Opin Rheumatol.* 2015;27(5):433–439. DOI: 10.1097/BOR.0000000000000199

14. Ananyeva LP. The role of autoantibodies in the early diagnosis of systemic immunoinflammatory rheumatic diseases. *Modern Rheumatology Journal.* 2019;13(1):5–10. (In Russ.). DOI: 10.14412/1996-7012-2019-1-5-10

15. Md Yusof MY, Psarras A, El-Sherbiny YM, et al. Prediction of autoimmune connective tissue disease in an at-risk cohort: prognostic value of a novel two-score system for interferon status. *Ann Rheum Dis.* 2018;77(10):1432–1439. DOI: 10.1136/annrheumdis-2018-213386

16. Mosca M, Tani C, Neri C, et al. Undifferentiated connective tissue diseases (UCTD). *Autoimmun Rev*. 2006;6(1):1–4. DOI: 10.1016/j.autrev.2006.03.004

17. Rothfield N, Marino C. Studies of repeat skin biopsies of nonlesional skin in patients with systemic lupus erythematosus. *Arthritis Rheum.* 1982;25(6):624–630. DOI: 10.1002/art.1780250604

18. Provost TT, Andres G, Maddison PJ, Reichlin M. Lupus band test in untreated SLE patients: correlation of immunoglobulin deposition in the skin of the extensor forearm with clinical renal disease and serological abnormalities. *J Invest Dermatol.* 1980;74(6):407–412. DOI: 10.1111/1523-1747.ep12544532
19. Crowson AN, Magro CM. Cutaneous histopathology of lupus erythematosus. *Diagnostic Histopathology*. 2009;15(4):157–185. DOI: 10.1016/j.mpdhp.2009.02.006
20. Mehta V, Sarda A, Balachandran C. Lupus band test. *Indian J Dermatol Venereol Leprol.* 2010;76(3):298–300. DOI: 10.4103/0378-6323.62983
21. Fabré VC, Lear S, Reichlin M, et al. Twenty percent of biopsy specimens from sun-exposed skin of normal young adults demonstrate positive immunofluorescence. *Arch Dermatol.* 1991;127(7):1006–1011. DOI: 10.1001/archderm.1991.01680060080008
22. Leibold AM, Bennion S, David-Bajar K, Schleve MJ. Occurrence of positive immunofluorescence in the dermo-epidermal junction of sun-exposed skin of normal adults. *J Cutan Pathol.* 1994;21(3):200–206. DOI: 10.1111/j.1600-0560.1994.tb00261.x
23. Permin H, Juhl F, Wiik A. Immunoglobulin deposits in the dermo-epidermal junction zone. Nosographic occurrence in a number of medical diseases. *Acta Med Scand.* 1979;205(4):333–338. DOI: 10.1111/j.0954-6820.1979.tb06058.x
24. Leibowitch M, Droz D, Noël LH, et al. Clq deposits at the dermoepidermal junction: a marker discriminating for discoid and systemic lupus erythematosus. *J Clin Immunol*. 1981;1(2):119–124. DOI: 10.1007/BF00915389
25. Minz RW, Chhabra S, Singh S, et al. Direct immunofluorescence of skin biopsy: perspective of an immunopathologist. *Indian J Dermatol Venereol Leprol.* 2010;76(2):150–157. DOI: 10.4103/0378-6323.60561
26. Ullman S, Halberg P, Wolf-Jürgensen P. Deposits of immunoglobulins and complement C3 in clinically normal skin of patients with lupus erythematosus. *Acta Derm Venereol.* 1975;55(2):109–112.
27. Akarsu S, Ozbagcivan O, Ilknur T, et al. Lupus band test in patients with borderline systemic lupus erythematosus with discoid lesions. *Acta Dermatovenerol Croat.* 2017;25(1):15–21.
28. Goldstein R, Thompson FE, McKendry RJ. Diagnostic and predictive value of the lupus band test in undifferentiated connective tissue disease. A followup study. *J Rheumatol.* 1985;12(6):1093–1096.

СПИСОК ЛИТЕРАТУРЫ

1. Reich A., Marcinow K., Bialynicki-Birula R. The lupus band test in systemic lupus erythematosus patients // Ther. Clin. Risk. Manag. 2011. Vol. 7. P. 27–32. DOI: 10.2147/TCRM.S10145
2. Лапин С.В., Тотолян А.А. Иммунологическая лабораторная диагностика аутоиммунных заболеваний. Санкт-Петербург: Человек, 2010.
3. Лила В.А., Мазуров В.И., Лапин С.В. и др. Современные возможности ранней диагностики системной красной волчанки // Современная ревматология. 2018. Т. 12, № 3. С. 3439. DOI: 10.14412/1996-7012-2018-3-34-39
4. George R., Kurian S., Jacob M., Thomas K. Diagnostic evaluation of the lupus band test in discoid and systemic lupus erythematosus // Int. J. Dermatol. 1995. Vol. 34, No. 3. P. 170–173. DOI: 10.1111/j.1365-4362.1995.tb01560.x
5. Махнева Н.В. Клеточные и гуморальные компоненты иммунной системы кожи // Российский журнал кожных и венерических болезней. 2016. Т. 19, № 1. С. 12–17. DOI: 10.18821/1560-9588-2016-19-1-12-17
6. Gangaram H.B., Kong N.C., Phang K.S., Suraiya H. Lupus band test in systemic lupus erythematosus // Med. J. Malaysia. 2004. Vol. 59, No. 5. P. 638–648.
7. Zecevic RD. Significance of deposits of immunoglobulins G, A, M and C3 complement component in the basal membrane zone of clinically unchanged skin for the diagnosis and evaluation of systemic lupus erythematosus activity // Vojnosanit. Pregl. 2001. Vol. 58, No. 4. P. 369–374. (In Serbian)
8. Лила В.А. Клинико-лабораторные взаимосвязи у пациентов с различными вариантами течения системной красной волчанки // Современная ревматология. 2020. Т. 14, № 1. С. 26–31. DOI: 10.14412/1996-7012-2020-1-26-31
9. Davis B.M., Gilliam J.N. Prognostic significance of subepidermal immune deposits in uninvolved skin of patients with systemic lupus erythematosus: a 10-year longitudinal study // J. Invest. Dermatol. 1984. Vol. 83, No. 4. P. 242–247. DOI: 10.1111/1523-1747.ep12340246
10. Zecević R.D., Pavlović M.D., Stefanović D. Lupus band test and disease activity in systemic lupus erythematosus: does it still matter? // Clin. Exp. Dermatol. 2006. Vol. 31, No. 3. P. 358–360. DOI: 10.1111/j.1365-2230.2006.02113.x
11. Luo Y.J., Tan G.Z., Yu M. et al. Correlation of cutaneous immunoreactants in lesional skin with the serological disorders and disease activity of systemic lupus erythematosus // PLoS One. 2013. Vol. 8, No. 8. P. e70983. DOI: 10.1371/journal.pone.0070983
12. Al Attia H.M. Borderline systemic lupus erythematosus (SLE): a separate entity or a forerunner to SLE? // Int. J. Dermatol. 2006. Vol. 45, No. 4. P. 366–369. DOI: 10.1111/j.1365-4632.2006.02508.x
13. Bourn R., James J.A. Preclinical lupus // Curr. Opin. Rheumatol. 2015. Vol. 27, No. 5. P. 433–439. DOI: 10.1097/BOR.0000000000000199
14. Ананьева Л.П. Роль аутоантител в ранней диагностике системных иммуновоспалительных ревматических заболеваний // Современная ревматология. 2019. Т. 13, № 1. С. 5–10. DOI: 10.14412/1996-7012-2019-1-5-10
15. Md Yusof M.Y., Psarras A., El-Sherbiny Y.M. et al. Prediction of autoimmune connective tissue disease in an at-risk cohort: prognostic value of a novel two-score system for interferon status // Ann. Rheum. Dis. 2018. Vol. 77, No. 10. P. 1432–1439. DOI: 10.1136/annrheumdis-2018-213386
16. Mosca M., Tani C., Neri C. et al. Undifferentiated connective tissue diseases (UCTD) // Autoimmun. Rev. 2006. Vol. 6, No. 1. P. 1–4. DOI: 10.1016/j.autrev.2006.03.004
17. Rothfield N., Marino C. Studies of repeat skin biopsies of nonlesional skin in patients with systemic lupus erythematosus // Arthritis Rheum. 1982. Vol. 25, No. 6. P. 624–630. DOI: 10.1002/art.1780250604
18. Provost T.T., Andres G., Maddison P.J., Reichlin M. Lupus band test in untreated SLE patients: correlation of immunoglobulin deposition in the skin of the extensor forearm with clinical renal disease and serological abnormalities // J. Invest. Dermatol. 1980. Vol. 74, No. 6. P. 407–412. DOI: 10.1111/1523-1747.ep12544532

19. Crowson A.N., Magro C.M. Cutaneous histopathology of lupus erythematosus // Diagnostic Histopathology. 2009. Vol. 15, No. 4. P. 157–185. DOI: 10.1016/j.mpdhp.2009.02.006
20. Mehta V., Sarda A., Balachandran C. Lupus band test // Indian J. Dermatol. Venereol. Leprol. 2010. Vol. 76, No. 3. P. 298–300. DOI: 10.4103/0378-6323.62983
21. Fabré V.C., Lear S., Reichlin M. et al. Twenty percent of biopsy specimens from sun-exposed skin of normal young adults demonstrate positive immunofluorescence // Arch. Dermatol. 1991. Vol. 127, No. 7. P. 1006–1011. DOI: 10.1001/archderm.1991.01680060080008
22. Leibold A.M., Bennion S., David-Bajar K., Schleve M.J. Occurrence of positive immunofluorescence in the dermo-epidermal junction of sun-exposed skin of normal adults // J. Cutan. Pathol. 1994. Vol. 21, No. 3. P. 200–206. DOI: 10.1111/j.1600-0560.1994.tb00261.x
23. Permin H., Juhl F., Wiik A. Immunoglobulin deposits in the dermo-epidermal junction zone. Nosographic occurrence in a number of medical diseases // Acta Med. Scand. 1979. Vol. 205, No. 4. P. 333–338. DOI: 10.1111/j.0954-6820.1979.tb06058.x
24. Leibowitch M., Droz D., Noël L.H. et al. Clq deposits at the dermoepidermal junction: a marker discriminating for discoid and systemic lupus erythematosus // J. Clin. Immunol. 1981. Vol. 1, No. 2. P. 119–124. DOI: 10.1007/BF00915389
25. Minz R.W., Chhabra S., Singh S. et al. Direct immunofluorescence of skin biopsy: perspective of an immunopathologist // Indian J. Dermatol. Venereol. Leprol. 2010. Vol. 76, No. 2. P. 150–157. DOI: 10.4103/0378-6323.60561
26. Ullman S., Halberg P., Wolf-Jürgensen P. Deposits of immunoglobulins and complement C3 in clinically normal skin of patients with lupus erythematosus // Acta Derm. Venereol. 1975. Vol. 55, No. 2. P. 109–112.
27. Akarsu S., Ozbagcivan O., Ilknur T. et al. Lupus band test in patients with borderline systemic lupus erythematosus with discoid lesions // Acta Dermatovenerol. Croat. 2017. Vol. 25, No. 1. P. 15–21.
28. Goldstein R., Thompson F.E., McKendry R.J. Diagnostic and predictive value of the lupus band test in undifferentiated connective tissue disease. A followup study // J. Rheumatol. 1985. Vol. 12, No. 6. P. 1093–1096.

AUTHORS INFO

***Viktoria A. Lila**, MD, PhD student;
address: 41 Kirochnaya str., Saint Petersburg, 191015, Russia;
ORCID: https://orcid.org/0000-0001-5006-3358;
eLibrary SPIN: 8348-2910; e-mail: liu_lo@mail.ru

Vadim I. Mazurov, MD, Dr. Sci. (Med.), Professor,
Honoured Science Worker, Academician of the RAS;
ORCID: https://orcid.org/0000-0002-0797-2051;
eLibrary SPIN: 6823-5482; Scopus Author ID: 16936315400;
ResearcherId: A-8944-2016; e-mail: maz.nwgmu@yandex.ru

ОБ АВТОРАХ

***Виктория Александровна Лила**, аспирант;
адрес: Россия, 191015, Санкт-Петербург, Кирочная ул., д. 41;
ORCID: https://orcid.org/0000-0001-5006-3358;
eLibrary SPIN: 8348-2910; e-mail: liu_lo@mail.ru

Вадим Иванович Мазуров, д-р мед. наук, профессор,
заслуженный деятель науки РФ, академик РАН;
ORCID: https://orcid.org/0000-0002-0797-2051;
eLibrary SPIN: 6823-5482; Scopus Author ID: 16936315400;
ResearcherId: A-8944-2016; e-mail: maz.nwgmu@yandex.ru