The clinical significance of anti-Smith antibodies in patients with systemic lupus erythematosus detected by chemiluminescent enzyme immunoassay: a single-center retrospective cohort study

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Background: Anti-Smith (anti-Sm) antibody is one of the representative autoantibodies especially detected in patients with systemic lupus erythematosus (SLE). For the detection of anti-Sm antibody, chemiluminescent enzyme immunoassay (CLEIA) is convenient but has not yet been fully evaluated for patients with SLE.

Objective: We investigated the CLEIA for measuring anti-Sm antibodies and the relationship between anti-Sm antibodies and clinical characteristics in patients with SLE.

Methods: The STACIA MEBLux test was used for the CLEIA on stored sera from patients with SLE (n = 127). To demonstrate the specificity and sensitivity for discriminating SLE in the CLEIA, sera from patients with rheumatic diseases other than SLE was used as a control (n = 140). All clinical data were reviewed and analyzed, retrospectively.

Results: The titer of anti-Sm antibody measured by CLEIA was significantly correlated to that measured by fluorescence enzyme immunoassay (FEIA) (r = 0.57, P < 0.01), with the confident sensitivity 44.9% and the specificity 99.3%, the area under curve (AUC) 0.860, and 95% confidence interval (CI) 0.813－0.906, respectively. Whereas FEIA showed the sensitivity 50.0%, specificity 92.3%, AUC 0.740 and 95% CI 0.674－0.805. In SLE patients positive for anti-Sm antibodies by CLEIA, a high odds ratio (OR) was found in the observation of pericarditis (OR 2.66, P = 0.054, 95% CI 1.01－7.58), arthritis (OR 1.95, P = 0.15, 95% CI 0.80－4.93) and higher serum C-reactive protein (OR 5.65, P = 0.15, 95% CI 0.60－74.5) and the presence of hypocomplementemia was a significant risk factor (OR 2.45, P = 0.037, 95% CI 1.08－5.90) indicated by the positivity of anti-Sm antibodies.

Conclusions: The measurement of anti-Sm antibodies by CLEIA comprehensively gave adequate results to detect SLE patients. The positivity of anti-Sm antibody by CLEIA may contribute to local inflammation mainly affecting the innate immune activation of arthritis and pericarditis in SLE.

Key words: systemic lupus erythematosus, autoantibody, anti-Smith antibody

Introduction

Autoantibodies are the most important items that define systemic lupus erythematosus (SLE) characteristics and the presence of SLE-specific antibodies such as anti-double-stranded (ds)-DNA (anti-dsDNA) antibodies, anti-Smith (anti-Sm) antibodies are included in recently revised classification criteria for SLE as a specific autoantibody only detected in SLE patients.[1,2] The main immunological pathogenesis of SLE is recently known to be abnormal and excessive activation in both innate and acquired immunity.[3] E.g., anti-ds-DNA antibodies can enhance immunocomplex formation with DNA which is integrated into the cell through Fc receptors in the cell surface and DNA complexing anti-ds-DNA antibodies can be recognized by a toll-like receptor, leading to activate innate immunity.[4] However, anti-ribosomal P protein antibodies have been reported to be associated with severe lupus phenotypes, e.g., autoimmune hepatitis,[5] type V lupus nephritis,[6] and

neuropsychiatric SLE (NPSLE), especially diffuse psychiatric/neuropsychological (diffuse NPSLE) syndromes.[7]

Anti-Sm antibodies are directed against proteins that constitute the common core of small nuclear ribonucleoprotein (RNP) antibodies and are specifically expressed in patients with SLE.[8] In Japan, to detect anti-Sm antibodies, the fluorescence enzyme immunoassay (FEIA) has been commonly used in clinical practice and the cost is covered by the national health insurance. However, chemiluminescent enzyme immunoassay (CLEIA) is an enzyme-linked sorbent assay that can detect antibodies in serum and is more practical due to its shorter reaction time and without the need of diluting the serum samples.

Methods

We first confirmed the utility of anti-Sm antibodies measured by FEIA and CLEIA with the STACIA MEBLux tests (Medical and Biological Laboratories, Nagoya) to detect SLE, respectively. We subsequently investigated which assay is more practical to detect and measure anti-Sm antibodies, the conventional FEIA or the CLEIA, which, we should point out, has until recently been considered more convenient than the FEIA. Lastly, we discussed the clinical significance of anti-Sm antibodies in patients with SLE, focusing on the relationship between clinical manifestations and anti-Sm antibodies.

Patients
Patients with active SLE who had required induction therapy for high disease activity and were admitted to Kitasato University Hospital from 2007 to 2019 were recruited for this study (n = 127). All the patients fulfilled the 1997 ACR (American College of Rheumatology) revised classification criteria for SLE.[9,10] To evaluate the specificity and the sensitivity of anti-Sm antibodies, patients with non-SLE autoimmune diseases were also recruited as controls (n = 140). All clinical information was reviewed based on the patients' medical records. All patients gave written informed consent, and the study was approved by the ethics committees at Kitasato University School of Medicine (approval number: B17-153).

Autoantibody measurements
The positivity for anti-DNA consisted of that for either anti-ds-DNA IgG (immunoglobulin) antibodies measured by enzyme linked immunosorbent assay (ELISA) or those by radioimmunoassay (SRL [Special Reference Laboratories], Tokyo). Anti-RNP antibodies and the ferritin levels were measured by CLEIA. Anti-cardiolipin and anti-cardiolipin β-glycoprotein I complex (β2GPI) antibodies were detected by ELISA (SRL). Lupus anticoagulant was determined by dilute Russell's viper venom time (SRL).

To determine the usefulness of anti-Sm antibodies, we used the CLEIA kit, STACIA MEBLux test (Medical and Biological Laboratories). To evaluate the utility of CLEIA to detect anti-Sm antibodies in patients with SLE, we used the value of anti-Sm antibodies measured by FEIA (Bio Medical Laboratories, Tokyo), which has been authorized to use for a diagnosis of SLE and is covered by the Japanese national health insurance.

Statistical analyses
The logistic regression model was used to analyze each risk. A comparison of patient profiles was performed using the Mann-Whitney U test or the χ^2 test. The effects of anti-Sm antibody positivity on mortality were analyzed by the log-rank test. Pearson's correlation coefficient was used to demonstrate a significant correlation. Statistical analyses were performed with JMP 5.1.2. (SAS Institute, Cary, NC, USA). Values of P < 0.05 were considered to indicate statistical significance.

Results

Utility of anti-Sm antibody measured by FEIA in SLE
First, we checked whether or not the FEIA to detect anti-Sm antibodies in patients with SLE in this study as a conventional measurement is covered by the Japanese national health insurance. The control patients' diseases are listed in Table 1, and the characteristics of the SLE patients are summarized in Table 2. The serum levels of anti-Sm antibodies detected by FEIA were significantly higher in patients with SLE than those in the control patients (P < 0.001) (Figure 1A). By using the cut-off level (>5.7 IU/ml) set from the highest likelihood ratio (69.5) given by the receiver operating characteristic (ROC) curve between the anti-Sm antibody titer in SLE patients and those in the control patients, the area under the curve (AUC) was 0.740, 95% confidence interval (CI) was 0.674−0.805, the sensitivity and the specificity of the anti-Sm antibodies with FEIA for SLE detection was 50.0% and 92.3%, and the positive predictive value (PPV) and negative predictive value (NPV) was 98.4% and 69.0%, respectively (Figure 1B). Whereas the sensitivity and specificity for detecting patients with SLE was 46.0% and 99.3%, respectively, even when applying the cut-off level (>7 IU/ml) generally used in clinical

Table 1. Control patients' characteristics

| Control patients (n = 140)	
Age (years)	55.9 ± 17.4
Gender (male : female)	31 : 109
Diseases	
pSjS	39
Vasculitis	31
PM/DM	41
AOSD	10
RA	7
SSc	7
BD	13
MCTD	1
RPC	1

Age is standard deviation ± mean.
pSjS, primary Sjögren syndrome; Vasculitis, systemic vasculitis (including Takayasu arteritis: giant cell arteritis and anti-nuclear cytoplasmic antigen-antibody associating vasculitis); PM/DM, polymyositis and dermatomyositis; AOSD, adult-onset Still's disease; RA, rheumatoid arthritis; SSc, systemic sclerosis; BD, Behçet's disease; MCTD, mixed connective disease; RPC, relapsing polychondritis

Table 2. SLE patients' characteristics

SLE (n = 127)	
Lupus nephritis	54 (42.5%)
NPSLE	34 (26.8%)
dNPSLE	17 (13.4%)
Acute confusional state	14
Mood disorder	2
Anxiety disorder	4
fNPSLE	17 (13.4%)
Cerebrovascular disease	5
Aseptic meningitis	4
Demyelinating syndromes	3
Headache	2
Peripheral neuropathy	3
Anti-DNA antibody	89 (70.1%)
Anti-phospholipid antibody	36 (16.9%)

SLE, systemic lupus erythematosus; NPSLE, neuropsychiatric syndromes in SLE; dNPSLE, diffuse psychiatric/neuropsychological syndromes in NPSLE; fNPSLE, focal/neurologic syndromes in NPSLE
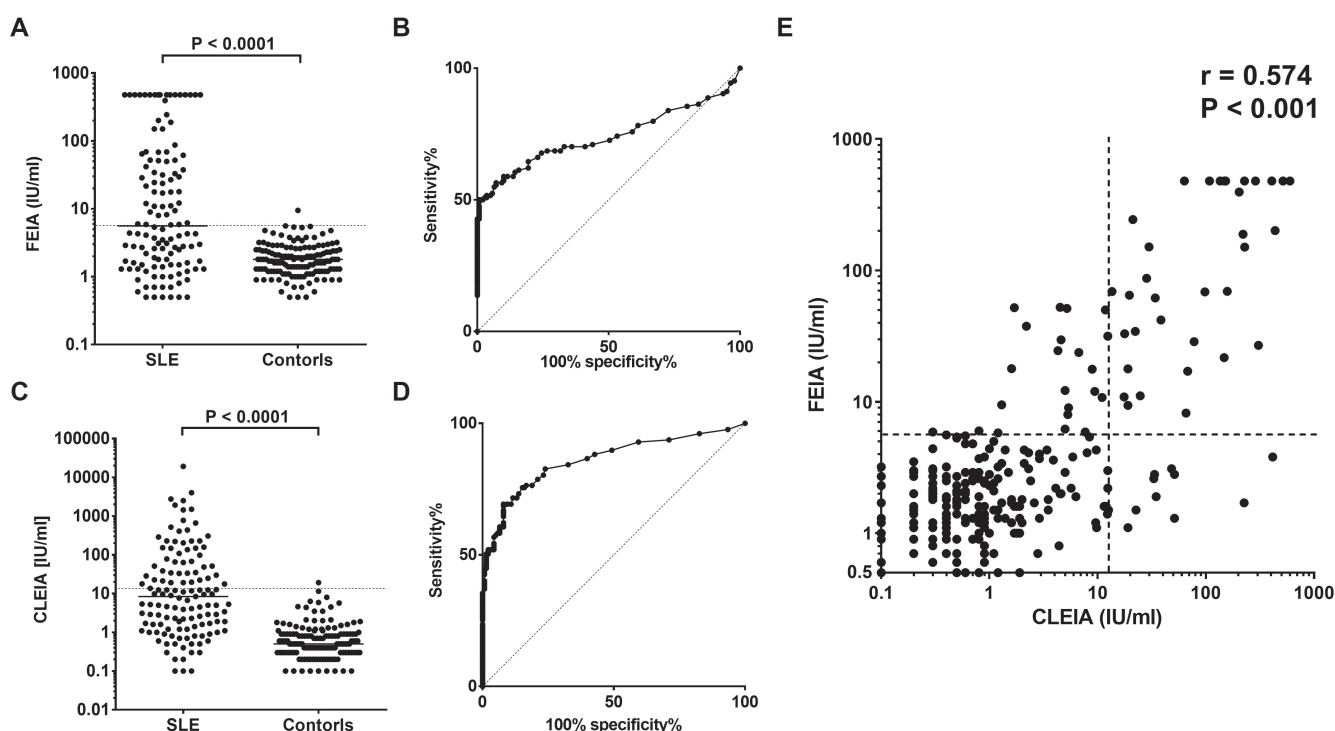
Figure 1. The utility of anti-Sm antibodies measured by CLEIA in patients with SLE

(**A**) The comparison of the anti-Sm antibody value, compared with the Mann-Whitney test by FEIA and (**C**) CLEIA with the STACIA MEBLux test. The solid line indicates the median value in each group. The dotted line is the cut-off level discriminating lupus patients from control patients. The receiver operating characteristic curve was described using the anti-Sm antibody values from the SLE and control patients to set the cut-off level to discriminate them in (**B**) FEIA and (**D**) CLEIA. (**E**) The correlation of FEIA and CLEIA with the statistical significance (r = 0.082, P < 0.001). The dotted lines are the cut-off levels, respectively. CLEIA, chemiluminescent enzyme immunoassay; FEIA, fluorescence enzyme immunoassay

practice, indicating that there is no significant difference between these two cut-off levels.

Among characteristics in SLE patients recruited in this study, older age was negatively related to (odds ratio [OR] 0.263, P = 0.092) positive for anti-Sm antibodies measured by FEIA. Higher CH50 was also negatively related (OR 0.284, P = 0.077). However, those values were not statistically significant. Anti-DNA antibody-positive patients had a significant risk (OR 2.198, P = 0.048) for being positive for anti-Sm antibody measured by FEIA (Table 3).

Utility of anti-Sm antibodies measured by CLEIA in SLE
We also investigated the utility of anti-Sm antibodies measured by CLEIA. The serum anti-Sm antibody level was significantly elevated in patients with SLE compared to that in the control patients: 8.4 (0.1－3,998) IU/ml (median, range) and 0.5 (0.1－19.1), respectively (P < 0.001) (Figure 1C). The ROC curve analysis referring to controls showed that the AUC was 0.860, 95% CI was 0.813－0.906, the sensitivity and the specificity of anti-Sm antibody for SLE were 44.9% and 99.3%, and the PPV and NPV were 98.3% and 66.2%, respectively when the cut-off level was set as 11.7 giving the highest likely ratio, 61.9 (Figure 1D). Among characteristics in SLE patients recruited in this study, the presence of facial rash (OR 2.200, P = 0.085) and pericarditis (OR 2.260, P = 0.054), and being positive for anti-DNA antibody (OR 2.216, P = 0.051), were related to being positive for anti-Sm antibodies measured by CLEIA. Also, higher complement 4 gave negative results related to being positive for anti-Sm antibodies by CLEIA (OR 0.262, P = 0.076) but were not statistically significant. Whereas hypocomplementemia (OR 2.452, P = 0.037) was significantly related to the anti-Sm antibody positivity (OR 2.198, P = 0.048), and higher C_3 (OR 0.105, P = 0.011) and CH50 (OR 0.211, P = 0.033) were significantly but negatively related to being positive for anti-Sm antibodies measured by CLEIA (Table 3).

Table 3. The risks indicated by the positivity of anti-Sm antibodies

Anti-Sm antibody SLE (n = 127)	FEIA single-positive (n = 64)			CLEIA single-positive (n = 57)		
	OR	95% CI	P	OR	95% CI	P
Age	0.263	0.053－1.211	0.092	0.649	0.138－2.954	0.577
Female	0.875	0.289－2.597	0.809	1.254	0.424－3.962	0.686
Lupus nephritis	0.855	0.421－1.730	0.663	0.654	0.318－1.330	0.244
NPSLE	0.978	0.444－2.559	0.957	0.959	0.430－2.110	0.917
dNPSLE	1.972	0.699－6.072	0.211	1.915	0.685－5.267	0.220
SLEDAI	0.915	0.167－4.987	0.917	1.670	0.305－9.328	0.554
Facial rash	1.656	0.687－4.141	0.267	2.200	0.908－5.507	0.085
Arthritis	0.981	0.400－2.404	0.966	1.953	0.799－4.929	0.145
Pleuritis	1.143	0.385－3.463	0.809	1.469	0.495－4.458	0.485
Pericarditis	1.587	0.607－4.344	0.352	2.660	1.005－7.580	0.054
AIHA	0.398	0.103－1.032	0.145	1.029	0.313－3.290	0.962
WBC <3,000/mm³	2.731	0.858－10.42	0.106	1.741	0.569－5.601	0.333
plt <10.0 × 10⁴/mm³	0.757	0.270－2.063	0.587	0.751	0.259－2.052	0.582
Hypocomplementemia	1.661	0.755－3.737	0.211	2.452	1.080－5.902	0.037
C_3	0.272	0.051－1.336	0.115	0.105	0.017－0.564	0.011
C_4	0.317	0.072－1.299	0.117	0.262	0.056－1.108	0.076
CH50	0.284	0.068－1.121	0.077	0.211	0.049－0.854	0.033
Anti-DNA antibody	2.198	1.017－4.890	0.048	2.216	1.012－5.065	0.051
Serum CRP	6.277	0.551－78.26	0.174	5.646	0.595－74.53	0.151
Serum ferritin	2.368	0.220－107.8	0.438	1.579	0.103－26.41	0.725
IL-6	0.119	0.000－3.030	0.311	0.391	0.001－18.32	0.649
Mortality	8.200	0.590－82.05	0.210	5.207	0.744－103.4	0.145

The risk of being positive to being negative for anti-Sm antibody in respective conditions, and the presence or being higher, was calculated by logistic regression analysis.
SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; AIHA, autoimmune hemolytic anemia; WBC, white blood cells; plt, platelets; CH50, 50% hemolytic component; CRP, C-reactive protein; IL, interleukin

Correlation of anti-Sm antibody titers between FEIA and CLEIA

The results by CLEIA were significantly correlated to those by FEIA (r = 0.574, P < 0.001), suggesting that CLEIA has almost the same sensitivity and accuracy as FEIA to diagnose SLE (Figure 1E).

Clinical differences in patients with dissociation of the positivity for anti-Sm antibodies between FEIA and CLEIA

Regarding each risk in SLE patients with only positive anti-Sm antibodies measured by FEIA, those with only positive anti-Sm antibodies by CLEIA, and those positive for both (Table 3), interestingly, the higher serum C-reactive protein (CRP) level had the highest OR 5.646, suggesting it as a possible independent risk factor. In the immunological test, hypocomplementemia was a significant risk given by the anti-Sm antibody positivity by CLEIA (OR 2.452, P = 0.037) but not by FEIA (OR 1.661, P = 0.211). In mortality during the observation period, patients with anti-Sm antibodies tended to have a higher risk, compared to those without anti-Sm antibodies, but there was no statistical difference (data not shown).

Positivity for anti-DNA antibodies was a common risk for the positivity of anti-Sm antibodies in FEIA and CLEIA (Table 3), we analyzed the relationship of the presence or absence of anti-DNA antibodies between these two groups to reveal a certain difference in the presence of anti-DNA antibodies in patients positive for anti-Sm antibodies detected by FEIA and CLEIA. Of 64 patients positive for anti-Sm antibody by FIEA, 50 patients were also positive for anti-DNA antibody (78.1%); and of 57 patients positive for anti-Sm antibodies by CLEIA, 45 patients were positive for anti-DNA antibody (78.9%). There was no significant difference in anti-DNA antibody positivity between them (P = 0.913, χ^2 test). Furthermore, because hypocomplementemia including low C_3/C_4 and CH50 was related to being positive for anti-Sm antibodies commonly observed by FEIA and CLEIA, we checked the confounding against the presence of anti-DNA antibody which is another pathogenic autoantibody in SLE and that of anti-Sm antibody by CLEIA. In multivariate analysis, the positivity of anti-DNA was significantly and independently related to hypocomplementemia (OR 4.266, 95% CI 1.800－10.38, P = 0.001), but not that of anti-Sm antibody (OR 1.094, 95% CI 0.429－2.666, P = 0.841), suggesting the presence of anti-DNA was strongly related to hypocomplementemia even in patients positive for anti-Sm antibody by CLEIA.

Table 4. Characteristics in patients positive for anti-Sm antibody by CLEIA or FEIA

Single positive for anti-Sm antibody	FEIA (n = 20)	CLEIA (n = 13)	P
Age	32.5 (16－58)	35 (19－68)	0.293
Female	17 (85.0%)	12 (92.3%)	0.882
Lupus nephritis	9 (45.0%)	4 (30.8%)	0.410
NPSLE	7 (35.0%)	5 (38.5%)	0.840
SLEDAI	12 (4－20)	10 (4－34)	0.985
Facial rash	5 (25.0%)	5 (38.5%)	0.414
Arthritis	2 (10.0%)	4 (30.8%)	0.148
Pleuritis	2 (10.0%)	2 (15.4%)	0.646
Pericarditis	2 (10.0%)	3 (23.1%)	0.318
WBC <3,000/mm^3	2 (10.0%)	1 (7.69%)	0.932
plt <10.0 × 10^4/mm^3	2 (10.0%)	0 (0.00%)	0.822
Hypocomplementemia	14 (70.0%)	11 (84.6%)	0.346
C_3 (mg/dl)	62 (18－148)	60 (24－95)	0.420
C_4 (mg/dl)	8 (4－31)	6 (2－33)	0.233
CH50 (/ml)	25 (0－52)	26 (5－50)	0.773
Anti-DNA antibody	14 (70.0%)	9 (69.2%)	0.963
Serum CRP (mg/ml)	0.40 (0.03－5.06)	0.22 (0.05－9.31)	0.912
Serum ferritin (ng/ml)	61 (7－6,837)	91 (12－1,930)	0.706

Values of age, SLEDAI, C3, C4, CH50, serum CRP, and serum ferritin are shown as median (range).

There were a few SLE patients who were positive for anti-Sm antibodies either by FEIA or CLEIA, therefore, we investigate the differences between the two groups. Of 127 patients with SLE, there were only 13 patients positive for anti-Sm antibodies measured by CLEIA; and there were only 20 patients positive for anti-Sm antibodies by FEIA. The PPV and the NPV of patients with anti-Sm antibodies by CLEIA to those with anti-Sm antibodies by FEIA was 77.2% and 71.4%, respectively. We also analyzed the background data of these patients to elucidate differences between patients only positive for anti-Sm antibodies by FEIA or CLEIA. Overall, regarding background data from these subgroups, there were no significant differences (Table 4). Thus, there was no clinical difference between anti-Sm antibodies measured by FEIA or CLEIA for diagnosing SLE patients in clinical practice.

SLE phenotypes in patients positive for anti-Sm antibodies by CLEIA

The anti-Sm antibody titer by CLEIA did not differ among the disease phenotype of SLE (Figure 2A), but among patients with NPSLE, the positive rate seemed to be higher in patients with diffuse psychiatric/neuropsychological syndromes in NPSLE, compared to those with neurologic syndromes of NPSLE or those with lupus nephritis (Figure 2B).

Discussion

We confirmed that anti-Sm antibody measured by CLEIA is equivalent to the conventional FEIA method to detect anti-Sm antibody with the high specificity required to discriminate SLE patients. Because the PPV and NPV were adequate and the patients' backgrounds were similar, the equivalence of CLEIA for SLE patients has, in the present study, been demonstrated. Regarding the specification to discriminate SLE patients from those with other diseases, CLEIA can be more advantageous, compared to FEIA, because of the larger area under the curve result from the ROC analysis. We also confirmed that anti-Sm antibodies detected by CLEIA are particular pathogenic autoantibodies strongly and specifically associated with SLE pathogenesis by type-III allergy hyperactivation and mainly consist of immunocomplex and low complement. That is due to the anti-Sm antibody positivity measured by CLEIA which presents a significant risk for the lower complement where anti-DNA antibody also contributed less than anti-Sm antibody according to the results of multivariate analyses. Moreover, anti-Sm antibody may tend to induce inflammation related to CRP elevation in SLE. Indeed, anti-Sm-antibody-positive patients diagnosed by CLEIA had a higher risk for manifesting arthritis and pericarditis,
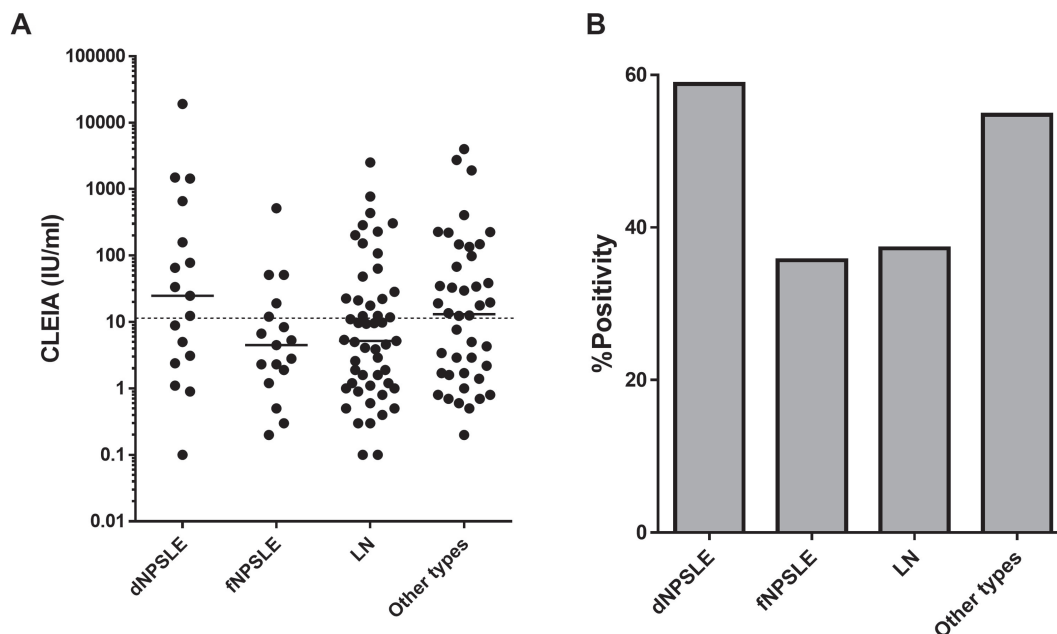

Figure 2. The titers and positive rate of anti-Sm antibody by phenotypes of SLE

(**A**) The anti-Sm antibody values are determined by CLEIA in each phenotype of the disease. The solid line indicates the median value in each group. (**B**) The positive rate of anti-Sm antibody values in each group. The dotted line indicates the cut-off level.

NPSLE, neuropsychiatric syndromes in SLE; dNPSLE, diffuse psychiatric/neuropsychological syndromes in NPSLE; fNPSLE, focal/neurologic syndromes in NPSLE; LN, lupus nephritis

unlike those diagnosed by FEIA. These are two of the conditions in which CRP elevation can be observed in patients with SLE. We demonstrated that anti-Sm antibody can up-regulate the inflammatory cytokines like interleukin (IL)-6 and tumor necrosis factor (TNF)-α by directly biding on the cell surface unknown molecules in macrophages from peripheral blood.[11] Furthermore, the effect is synergistically enhanced when there is co-stimulation of anti-Sm and anti-RNP antibodies. Noteworthy, all patients with positive serum anti-Sm antibodies also express serum anti-RNP antibodies in clinical practice.[8] Therefore, the synergistic effects of anti-Sm and anti-RNP antibodies demonstrated in the present study are considered to always take place *in vivo* and play a role in the development of inflammatory reactions in SLE. However, there was no correlation of IL-6 and CRP in the present study, even though CRP production is generally promoted by IL-6 stimulation. It has been shown that interferon-α can decrease CRP production through the reduction of IL-6 stimulation.[12] In active lupus patients, we speculate that there could be another pathway, such as the direct stimulation by anti-Sm antibody leading to CRP elevation. Anti-Sm antibody can have a potential function to induce activation leading to the elevation of CRP in SLE patients, which may have been associated with the higher risk for arthritis and pericarditis in the present study, especially when anti-Sm antibodies are detected by CLEIA.

From these results, although anti-Sm antibody can induce some inflammation in the pathogenesis of SLE related to mild complications such as arthritis and pericarditis as well as fatal involvement such as diffuse NPLSE, to our knowledge, there is no drug that reduces the production of autoantibodies, including anti-Sm antibodies. Therefore, belimumab, a monoclonal antibody targeting B cell-activating factor in the TNF family, may be a possible candidate. Belimumab is a newly developed, unique and specific therapeutic agent for patients with SLE that can reduce the level of autoantibodies[13] including anti-Sm autoantibodies that are specific for SLE.[2] According to a recent clinical trial, belimumab was most beneficial for SLE patients with arthritis and was effective even in SLE patients without anti-DNA autoantibodies.[14] These results demonstrate the effectiveness of B cell modulators like belimumab for arthritis and indicate that with them, anti-Sm-positive SLE patients detected by CLEIA may have a better treatment response.

In conclusion, these results demonstrated that in SLE patients the detection method of anti-Sm antibody by CLEIA was equivalent to that by FEIA. Furthermore,

CLEIA may be more sensitive to detect arthritis, one of the main conditions that causes the elevation of CRP in patients with SLE. Recognizing the presence of anti-Sm antibodies in SLE patients, and considering the pathogenic role of anti-Sm antibodies, provides a better opportunity to make a more suitable choice of therapeutics to treat SLE patients.

Acknowledgments

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