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ORIGINAL ARTICLE

The Predictive Value of Autoantibody Spectrum on Organ Damage in Patients With Systemic Lupus Erythematosus

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ABSTRACT

Objectives: This study aims to investigate the positive detection rate and predictive value of autoantibodies, including anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies, anti-histone antibodies (AHAs), anti-ribosomal (anti-Rib) P antibodies, anti-Smith (anti-Sm) antibodies, anti-U1 ribonucleoprotein (anti-U1RNP) antibodies, anti-Sjögren's syndrome type A antibodies and anti-Sjögren's syndrome type B antibodies, on organ damage in patients with systemic lupus erythematous (SLE).

Patients and methods: A total of 225 patients with SLE (37 males, 188 females; mean age 37.4±15.9 years; range, 7 to 80 years) were evaluated retrospectively. Statistical analysis was performed to obtain the positive detection rate of autoantibodies and to investigate the predictive value.

Results: There were statistically significant differences of positive anti-dsDNA antibodies in renal damage, photosensitization, hematological abnormalities and serositis ($p<0.05$) and a statistically significant difference of positive AHAs in photosensitization ($p<0.05$). There was statistically significant difference of positive anti-U1RNP antibodies in renal damage ($p<0.05$). There were also statistically significant differences of positive anti-Smith antibodies in renal damage, arthritis, photosensitization, oral ulcers, hematological abnormalities and serositis ($p<0.05$) and of positive anti-Rib antibodies in renal damage, arthritis, photosensitization, malar rash, hematological abnormalities and serositis ($p<0.05$). However, there were no statistically significant differences of positive anti-Sjögren's syndrome type B antibodies and anti-Sjögren's syndrome type A antibodies in renal damage, arthritis, malar rash, neuropsychiatric disorders, hematological abnormalities and serositis ($p>0.05$).

Conclusion: Autoantibody spectrum is an important serological basis for SLE diagnosis. There are differences in the autoantibodies distribution of SLE patients with different organ damage, suggesting a certain clinical value for prediction of organ damage in SLE.

Keywords: Autoantibodies; organ damage; systemic lupus erythematous.

Systemic lupus erythematosus (SLE) is a multi-organ autoimmune disease with a broad spectrum of clinical presentations and complicated pathogenesis.[1] The SLE prevalence rates ranged from 40 to 122 per 100,000.[2] SLE can affect virtually any organ and can involve the skin, joints, heart, lungs, kidneys and central nervous system. It is characterized by excessive production of various autoantibodies that are then deposited in tissues. Some antibodies are associated with certain organ damage, e.g., anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies are associated with nephritis.[3-5] Anti-Smith (anti-Sm) antibodies have shown associations with constitutional symptoms,[6] lupus nephritis[3,5] and diseases of the central nervous system.[7] However, certain autoantibody profiles that correlate with organ damage in SLE have not been well-studied. Therefore, in this study, we aimed to investigate the positive detection rate and predictive value of various autoantibodies, including anti-dsDNA antibodies, anti-histone antibodies (AHAs), anti-ribosomal (anti-Rib) P antibodies, anti-Sm antibodies, anti-U1 ribonucleoprotein (anti-U1RNP) antibodies, anti-Sjögren's syndrome type A (anti-SSA) antibodies and anti-Sjögren's syndrome type B (anti-SSB) antibodies, on organ damage in patients with SLE.

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PATIENTS AND METHODS

The study population consisted of 225 patients (37 males, 188 females; mean age 37.4±15.9 years; range, 7 to 80 years) who were first diagnosed with SLE between August 2013 and November 2015 at Affiliated Hospital of Youjiang Medical University For Nationalities. All patients fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria for SLE.[8] Patients suffering from rheumatoid arthritis, skin inflammation, systemic sclerosis, nodular polyarthritis, epilepsy, organic brain disease, psychosis, idiopathic thrombocytopenic purpura, primary glomerular disease and other diseases were excluded from the study. The study protocol was approved by the Affiliated Hospital of Youjiang Medical University For Nationalities Ethics Committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients were divided into either a positive or negative group according to the levels of serum antibodies. Correlations between the levels of serum antibody and renal damage, arthritis, photosensitivity, cheek erythema, neurologic disorders, hematological abnormalities and serosa inflammation were analyzed respectively.

The diagnostic indexes for renal disease were persistent proteinuria >0.5 g/day or greater than 3+ by dipstick and/or urine cellular casts including red blood cells, hemoglobin, granular, tubular or mixed. The diagnostic indexes for arthritis were non-erosive arthritis, involving two or more surrounding joints, characterized by swelling and pain in the joints. The diagnostic index for photosensitization was skin allergy caused by sunlight. The diagnostic index for malar rash was a flat or higher level of erythema in the buccal region than in the skin. The diagnostic indexes for neuropsychiatric disorders were convulsions (non-drug or metabolic disorders, such as uremia, ketoacidosis and electrolytes disorder) and mental symptoms (non-drug or metabolic disorder [as described above]). The diagnostic index for oral ulcers was a painless ulcer of the mouth or nasopharynx. The diagnostic indexes for hematology abnormality were hemolytic anemia with a granulophilocyte increase or when aleukocytosis decrease was detected to be lower than 4×10^9/L on two or more occasions. Lymphopenia was defined as $<1.5\times10^9$/L on two or more occasions and platelets count $<100\times10^9$/L without any other identifiable causes. The diagnostic indexes for serositis were pleuritis (chest pain, pleuralrale and pleural effusion) or pericarditis (abnormal electrocardiogram, pericardial rub or pericardial effusion).

Autoantibodies were analyzed by the Clinical Immunology Laboratory in the Affiliated Hospital of Youjiang Medical University For Nationalities. Peripheral blood samples were obtained from SLE. Fasting venous blood was obtained from all cases in the morning and serum was separated by centrifugation, and then stored in -20° to be measured. All the experimental procedures followed the manufacturer's recommended protocols, and the experimental reagents were purchased from EUROIMMUN Medical Laboratory Diagnostics Company, Lubeck, Germany. Immunoblotting was used for detection and the results were expressed as negative, suspicious positive, 1+, 2+ and 3+.

Statistical analysis

Statistical analysis of the data was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Chi-square test was used to compare the categorical data and t-test to compare the means between two groups. A t-test was applied when the test statistics followed a normal distribution. Data distribution was tested by the Shapiro-Wilk method. Two-sided $p<0.05$ was considered to be statistically significant.

RESULTS

The positive rates of seven types of autoantibodies were statistically significantly different in 225 specimens from all the SLE patients. The positive rate of anti-SSA antibodies was as high as 66.22%, anti-dsDNA antibodies (48.0%) was the second highest, followed by anti-Sm antibodies (41.78%), anti-Rib antibodies (38.22%), anti-U1RNP antibodies (36.0%), AHAs (28.0%), and anti-SSB antibodies (21.33%).

Of these 225 patients, 166 patients had renal damage, 59 patients had no renal damage, 130 had arthritis, 95 had no arthritis, 34 were

Table 1. Comparison between anti-double stranded deoxyribonucleic acid antibody and organ damage

Clinical manifestations	+/-	Positive number	Positive rate	Negative number	Negative rate	χ^2 value	*p*
Renal damage	+	90	40.00	76	33.78	9.803	0.002
	-	18	80.00	41	18.22		
Arthritis	+	60	26.67	70	31.11	0.420	0.517
	-	48	21.33	47	20.89		
Photosensitivity	+	10	4.44	24	10.67	5.544	0.019
	-	98	43.56	93	41.33		
Malar rash	+	30	13.33	43	19.11	2.064	0.151
	-	78	34.67	74	32.89		
Neuropsychiatric disorders	+	4	1.78	9	4.00	1.641	0.200
	-	104	46.22	108	48.00		
Oral ulcers	+	14	6.22	10	4.44	1.149	0.284
	-	94	41.78	107	47.56		
Hematological abnormality	+	91	40.44	81	36.00	7.044	0.008
	-	17	7.56	36	16.00		
Serositis	+	48	21.33	34	15.11	5.739	0.017
	-	60	26.67	83	36.89		

photosensitive, 191 were not photosensitive, 73 had malar rash, 152 had no malar rash, 13 had neuropsychiatric disorders, 212 had no neuropsychiatric lupus, 24 had oral ulcers, 201 had no oral ulcers, 149 had hematology abnormalities, 76 had no hematology abnormality, 82 had serositis and 143 had no serositis. There were no statistically significant differences in the incidence of arthritis, malar rash, neuropsychiatric disorders and oral ulcers between anti-dsDNA antibody positive and negative groups. However, there were statistically significant differences among patients with renal damage, photosensitivity, hematology abnormalities and serositis ($p<0.05$) (Table 1).

Table 2. Comparison between anti-histone antibody and organ damage

Clinical manifestations	+/-	Positive number	Positive rate	Negative number	Negative rate	χ^2 value	*p*
Renal damage	+	52	23.11	114	50.67	3.472	0.062
	-	11	4.89	48	21.33		
Arthritis	+	38	16.89	92	40.89	0.231	0.631
	-	25	11.11	70	31.11		
Photosensitivity	+	3	1.33	31	13.78	7.306	0.007
	-	60	26.67	131	58.22		
Malar rash	+	24	10.67	49	21.78	1.275	0.259
	-	39	17.33	113	50.22		
Neuropsychiatric disorders	+	1	0.44	12	5.33	1.855	0.173
	-	62	27.56	150	66.67		
Oral ulcers	+	8	3.56	16	7.11	0.379	0.538
	-	55	24.44	146	64.89		
Hematological abnormality	+	52	23.11	120	53.33	1.805	0.179
	-	11	4.89	42	18.67		
Serositis	+	20	8.89	62	27.56	0.834	0.361
	-	43	19.11	100	44.44		

Table 3. Comparison between anti-U1 ribonucleoprotein antibody and organ damage

Clinical manifestations	+/-	Positive number	Positive rate	Negative number	Negative rate	χ^2 value	*p*
Renal damage	+	66	29.33	100	44.44	3.882	0.049
	-	15	6.67	44	19.56		
Arthritis	+	50	26.67	80	31.11	0.810	0.368
	-	31	13.78	64	28.44		
Photosensitivity	+	17	7.56	17	7.56	3.407	0.065
	-	64	28.44	127	56.44		
Malar rash	+	27	12.00	46	20.44	0.046	0.831
	-	54	24.00	98	43.56		
Neuropsychiatric disorders	+	5	2.22	8	3.56	0.000	1.000
	-	76	33.78	136	60.44		
Oral ulcers	+	11	4.89	13	5.78	1.128	0.288
	-	70	31.11	131	58.22		
Hematological abnormality	+	69	30.67	103	45.78	1.110	0.292
	-	12	5.33	41	18.22		
Serositis	+	36	16.00	46	20.44	3.497	0.061
	-	45	20.00	98	43.56		

There were no statistically significant differences in the incidence of renal damage, arthritis, malar rash, neuropsychiatric disorders, oral ulcers, hematology abnormalities and serositis between AHA positive and negative groups ($p>0.05$); on the other hand, there were statistically significant differences among patients with photosensitivity ($p<0.05$) (Table 2).

There were no statistically significant differences in the incidence of arthritis, photosensitivity, malar rash, neuropsychiatric disorders, oral ulcers, hematology abnormalities and serositis between anti-U1RNP antibody positive and negative groups ($p>0.05$); meanwhile, there were statistically significant differences among patients with renal damage ($p<0.05$) (Table 3).

Table 4. Comparison between anti-Smith antibody and organ damage

Clinical manifestations	+/-	Positive number	Positive rate	Negative number	Negative rate	χ^2 value	*p*
Renal damage	+	86	38.22	80	35.56	26.179	<0.001
	-	8	3.56	51	22.67		
Arthritis	+	3	1.33	127	56.44	197.199	<0.001
	-	91	40.44	4	1.78		
Photosensitivity	+	20	8.89	14	6.22	4.784	0.029
	-	74	32.89	117	52.00		
Malar rash	+	29	12.89	44	19.56	0.187	0.665
	-	65	28.89	87	38.67		
Neuropsychiatric disorders	+	3	1.33	10	4.44	1.984	0.159
	-	91	40.44	121	53.78		
Oral ulcers	+	16	7.11	8	3.56	6.842	0.009
	-	78	34.67	123	54.67		
Hematological abnormality	+	80	35.56	92	40.89	6.727	0.009
	-	14	6.22	39	17.33		
Serositis	+	54	24.00	28	12.44	30.746	<0.001
	-	40	17.78	103	45.78		

Table 5. Comparison between anti-ribosomal P protein antibody and organ damage

Clinical manifestations	+/-	Positive number	Positive rate	Negative number	Negative rate	χ^2 value	*p*
Renal damage	+	75	33.33	91	40.44	16.663	<0.001
	-	9	4.00	50	22.22		
Arthritis	+	57	5.33	73	32.44	5.582	0.018
	-	27	12.00	68	30.22		
Photosensitivity	+	18	8.00	16	7.11	4.170	0.041
	-	66	29.33	125	55.56		
Malar rash	+	44	19.56	29	12.89	24.307	<0.001
	-	40	17.78	112	49.78		
Neuropsychiatric disorders	+	3	1.33	10	4.44	0.639	0.424
	-	81	36.00	131	58.22		
Oral ulcers	+	12	5.33	12	5.33	1.842	0.175
	-	72	32.00	129	57.33		
Hematological abnormality	+	79	35.11	93	41.33	23.067	<0.001
	-	5	2.22	48	21.33		
Serositis	+	42	18.67	40	17.78	10.634	0.001
	-	42	18.67	101	44.89		

There were no statistically significant differences in the incidence of malar rash and neuropsychiatric disorders between anti-Sm antibody positive and negative groups ($p>0.05$); however, there were statistically significant differences among patients with renal damage, arthritis, photosensitivity, oral ulcers, hematology abnormalities and serositis ($p<0.05$) (Table 4).

There were no statistically significant differences in the incidence of neuropsychiatric disorders and oral ulcers between the anti-Rib antibody positive and negative groups ($p>0.05$); on the other hand, there were statistically significant differences among patients with renal damage, arthritis, malar rash, photosensitivity, hematology abnormalities and serositis ($p<0.05$) (Table 5).

There were no statistically significant differences in the incidence of renal damage, arthritis, malar rash, photosensitivity, neuropsychiatric disorders, oral ulcers, hematology abnormalities and serositis between the anti-SSA antibody positive and negative groups ($p>0.05$). And it was the same to anti-SSB antibody positive and negative groups ($p>0.05$).

Among the patients with renal damage, there was no statistically significant difference in the

Table 6. Comparison between antibodies, urine protein, and creatinine clearance rate

Antibody	+/-	24-hour urinary protein (g)	Creatinine clearance rate (mL/min)
		Mean±SD	Mean±SD
Anti-dsDNA	+	2.2±1.6	45.1±22.5*
	-	2.7+2.3	71.9±29.9
Anti-U1RNP	+	2.3±1.6	63.4+25.4
	-	2.5±2.2	67.8±30.0
Anti-Smith	+	2.4±1.6	63.4+27.1
	-	2.4±2.5	70.5±29.7
Anti-ribosomal P protein	+	2.4±1.7	63.4±27.1
	-	2.4±2.2	69.1±30.5

SD: Standard deviation; dsDNA: Double stranded deoxyribonucleic acid; U1RNP: U1 ribonucleoprotein; * Compared to systemic lupus erythematosus with negative anti-dsDNA; $p<0.05$.

24-hour urinary protein between the anti-dsDNA antibody positive and negative groups ($p>0.05$). There was a statistically significant difference in the creatinine clearance rate between the anti-dsDNA antibody positive and negative groups ($p<0.05$); however, there were no statistically significant differences in the 24-hour urinary protein excretion and creatinine clearance rate between the anti-U1RNP antibody, anti-Sm antibody and anti-Rib antibody positive and negative groups ($p>0.05$) (Table 6).

DISCUSSION

Systemic lupus erythematosus is an autoimmune disease characterized by multiple system and organ damage, and its clinical manifestations vary greatly from one individual to other. Because of the specific or relatively specific autoantibodies that may be found in the sera of patients with SLE, clinicians can diagnose the disease according to their autoantibodies. Anti-dsDNA antibody, AHA and extractable nuclear antigen (ENA) are the most common autoantibodies in SLE patients. ENA contains a variety of antibodies, such as anti-U1RNP, anti-Sm, anti-Rib, anti-SSA, anti-SSB, and anti-Scl-70 antibodies. This study aimed to determine the above autoantibodies and correlate them to SLE.

Anti-double stranded deoxyribonucleic acid antibody is only found in SLE patients and it is a high specific antibody of SLE. Several researchers have proven that anti-dsDNA antibodies correlate with the clinical manifestation, severity of illness, and disease activity and they may assist in assessing the condition and prognosis.[9] It is generally accepted that renal damage usually occurs in active stage of disease, and anti-dsDNA antibodies were considered to play an important pathogenic role in that and to be a risk factor for lupus nephritis (LN).[10] The results of this study showed that anti-dsDNA antibodies were associated with renal damage, photosensitization, hematological abnormality and serositis. Among the patients with renal damage, there was a significant decrease in creatinine clearance in patients with anti-dsDNA antibodies, suggesting that patients with anti-dsDNA antibodies are prone to renal damage and the extent of damage is more severe. In recent years, more and more studies have shown that anti-dsDNA antibodies had no correlation with renal damage and severity.[11] Recent studies have found that 30% of LN patients have negative anti-dsDNA antibodies while 25% of SLE patients have positive anti-dsDNA antibodies but no LN occurrence.[12] Therefore, more pathogenic antibodies and injury mechanisms of LN needed to be further studied. With more research in this field, it is becoming clear that nucleosomes and their antibody molecules appear to be more and more important in the pathogenesis of LN.[13] Napirei et al.[14] found that the activity of anti-dsDNA antibodies disappeared after removal of nucleosomes and their antibody molecules. This suggests that nucleosomes and their antibody molecules play a bridging role in the process of the binding of antigens between the antibodies and the kidneys, and this may be the initiating antigen of LN pathological process. Therefore, the relationship between anti dsDNA antibody and renal damage needs to be further studied. Thus, we suggest that the severity of LN should be assessed based on the level of organ damage rather than the level of antibodies.

Histone is an alkaline protein, consisting of five subunits of H-1, H-2A, H-2B, H-3 and H-4, and each subunit has its specific antibodies, collectively known as AHA. AHAs can appear in a variety of connective tissue diseases. In SLE, the positive rate is about 30%.[15] AHA can be detected in approximately 75% of drug-induced lupus patients as well as in idiopathic SLE patients.[16] Regarding the specificity of this antibody to the diagnosis of SLE, different scholars have different views and even opposite conclusions. It is reported that AHAs are related to SLE renal damage and disease activity, and the specificity is better than the anti-dsDNA antibodies.[17]

Ribonucleoprotein antigens are sensitive to ribonucleotide enzyme and trypsin and are inactivated when heated. Therefore, only the U1 part can be precipitated, a type of ribonucleic acid proteins containing eight units, called anti-U1RNP antibody.[18] Anti-U1RNP antibody is an important serological basis for the diagnosis of mixed connective tissue disease (MCTD), and is the marker antibody for MCTD.[19] In SLE, the positive rate is 30%~40%; however, the specificity is not high, and it may also be positive in the combination of other rheumatoid

diseases.[20] Studies have shown that the incidence of photosensitization, arthritis and renal damage in SLE patients with positive anti-U1RNP antibody is higher than that of negative patients.[21] In this study, the positive rate was 36.0%, and the incidence of renal damage was much higher in the anti-U1RNP antibody positive group, which was consistent with the relevant report. However, some scholars believe that patients with positive anti-U1RNP antibody often have negative anti-dsDNA antibody, and their kidneys are less affected.[22] Therefore, it is necessary to further study whether the anti-U1 RNP antibody is related to renal damage and its relevance.

Anti-Smith antibodies target at the level of small ribosomal proteins in the nucleus, and are almost always accompanied by RNP antibodies. The positive rate is 30%~70% in SLE patients.[23] Although the detection rate is low (30%~40%),[24] the specificity is as high as 92.2%~99% and they are included in the diagnostic criteria of SLE. SmBB' and D are the substances that can react with anti-Sm antibody in the anti-Sm antigen. However, SmBB' and U1 RNP have the antigenic determinant, PPPGMRPP, which can cause cross-reactions, and so SmD is considered to be the most specific Sm antigen in SLE. The most immunologically active protein in SmD antigens is SmD1, so anti-SmD1 antibody is considered to be a good marker antibody for SLE.[25] As the patient's anti-Sm antibody continues to be positive, it is suitable for the diagnosis of early, atypical and anti-dsDNA antibody negative SLE cases, as well as a retrospective diagnostic index for SLE.[26] Studies have shown that anti-Sm antibody is associated with arthritis, renal damage, oral ulcers and hematological abnormalities. In this study, the incidence of renal damage, arthritis and hematological abnormalities in SLE patients with positive anti-Sm antibodies was much higher, which was consistent with the reported results.

Anti-ribosomal P protein antibody (ARPA) is a type of antibody that mainly targets at the P0, P1 and P2 of the cytoplasm subunit phosphoric acid protein. The positive rate of patients with SLE was 14.0%~22.0%.[27] Its specificity is high and the antibody positive patients often also present with nervous neurological damage. The anti-Rib antibody is often present during the duration of SLE activity, which is parallel to the abasement of dsDNA, and the difference is that the former will not disappear immediately with the remission of the disease, and will not be transferred for one year or two. It was found that the ARPA's positive rate and ARPA in cerebrospinal fluid were significantly higher than those in the control group.[28] However, there are also reports that there is no association between ARPA and SLE neurological damage.[29] In this study, the incidence of renal damage, arthritis, photosensitivity, malar rash, hematological abnormalities and serositis in SLE patients with anti-Rib antibody positive group was much higher.

Researchers extracted and discovered SSA and SSB antigens in the blood of patients with Sjögren's syndrome (SS). There are proteins of molecular weights 52 and 60 KDa in SSA antigen, so the anti-SSA antibody has the corresponding anti-52000 and anti-60000 anti-peptide antibodies, namely anti-Ro52 antibody and anti-Ro60 antibodies.[30] It is reported that the positive rate of SSA/Ro antibodies in SLE patients is 30%~50%, 95%~100% in neonatal lupus and 60% in subacute cutaneous lupus erythematosus.[31] The presence of only anti-Ro52 antibodies is very common in SS, while the presence of only anti-Ro60 antibodies is more common in SLE. The anti-SSB antibodies have the same significance as anti-SSA antibodies. But the anti-SSB antibodies positive rate is lower than anti-SSA antibodies, which are always accompanied by each other. Studies have shown that anti-SSA antibodies are associated with pulmonary hypertension, and anti-SSB antibodies are associated with hematological abnormalities.[32] Anti-Scl-70 antibodies were mainly found in patients with systemic sclerosis. In this study, the positive detection rate was low (2.22%); thus, no statistical analysis was performed.

The main limitation of this study is the lack of any pathological diagnosis. Thus, further studies are needed based on renal biopsies to explore the predictive value of autoantibodies in the diagnosis and prognosis of SLE.

In conclusion, *(i)* anti-dsDNA, anti-U1RNP, anti-Sm and anti-Rib antibodies positive patients are more prone to renal damage; *(ii)* anti-Sm and anti-Rib antibodies positive patients are more vulnerable to arthritis; *(iii)* anti-dsDNA, anti-histone, anti-Sm and anti-Rib antibodies positive patients are more prone to photosensitization; and

(iv) anti-dsDNA, anti-Sm and anti-Rib antibodies positive patients are more prone to hematological abnormalities and serositis. Therefore, the detection of these autoantibodies can aid clinicians in assessing the organ damage in SLE patients and provide a powerful basis for early intervention and treatment while evaluating the severity and prognosis of the disease accordingly.

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