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Original Article

The Presence of Anti-ribonucleoprotein at Diagnosis Is Associated with the Flare during the First Follow-up Year in Korean Patients with Systemic Lupus Erythematosus

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Objective. The aim of this study was to examine whether the presence of anti-ribonucleoprotein (anti-RNP) antibodies at diagnosis is associated with systemic lupus erythematosus (SLE) flares in newly diagnosed patients during the first year of follow-up. **Methods.** The medical records of 71 newly diagnosed SLE patients without other concomitant autoimmune disease, serious infection, or malignancy were reviewed retrospectively. SLE flares were defined according to the SLE Disease Activity Index 2000. Patients were divided into 2 groups according to the presence or absence of anti-RNP, and variables were compared between the groups. **Results.** During the first year of follow-up, SLE patients with anti-RNP at diagnosis more frequently presented with mucosal ulcers ($p=0.003$), rash ($p=0.001$), and arthritis ($p=0.007$), compared to those without anti-RNP. The SLE flare incidence was remarkably higher in patients with anti-RNP than in those without anti-RNP (62.5% vs. 23.1%, $p=0.001$). SLE patients with anti-RNP at diagnosis had a significantly higher risk of ever experiencing a SLE flare during the first year of follow-up, compared to those without anti-RNP (odds ratio = 8.250). **Conclusion.** In conclusion, SLE patients with anti-RNP at diagnosis were more than 8-fold more likely to experience an SLE flare during the first year of follow-up. **(J Rheum Dis 2016;23:154-160)**

Key Words. Anti-ribonucleoprotein, Flare, Systemic lupus erythematosus, Systemic lupus erythematosus disease activity index

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by various clinical manifestations, depending on the affected organs and tissues. Dendritic cells and B cells are considered important players in the pathogenesis of SLE. In particular, the B cell populations of patients with SLE may increase in both number and sensitivity to pro-inflammatory cytokine stimulation [1]. These cells can also produce diverse autoantibodies against self-antigens such as double-stranded (ds) DNA [1], and immune complexes containing these pathogenic autoantibodies may then deposit in organs and tissues and occasionally cause irreversible damage [2].

Anti-ribonucleoprotein (anti-RNP) autoantibodies, which recognize small nuclear RNA-protein complexes [3,4], are normally detected in a majority of patients with mixed connective tissue disease (MCTD), and anti-RNP titers have been reported to be correlate with the diseases and outcomes associated with MCTD [5,6]. In addition, anti-RNP has been detected in a considerable proportion of SLE patients, although the role and clinical relevance of these autoantibodies in SLE activity remain controversial [7]. According to previous studies, the presence of anti-RNP was thought to correlate with typical symptoms of MCTD, Raynaud's phenomenon, and mild renal diseases in SLE patients [6,8]. In addition, SLE patients with anti-RNP were found to more frequently manifest malar

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rash, arthritis, and serositis [9], as well as a much higher prevalence of pulmonary hypertension or lung fibrosis higher SLE Disease Activity Index (SLEDAI) scores, compared to SLE patients without anti-RNP [10,11]. However, to our knowledge, few studies have clarified the association between anti-RNP and changes in SLE activity, especially SLE flares, during a considerable follow-up period. Hence, in this study, we investigated whether the presence of anti-RNP at diagnosis was be associated with the incidence of SLE flares, defined according to the SLEDAI 2000 (SLEDAI-2K), in newly diagnosed SLE patients during the first year of follow-up [12,13].

MATERIALS AND METHODS

Patients

Using identification numbers, we retrospectively and consecutively reviewed the medical records of 105 patients who were initially diagnosed with SLE at Yonsei University Health System from January 2009 to December 2014. We finally enrolled 71 SLE patients who fulfilled the following inclusion criteria: (i) SLE diagnosis according to the 1997 American College of Rheumatology (ACR) classification criteria [12]; (ii) testing for complement components and anti-nuclear antibodies (ANA), anti-ds DNA, anti-Smith, anti-RNP, anti-Sjögren's syndrome-related antigen A, anti-Sjögren's syndrome-related antigen B, lupus anticoagulant, anti-cardiolipin, and anti-beta-2-glycoprotein-1 at diagnosis, in addition to tests for items listed in the SLEDAI-2K [13]; (iii) regular visits to our institute for at least 1 year after SLE diagnosis; and (iv) documented SLEDAI-2K scores at each visit during at least the first year of follow-up. We excluded SLE patients with other concomitant connective tissue diseases such as MCTD, serious infection, and/or malignancy, and those who were referred to our institute for previously diagnosed SLE. MCTD patients were excluded based on the criteria developed by Alargon-Segovia and by Kahn [14]. In this study, all patients were divided into 2 groups according to the presence of anti-RNP, and evaluated variables were compared between the groups. This study was approved by the Institutional Review Board of Severance Hospital, Seoul, South Korea.

Systemic lupus erythematosus disease activity

In the present study, we used SLEDAI-2K scores to assess SLE disease activity; this was calculated using scores assigned to each SLEDAI-2K item present in the medical records of all patients [13]. We analyzed both the baseline SLEDAI-2K scores at diagnosis and the follow-up SLEDAI-2K scores either at the time of an SLE flare or during the last visit for SLE without flare during the first year of follow-up. An SLE flare was defined as a changes in the SLEDAI-2K score >4 points relative to the score from the previous visit. SLE without flare was defined as the absence of changes in SLEDAI-2K sufficient to meet the definition of SLE flare [15].

Clinical and laboratory data

All clinical manifestations were examined and documented in medical records by independent physicians at each visit [13,15]. Several clinically pathologic conditions were defined as follows: intestinal lung disease as the presence of reticular and/or interstitial opacities with or without ground glass opacities and/or honeycombing on chest X-ray or computed tomography scan; pleurisy on chest imaging as the presence of pleural effusion and pleural thickening; and pulmonary arterial hypertension as a pulmonary artery systolic pressure >35 mmHg via echocardiography [16]. The descriptions and definitions on the SLEDAI-2K data collection form were used as a reference for each clinical or laboratory item [13]. As a majority of patients with anti-RNP and Raynaud's phenomenon had been classified as MCTD during the follow-up period, we did not include Raynaud's phenomenon in the tables. ANA analysis was performed using an immunofluorescent method (MBL International, Woburn, MA, USA); other antibodies, including anti-RNP, were measured using an automated fluoroimmunoassay analyzer (Elia; Phadia, Uppsala, Sweden). Lupus anticoagulants were assessed using the IL Test TM LAC Screen/Confirm Kit (Instrumentation Laboratory Co., Bedford, MA, USA).

Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Data and results are expressed as numbers (percentages) or medians (interquartile ranges). The chi-square test and Fisher's exact test were applied to determine significant differences in categorical data between the 2 groups. For SLE flare, the odds ratio (OR) associated with the presence of anti-RNP was analyzed using a contingency table and the chi-square test. p-values <0.05 were considered statistically significant.

RESULTS

Baseline characteristics of SLE patients and comparison of variables between patients with and without anti-RNP

The baseline characteristics are described in Table 1. The median age of the total cohort of 71 patients (5 men, 66 women) was 43.2 years. The most common clinical feature was rash (39.4%), followed by arthritis (33.8%) and fever (12.7%). Of the laboratory results, low complement levels were found in 31 of 71 patients (43.7%), whereas increased DNA binding (anti-ds DNA) and leukopenia were observed in 21 patients (29.6%) and 17 patients (23.9%), respectively. The overall median SLEDAI-2K score was 6.0 (4.0 to 9.0).

Anti-RNP was detected in 35 of 71 patients (49.3%). When patients were divided into 2 groups according to the presence of anti-RNP, SLE patients with anti-RNP more frequently manifested rash (18 [51.4%] vs. 10 [27.8%], p=0.041) and arthritis (16 [45.7%] vs. 8 [22.2%], p=0.036) than did those without anti-RNP at SLE diagnosis. The two groups did not differ significantly in other clinical features and laboratory results relevant to SLEDAI-2K. However, SLE patients with anti-RNP had a higher median baseline SLEDAI-2K score than did those without anti-RNP (8.0 vs. 5.0, p=0.002). Anti-Smith antibodies were only detected in 11 SLE patients with anti-RNP ($p<0.001$).

Comparison of variables related to the follow-up SLEDAI-2K scores and SLE flare rate during the first year of follow-up, according to the presence of anti-RNP

During the first follow-up year, SLE patients with RNP at diagnosis more frequently presented with mucosal ulcers (15 [42.9%] vs. 4 [11.1%], p=0.003), rash (14 [40.0%] vs. 2 [5.6%], p=0.001), and arthritis (12 [34.3%] vs. 3 [8.3%], p=0.007) than did those without anti-RNP. However, the groups did not differ significantly with regard to diffuse interstitial lung disease or pulmonary arterial hypertension (Table 2). SLE patients with anti-RNP had a higher median follow-up SLEDAI-2K score, compared to those without anti-RNP (9.0 vs. 4.0, $p<0.001$). The median changes in SLEDAI-2K scores in patients with and without anti-RNP were 0.7 and −0.9, respectively, a non-significant difference. However, the SLE flare incidence was remarkably higher in patients with anti-RNP than in those without anti-RNP (62.5% vs. 23.1%, p=0.001). Furthermore, patients with anti-RNP at the time of SLE diagnosis had a significantly higher risk of experienced any SLE flare during the first year of follow-up, compared to those without anti-RNP (OR=8.250, 95% confidence interval [CI] 2.121 to 32.090).

The 71 patients were further divided into 2 groups according to the presence or absence of anti-Smith antibodies at diagnosis (11 patients with anti-Smith vs. 60 without), and the groups were compared with respect to the SLE flare rate. Notably, this rate (change in SLEDAI-2K score ≥ 4) was significantly higher in patients with anti-Smith antibodies than in those without anti-Smith antibodies (54.6% vs. 20.0%, p=0.025). Furthermore, patients with anti-Smith antibodies at the time of SLE diagnosis had a significantly higher risk of experiencing SLE flare during the first year of follow-up (OR=4.800, 95% CI 1.251 to 18.421).

Anti-RNP titers were measured in 64 patients (31 patients with RNP, 33 patients without RNP). Consequently, a positive correlation was observed between the RNP titer and the SLE flare incidence (correlation coefficient=0.422, p=0.001). Finally, 57 of 71 patients (80.3%) received systemic steroid treatment, and additional immunosuppressants (azathioprine, mycophenolate mofetil, cyclophosphamide) were administered to some patients (azathioprine 19.7%, mycophenolate mofetil 11.3%, cyclophosphamide 5.6%). However, no statistically significant differences were observed between the two groups (Table 2).

DISCUSSION

In this study, we found that SLE patients with anti-RNP at the time of the initial SLE diagnosis exhibited larger increases in SLEDAI-2K scores during the first year of follow-up than did patients without anti-RNP. In addition, the presence of anti-RNP appeared to predict an approximately 8-fold increase in the SLE flare incidence during the same follow-up period. Moreover, our results suggested that the presence of anti-RNP at diagnosis is associated a greater incidence of arthritis and rash and may significantly promote the development of arthritis, rash, and mucosal ulcers, thus contributing to SLE flare according to the SLEDAI-2K definition, a finding that was consistent with the results of a previous study [9]. On the other hand, in contrast to previously reported results, the incidence of diffuse interstitial lung disease and pulmonary arterial hypertension did not differ according to the

Table 1. Baseline characteristics of patients with systemic lupus erythematosus and comparison of variables between patients with and without anti-RNP

Characteristic	Total (n = 71)	Patient with anti-RNP (n = 35)	Patient without anti-RNP (n = 36)	p-value
Demographic data				
Age (yr)	43.2 (37.0～55.0)	43.0 (37.0～53.0)	46.0 (35.0～57.0)	0.328
Female gender	66 (93.0)	33 (94.3)	33 (91.7)	1.000
SLEDAI-2K				
Clinical features				
Seizure	1 (1.4)	0 (0)	1 (2.8)	1.000
Psychosis	0 (0)	0 (0)	0 (0)	1.000
Organic brain syndrome	0 (0)	0 (0)	0 (0)	1.000
Visual disturbance	0 (0)	0 (0)	0 (0)	1.000
Lupus headache	0 (0)	0 (0)	0 (0)	1.000
Cerebrovascular accident	0 (0)	0 (0)	0 (0)	1.000
Vasculitis	0 (0)	0 (0)	0 (0)	1.000
Arthritis	24 (33.8)	16 (45.7)	8 (22.2)	0.036
Myositis	0 (0)	0 (0)	0 (0)	1.000
Pleurisy	6 (8.5)	3 (8.6)	3 (8.3)	1.000
Pericarditis	2 (2.8)	2 (5.7)	0 (0)	0.239
Rash	28 (39.4)	18 (51.4)	10 (27.8)	0.041
Alopecia	3 (4.2)	1 (2.9)	2 (5.6)	1.000
Mucosal ulcers	6 (8.5)	5 (14.3)	1 (2.8)	0.107
Fever	9 (12.7)	5 (14.3)	4 (11.1)	0.735
Laboratory results				
Urinary casts	1 (1.4)	1 (2.9)	0 (0)	0.493
Hematuria	14 (19.7)	10 (28.6)	4 (11.1)	0.065
Proteinuria	16 (22.5)	10 (28.6)	6 (16.7)	0.230
Pyuria	13 (18.3)	8 (22.9)	5 (13.9)	0.329
Low complements	31 (43.7)	14 (40.0)	17 (47.2)	0.540
Increased DNA binding	21 (29.6)	9 (25.7)	12 (33.3)	0.482
Thrombocytopenia	12 (16.9)	3 (8.6)	9 (25.0)	0.065
Leukopenia	17 (23.9)	9 (25.7)	8 (22.2)	0.730
Score	6.0 (4.0～9.0)	8.0 (5.0～11.0)	5.0 (3.0～6.0)	0.002
Autoantibodies				
Antinuclear antibody	66 (93.0)	34 (97.1)	32 (88.9)	0.357
Anti-double strand DNA	21 (29.6)	9 (25.7)	12 (33.3)	0.482
Anti-Smith	11 (15.5)	11 (31.4)	0 (0)	＜0.001
Anti-SSA/Ro	35 (49.3)	20 (57.1)	15 (41.7)	0.192
Anti-SSB/La	14 (19.7)	8 (22.9)	6 (16.7)	0.512
Lupus anticoagulant	13 (18.3)	9 (25.7)	4 (11.1)	0.112
Anti-cardiolipin	8 (11.3)	3 (8.6)	5 (13.9)	0.710
Anti-beta2-glycoprotein1	8 (11.3)	5 (14.3)	3 (8.3)	0.478
Other clinical features				
Diffuse interstitial lung diseases	1 (1.4)	1 (2.9)	0 (0)	0.493
Pulmonary arterial hypertension	0 (0)	0 (0)	0 (0)	1.000

Values are presented as median (interquartile range) or number (%). SLEDAI-2K: systemic lupus erythematosus Disease Activity Index 2000, RNP: ribonucleoprotein, SSA/Ro: Sjögren's syndrome-related antigen A, SSB/La: Sjögren's syndrome-related antigen B.

presence of anti-RNP [10]. However, a 1-year follow-up period might not be sufficient to identify histological alterations that lead to clinical symptoms.

In general clinical situations, physicians tend to monitor follow-up anti-ds DNA titer and complement component levels to assess SLE disease activity; however, no current

Table 2. Comparison of variables of the follow-up SLEDAI-2K scores and SLE flare rate during the first follow-up year between SLE patients with and without anti-RNP

Characteristic	Patient with anti-RNP (n=35)	Patient without anti-RNP (n=36)	p-value
Demographic data			
Follow-up period (mo)	11.0 (8.0~11.0)	11.0 (11.0~12.0)	0.077
SLEDAI-2K at flare			
Clinical features			
Seizure	0 (0)	0 (0)	NA
Psychosis	0 (0)	1 (2.8)	1.000
Organic brain syndrome	0 (0)	0 (0)	NA
Visual disturbance	0 (0)	0 (0)	NA
Lupus headache	2 (5.7)	0 (0)	0.239
Cerebrovascular accident	0 (0)	0 (0)	NA
Vasculitis	0 (0)	0 (0)	NA
Arthritis	12 (34.3)	3 (8.3)	0.007
Myositis	0 (0)	0 (0)	NA
Pleurisy	4 (11.4)	3 (8.3)	0.710
Pericarditis	1 (2.9)	1 (2.8)	1.000
Rash	14 (40.0)	2 (5.6)	0.001
Alopecia	4 (11.4)	2 (5.6)	0.429
Mucosal ulcers	15 (42.9)	4 (11.1)	0.003
Fever	6 (17.1)	2 (5.6)	0.151
Laboratory results			
Urinary casts	5 (14.3)	0 (0)	0.025
Hematuria	4 (11.4)	5 (13.9)	0.036
Proteinuria	10 (28.6)	6 (16.7)	0.230
Pyuria	11 (31.4)	4 (11.1)	0.329
Low complement	13 (37.1)	11 (30.6)	0.557
Increased DNA binding	8 (22.9)	10 (27.8)	0.634
Thrombocytopenia	9 (25.7)	9 (25.0)	0.945
Leukopenia	11 (31.4)	11 (30.6)	0.937
Score	9.0 (7.0~10.0)	4.0 (2.0~6.8)	<0.001
Change in score	0.7	−0.9	0.142
Flare of SLE	15 (62.5)	3 (23.1)	0.001
Other clinical features			
Diffuse interstitial lung diseases	4 (11.4)	0 (0)	0.054
Pulmonary arterial hypertension	3 (8.6)	1 (2.8)	0.357
Treatment			
Hydroxychloroquine	31 (88.6)	30 (83.3)	0.735
Steroid	27 (77.1)	30 (83.3)	0.563
Azathioprine	7 (20.0)	7 (19.4)	1.000
Mycophenolate mofetil	5 (14.3)	3 (8.3)	0.478
Cyclophosphamide	3 (8.6)	1 (2.8)	0.357

Values are presented as median (interquartile range) or number (%). NA: not available, RNP: ribonucleoprotein, SLE: systemic lupus erythematosus, SLEDAI-2K: SLE Disease Activity Index 2000.

recommendations encourage the evaluation of other autoantibodies, including anti-RNP. In contrast to anti-ds DNA, anti-RNP can be detected in the peripheral blood for more than 1 year. In addition, because anti-RNP is produced by long-lived plasma cells and supported by the enhanced differentiation of anti-RNP-related memory B cells to plasma cells, the circulating anti-RNP concentration might also be maintained despite the lack of an exact established blood-survival time [14,17]. The long stability of anti-RNP renders it unsuitable as a marker of rapid alterations in SLE disease activity. Nevertheless, anti-RNP may be useful for anticipating SLE flare, improve-

ment, or remission during a lengthy follow-up period once its clinical relevance has been determined. Accordingly, our present study of the potentially predictive and reflective role of anti-RNP positivity at the time of SLE diagnosis with regard to alterations in SLE disease activity within the first year of follow-up year after diagnosis was conducted against the backdrop of these concepts and characteristics of anti-RNP.

Because the anti-ds DNA titer and complement component levels are SLEDAI-2K items and are known to be reflective of changes in activity within a relatively short time period, we did not analyze their predictive potential for SLE flare in this study. In contrast, we assumed that the presence of anti-Smith antibodies might be predictive of SLE flare in the early phase of disease, as all 11 patients with anti-Smith antibodies were also anti-RNP-positive. Anti-Smith antibodies and anti-RNP might be simultaneously detected at a high rate in SLE patients, as these autoantibodies were classified and analyzed in the same cluster in previous studies [9,17]. In the present study; however, anti-Smith antibodies were only detected in patients having anti-RNP, and therefore we could not distinguish the direct effect of anti-Smith antibodies from the mutual effect of both types of autoantibodies. Therefore, the predictive potential of anti-Smith antibodies with regard to SLE flare should be addressed in future studies involving a greater number of anti-Smith antibody-positive SLE patients.

One feature of our study that we consider to be a strength is that it is the first to propose the potential of anti-RNP at diagnosis to predict the development of SLE flare during the first year of follow-up using the well- documented SLEDAI-2K at each visit. However, our study also had several limitations. First, the study featured a small number of SLE patients and a relatively short follow-up period because of the exclusion criteria for concomitant MCTD and the retrospective design. Second, we were unable to explain the mechanism linking anti-RNP and the clinical items of SLEDAI-2K that contribute to SLE flare. Third, given the small number of patients, differences in baseline SLEDAI-2K scores between the two groups might have affected the SLE flare rate, despite speculation regarding the relationship between the presence of anti-RNP and baseline SLEDAI-2K scores. Future studies will be needed to compensate for these limitations and clarify the clinical role of anti-RNP for the prediction of the disease activity in newly diagnosed SLE patients.

CONCLUSION

In conclusion, our study determined that among Korean SLE patients, those with anti-RNP at the time of diagnosis were 8.3-fold more likely to experience an SLE flare according to the SLEDAI-2K definition during the first year of follow-up relative to those without anti-RNP, thus indicating the potential predictive value of this autoantibody.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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