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Anti-Smith antibody is associated with disease activity in patients with new-onset systemic lupus erythematosus

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Abstract

Although anti-Smith (Sm) antibody is a highly specific antibody for systemic lupus erythematosus (SLE), the significance of anti-Sm antibody in patients with SLE is unclear. This study aimed to evaluate the association between anti-Sm antibodies and disease activity in patients with new-onset SLE. We included patients who were tested for anti-Sm antibodies at SLE diagnosis and within 12 months after diagnosis. SLE disease activity index (SLEDAI) was obtained at the time of the anti-Sm antibody test. The baseline disease activity was compared between patients with and without anti-Sm antibodies. The longitudinal association between disease activity and anti-Sm antibodies was also evaluated in total patients and in those with anti-Sm antibodies. Among 92 patients who were tested for anti-Sm antibodies at SLE diagnosis, 67 and another 67 patients were followed up for the presence of anti-Sm antibodies at 6 and 12 months, respectively. Although the baseline SLEDAI was comparable in patients with and without anti-Sm antibodies, the serum level of anti-Sm antibody was significantly correlated with SLEDAI ($P=0.003$). At 12 months, anti-Sm antibody positivity was associated with higher SLEDAI and anti-dsDNA titer ($P=0.002$, both). In addition, the changes in anti-Sm antibody titer over 12 months were correlated with the alterations in SLEDAI ($P=0.029$).Anti-Sm antibody was associated with the baseline disease activity and the alteration of disease activity in patients with new-onset SLE. Monitoring of anti-Sm antibody titer may help assess the disease activity in SLE.

Keywords Systemic lupus erythematosus · Anti-Smith antibody · Disease activity · Systemic lupus erythematosus disease activity index

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that predominantly affects women of reproductive age [1]. The hallmark of SLE is the excessive production of pathogenic antibodies recognizing self-antigens and the formation of antigen–antibody complexes that trigger the immune response to cause multiple organ injury [2]. Antinuclear antibodies (ANAs) are found in almost all patients with SLE, and a variety of anti-extractable nuclear antigen

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(ENA) antibodies are detected in SLE patients at diagnosis and during disease progression [3].

Owing to the pathophysiological significance of autoantibodies in SLE, several studies have attempted to elucidate the association between anti-ENA antibodies and SLE-specific clinical features. Among autoantibodies against ENA, anti-double-stranded DNA (dsDNA) antibodies and anti-Smith (Sm) antibodies are highly specific for SLE, and the presence of anti-dsDNA and/or anti-Sm antibodies is one of the important criteria for the classification of SLE [4, 5]. Notably, serum anti-dsDNA antibody titer has been well known to be correlated with disease activity, and thus, anti-dsDNA antibody titer is regarded as an important surrogate marker to assess the disease activity of SLE [6, 7]. Anti-dsDNA antibody titer has been reported to be consistently associated with the development of lupus nephritis and disease flare in patients with SLE [8, 9]. However, the clinical significance of other anti-ENA antibodies, including anti-Sm antibodies, still remains unclear.

Anti-Sm antibodies are directed against seven proteins that consist of a core of small nuclear ribonucleoprotein (snRNP) particles [10]. The specificity of anti-Sm antibodies for classification of SLE reached 90% in a previous study [11]. Despite the remarkable specificity of anti-Sm antibodies for SLE, the association between anti-Sm antibody titer and the clinical manifestation of SLE is still unclear. Previous studies have suggested that patients with anti-Sm antibodies are more likely to have renal involvement and central nervous system dysfunction [12–14]. However, inconsistent results are present among studies, and most of the studies were performed cross-sectionally. In addition, the longitudinal association between anti-Sm antibodies and SLE disease activity is largely unknown to date.

To elucidate the clinical significance of anti-Sm antibody in patients with SLE, we compared the clinical and laboratory features of SLE patients with and without anti-Sm antibodies at the initial presentation, and investigated the association between anti-Sm antibody titer and disease activity in patients with new-onset SLE. In addition, we evaluated whether the changes in anti-Sm antibody titer are correlated with the alteration of disease activity during follow-up in patients with new-onset SLE.

Patients and methods

Patients

We reviewed the medical records of 556 patients who were tested for anti-Sm antibodies on at least two occasions between December 2005 and March 2018 in Severance Hospital under a diagnosis of SLE. To evaluate the clinical significance of anti-Sm antibodies in new-onset SLE, this study included patients who met the criteria as follows: (i) patients diagnosed with SLE according to the 1997 revised ACR classification criteria [4] or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria [5]; (ii) patients who were tested for anti-Sm antibodies at the diagnosis of SLE; (iii) patients who were followed up for measurement of anti-Sm antibody titer within 12 months after the diagnosis of SLE. Among 556 patients, a total of 92 patients were finally included (Fig. 1). This study was approved by the Institutional Review Board of Severance Hospital (4-2018-1042) and was conducted in accordance with the principles set forth in the Declaration of Helsinki.

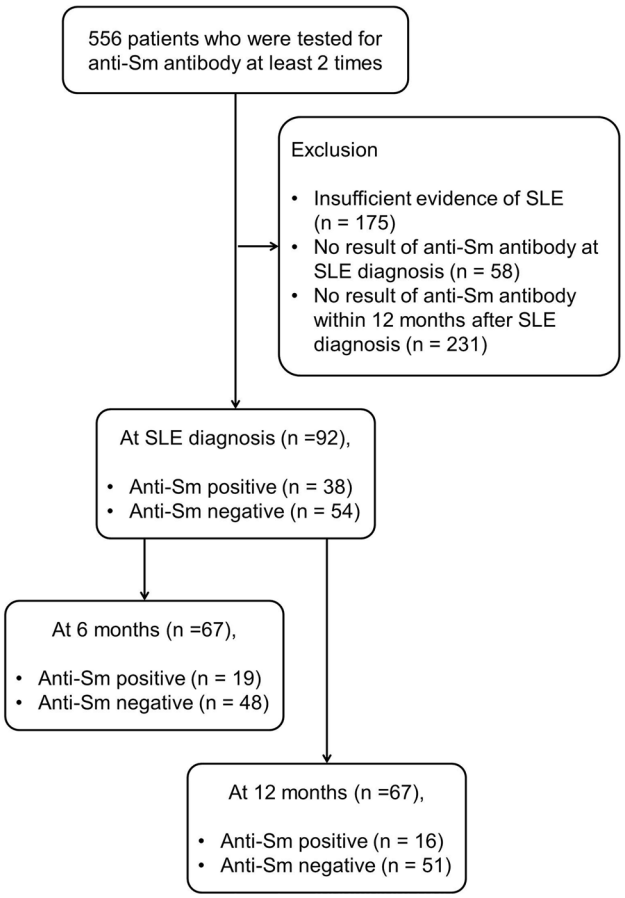

Fig. 1 Flowchart of patient inclusion and follow-up. This study included patients with SLE who were tested for anti-Sm antibody at diagnosis and within 12 months of diagnosis of SLE on at least two occasions. Among 92 selected patients, 67 patients and another 67 patients were followed up for anti-Sm antibody testing at 6 months and 12 months, respectively. *SLE* systemic lupus erythematosus, *anti-Sm* anti-Smith antibody

Clinical and laboratory data

The demographic data of age and sex, and SLE disease activity index-2000 (SLEDAI)-2 K at SLE diagnosis were collected for all study participants [15]. Clinical manifestations

of SLE including skin rash, photosensitivity, oral ulcer, arthritis, serositis, nephritis as well as neurologic, hematologic, and immunologic disorders were also investigated. The clinical features were defined according to the 1997 ACR criteria [5]. For laboratory analysis, complete blood count, platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and complement level were obtained at the date of diagnosis of SLE. Autoantibodies against double-stranded DNA (dsDNA), ribonucleoprotein (RNP), Smith (Sm), and Sjogren syndrome-related antigen (SSA/Ro and SSA/La) were measured using an automated fluoro-immunoassay analyzer (Elia; Phadia, Uppsala, Sweden). In patients who were tested for anti-Sm within 12 months, SLEDAI-2 K, anti-dsDNA, and anti-Sm titer were collected at the follow-up date of the anti-Sm antibody test. The delta (Δ) value of SLEDAI-2 K, anti-dsDNA, and anti-Sm was defined as the change in absolute values at 6 or 12 months, compared to the baseline value.

Statistical analysis

The normal distribution of continuous variables was determined by the Kolmogorov–Smirnov test. Continuous variables with normal distribution were presented as mean ± standard deviation and evaluated using the Student's *t* test. Otherwise, continuous variables were presented as median with interquartile range (IQR) and evaluated using the Mann–Whitney *U* test. Categorical variables were presented as frequencies and percentages, and the difference in categorical variables was compared by Chi-square or Fisher's exact test, as appropriate. The associations between SLEDAI-2 K and laboratory variables were estimated using Pearson's correlation analysis. Statistical analyses were performed using MedCalc statistical software version 18.9 (MedCalc Software, Ostend, Belgium), and a two-tailed $P < 0.05$ was regarded statistically significant.

Results

Baseline characteristics

The baseline characteristics of 92 patients are presented in Table 1. The mean patient age was 27.1 years, and 85 (92.4%) patients were female. The mean SLEDAI-2 K at the diagnosis of SLE was 7.1, suggesting that patients had active SLE. Immunologic and hematologic disorders were the most common clinical manifestations, followed by skin rash and nephritis. Patients were divided into two groups according to the presence of anti-Sm antibodies at SLE diagnosis: 38 (41.3%) patients showed positive results for anti-Sm antibodies and 54 (58.7%) patients showed negative results for anti-Sm antibodies. Age, sex, and baseline SLEDAI were not significantly different in patients with or without anti-Sm antibodies. However, immunologic disorder, lymphopenia, and hypocomplementemia were more common in patients with anti-Sm antibodies. Although the serum level of anti-dsDNA was not different between the two groups, patients with anti-Sm antibodies were more likely to have anti-RNP and anti-Ro antibodies ($P < 0.001$ and $P = 0.037$, respectively).

Association between anti-Sm antibodies and disease activity at SLE diagnosis

To elucidate the association between anti-Sm antibodies and disease activity at the time of SLE diagnosis, we performed Pearson's correlation analysis (Table 2). In the entire study population, serum anti-Sm antibody titer was significantly correlated with SLEDAI-2 K ($r = 0.303$, $P = 0.003$), complement levels ($r = -0.370$, $P < 0.001$ and $r = -0.237$, $P = 0.023$ for C3 and C4, respectively), and serum anti-dsDNA antibody titer ($r = 0.233$, $P = 0.026$). A subgroup analysis in patients with anti-Sm antibodies revealed that anti-Sm titer was also associated with SLEDAI-2 K ($r = 0.344$, $P = 0.034$) and C3 level ($r = -0.425$, $P = 0.008$) but not significantly associated with anti-dsDNA titer ($r = 0.271$, $P = 0.100$) (Fig. 2).

Correlation between changes in anti-Sm titer and alteration of disease activity

Follow-up tests for anti-Sm antibodies were performed in 67 patients at 6 months and in another 67 patients at 12 months after the diagnosis of SLE (Fig. 1). Sixty-seven patients who were tested for anti-Sm antibodies at 6 months and 12 months were not the same population. Nineteen (28.4%) patients showed positive result for anti-Sm antibodies at 6 months, and 16 (23.9%) patients showed positive result at 12 months. At 6 months, SLEDAI-2 K and anti-dsDNA titer were not significantly different between patients who showed positive results for anti-Sm antibodies and those who showed negative results for anti-Sm antibodies ($P = 0.267$ and $P = 0.534$, respectively). However, SLEDAI-2 K and anti-dsDNA titer were significantly higher in patients with anti-Sm antibodies than in patients without anti-Sm antibodies at 12 months ($P = 0.002$, both). At 12 months, the median values of SLEDAI-2 K and anti-dsDNA titer were 4.0 (IQR 2.0–4.8) and 53.5 IU/mL (IQR 0.0–150.0) in patients with anti-Sm antibodies, whereas the median values of SLEDAI-2 K and anti-dsDNA titer were 2.0 (IQR 0.0–3.0) and 0.0 IU/mL (0.0–22.0) in patients without anti-Sm antibodies.

Table 1 Baseline characteristics of patients with or without anti-Sm antibodies at SLE diagnosis

Variables	Total ($n=92$)	Anti-Sm (+) ($n=38$)	Anti-Sm (−) ($n=54$)	*P* value
Demographic data				
Age (years)	24 (15–39)	22 (16–37)	26 (14–42)	0.539
Female	85 (92.4)	33 (86.8)	52 (96.3)	0.121
Disease activity				
SLEDAI-2 K	6.0 (4.0–9.0)	8.0 (5.0–11.0)	6 (4.0–8.3)	0.083
Clinical features				
Skin rash	46 (50.0)	20 (52.6)	26 (48.1)	0.674
Photosensitivity	17 (18.5)	3 (7.9)	14 (25.9)	0.032
Oral ulcer	10 (10.9)	4 (10.5)	6 (11.1)	0.999
Arthritis	18 (19.6)	9 (23.7)	9 (16.7)	0.406
Serositis	16 (17.4)	8 (21.1)	8 (14.8)	0.440
Nephritis	27 (29.3)	12 (31.6)	15 (27.8)	0.695
Neurologic disorder	2 (2.2)	0 (0.0)	2 (3.7)	0.510
Hematologic disorder	79 (85.9)	34 (89.5)	45 (83.3)	0.547
Immunologic disorder	80 (87.0)	38 (100.0)	42 (77.8)	0.001
Laboratory data				
WBC (/μL)	4350 (3245–6340)	4085 (3060–5600)	4490 (3410–7260)	0.249
Lymphocyte (/μL)	1080 (795–1560)	940 (623–1200)	1255 (883–1893)	0.002
Hemoglobin (g/dL)	11.5 ± 1.8	11.1 ± 1.9	11.7 ± 1.7	0.100
Platelet (× 1000/μL)	201 ± 94	206 ± 83	197 ± 102	0.686
ESR (mm/h)	43 (23–70)	43 (24–71)	44 (22–70)	0.794
CRP (mg/L)	1.8 (0.9–6.3)	1.5 (1.0–13.8)	2.0 (0.7–4.8)	0.657
Creatinine (mg/dL)	0.6 (0.5–0.7)	0.6 (0.5–0.8)	0.6 (0.5–0.7)	0.141
Albumin (g/dL)	3.9 (3.1–4.4)	3.7 (3.0–4.2)	4.0 (3.2–4.5)	0.213
AST (IU/L)	24 (18–38)	27 (19–38)	23 (17–38)	0.418
ALT (IU/L)	18 (12–36)	24 (12–37)	17 (12–37)	0.528
Complement 3 (mg/dL)	78 ± 38	64 ± 34	88 ± 38	0.003
Complement 4 (mg/dL)	12 (7–21)	11 (3–18)	14 (10–22)	0.033
Autoantibodies				
Anti-dsDNA (IU/mL)	27.5 (0.0–160.0)	40.0 (0.0–170.7)	21.0 (0.0–110.2)	0.530
Anti-dsDNA positivity	61 (66.3)	23 (60.5)	38 (70.4)	0.325
Anti-RNP positivity	39 (42.4)	29 (76.3)	10 (18.5)	< 0.001
Anti-Ro positivity	51 (55.4)	26 (68.4)	25 (46.3)	0.037
Anti-La positivity	18 (19.6)	10 (26.3)	8 (14.8)	0.173

Continuous variables with normal distribution were expressed as the mean ± standard deviation and evaluated using the Student's *t* test. Otherwise, continuous variables were expressed as the median (interquartile range) and evaluated using the Mann–Whitney *U* test. Categorical variables were presented as *n* (%). SLEDAI-2 K, systemic lupus erythematosus disease activity index-2000

WBC white blood cell, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *RNP* ribonucleoprotein

To evaluate the association between the change of anti-Sm antibody titer and alteration of disease activity, the correlation between Δanti-Sm antibody titer and ΔSLEDAI-2 K/Δanti-dsDNA antibody titer was analyzed at 6 months and 12 months in all patients who were followed up for anti-Sm antibodies and in patients who showed positive results for anti-Sm antibodies at diagnosis of SLE (Table 3). At 6 months, Δanti-Sm antibody titer was not significantly correlated with disease activity represented by ΔSLEDAI-2 K and Δanti-dsDNA antibody titer. However, Δanti-Sm antibody titer at 12 months showed a positive correlation with ΔSLEDAI-2 K in both total patients and patients with anti-Sm antibodies at diagnosis of SLE ($r=0.267$, $P=029$, and $r=0.397$, $P=040$, respectively) (Fig. 2).

Table 2 Correlation between anti-Sm antibody titer and disease activity at SLE diagnosis

Variable	Total patients ($n = 92$)			Anti-Sm-positive patients ($n = 38$)		
	Correlation coefficient (r)	95% CI	P value	Correlation coefficient (r)	95% CI	P value
SLEDAI-2K	0.303	0.104. 0.478	0.003	0.344	0.028, 0.598	0.034
Hemoglobin (g/dL)	−0.183	−0.384, 0.023	0.082	−0.164	−0.460, 0.164	0.324
Lymphocyte (/μL)	−0.194	−0.384, 0.011	0.064	−0.184	−0.476, 0.144	0.270
Complement 3 (mg/dL)	−0.370	−0.535, −0.179	<0.001	−0.425	−0.656, −0.122	0.008
Complement 4 (mg/dL)	−0.237	−0.422, −0.034	0.023	−0.240	−0.520, 0.086	0.146
Anti-dsDNA (IU/mL)	0.233	0.029, 0.418	0.026	0.271	−0.053, 0.544	0.100

SLE systemic lupus erythematosus, *anti-Sm* anti-Smith antibody, *SLEDAI-2 K* systemic lupus erythematosus disease activity index-2000, *CI* confidence interval, *dsDNA* double-stranded DNA

Discussion

In the present study, we investigated the clinical and laboratory features of patients with new-onset SLE who showed positive result for anti-Sm antibodies, and evaluated the association between anti-Sm antibodies and disease activity. Compared to patients without anti-Sm antibodies, those with anti-Sm antibodies were likely to have higher disease activity, represented by lymphopenia, hypocomplementemia, and higher SLEDAI-2 K. Furthermore, the changes in anti-Sm titer were correlated with the alteration in disease activity, implicating that anti-Sm antibody could be a marker to assess disease activity in new-onset SLE.

Previous studies have suggested that anti-Sm antibodies can be associated with disease activity. To exclude the drug effect on antibody profile, we investigated the correlation of anti-Sm titer and SLEDAI in treatment-naïve patients with SLE. Although the difference of SLEDAI was not statistically significant between patients with and without anti-Sm antibodies ($P = 0.083$), the correlation between anti-Sm titer and SLEDAI score was statistically significant ($P = 0.003$ in total patients and $P = 0.034$ in anti-Sm-positive patients).

In terms of clinical manifestations, photosensitivity was more common in patients without anti-Sm antibodies than in those with anti-Sm antibodies. However, there was no significant difference in lupus nephritis, neurologic disorder, and serositis between patients with and without anti-Sm antibodies, which is inconsistent with previous studies [12–14, 16]. This discrepancy may arise from the difference in the patient population. The clinical characteristics of patients with SLE vary among ethnicities [17, 18], and the presence of anti-Sm antibodies is also affected by ethnicity and sex [19, 20]. Thus, the association between anti-ENA antibodies and clinical manifestation of SLE may depend on ethnicity. Moreover, the proportion of patients with anti-Sm antibodies in our study was 41.3%, which was higher than the corresponding proportion reported in previous studies. Further investigations involving a larger number of Korean patients are necessary to verify our observations.

Few studies have evaluated the direct association between anti-Sm antibodies and disease activity. Previously, Agarwal et al. reported that the anti-Sm antibody concentration showed no direct association with disease activity in patients with SLE [21]. However, a recent study by Emad et al. demonstrated that anti-Sm antibodies were correlated with disease activity in SLE [22]. This study included 70 patients, and 19 (27.1%) patients showed a positive result for anti-Sm antibodies and had high disease activity, represented by a mean SLEDAI score of 14. Owing to the inconsistent results of the previous studies, we investigated the clinical significance of anti-Sm antibodies with regard to the disease activity in SLE. In the present study, we found a significant correlation between serum anti-Sm titer and SLEDAI-2 K in all patients as well as in patients with anti-Sm antibodies at diagnosis of SLE. Although the underlying mechanism between anti-Sm antibodies and SLE disease activity remains uncertain, one study suggested that anti-Sm antibodies can promote complement activation in vivo [23]. Our study also showed a negative correlation between anti-Sm antibody concentration and complement level. Considering that complement activation is a critical pathway in the pathogenesis of SLE, complement activation by anti-Sm antibodies could be one of the mechanisms underlying the association between anti-Sm antibodies and SLE disease activity.

In this study, the change of anti-Sm antibody titer was also correlated with alteration in disease activity. A recent study performed by Flechsig et al. failed to show the longitudinal association between anti-Sm antibodies and disease activity in 51 patients with SLE [16]. This study evaluated the cross-sectional and longitudinal association between anti-Sm antibodies and the British Isles Lupus Activity Group (BILAG) index. Although anti-Sm antibodies had a cross-sectional correlation with BILAG score, the longitudinal analysis to evaluate the correlation

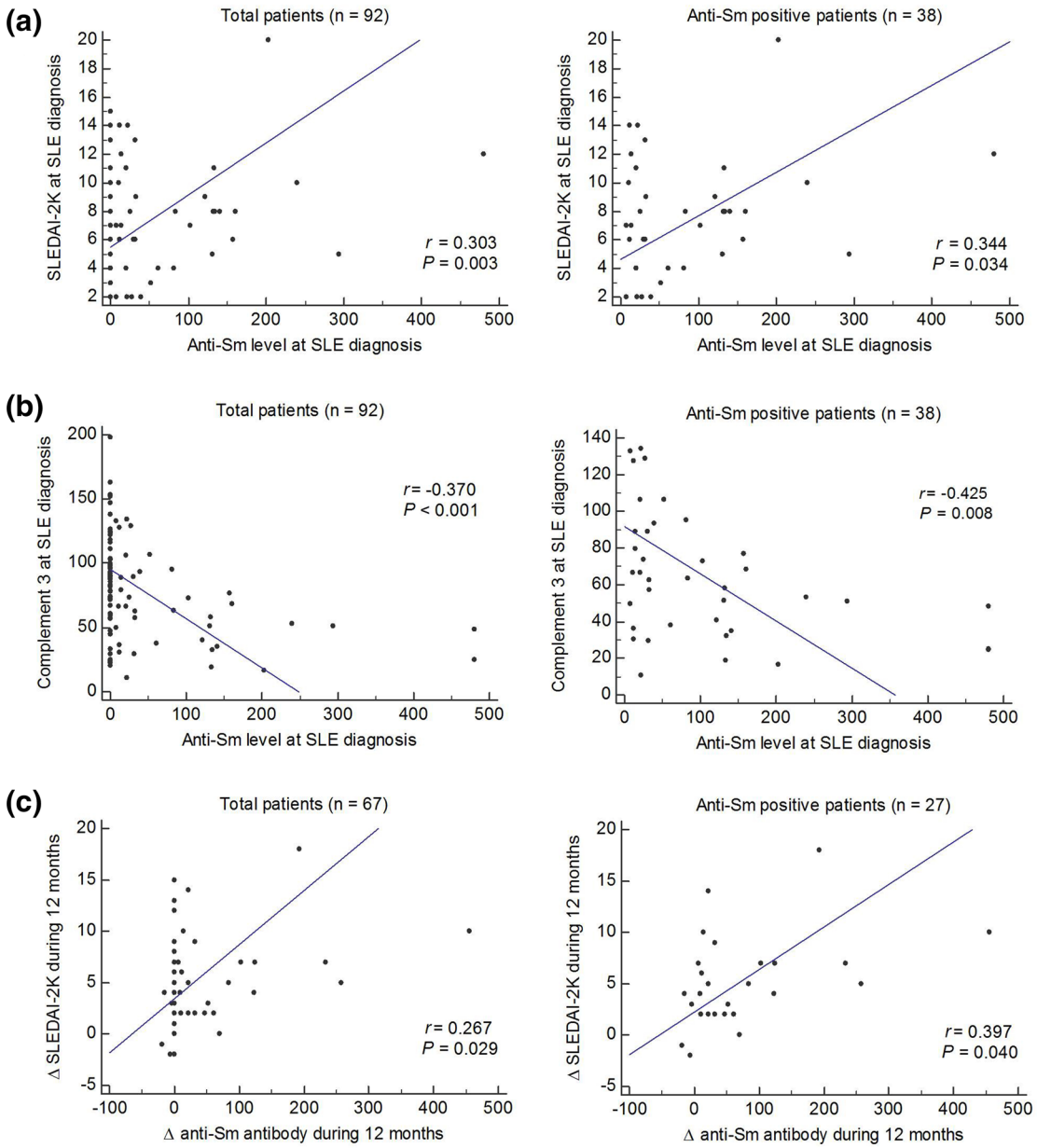

Fig. 2 Association between anti-Sm antibody and disease activity in patients with new-onset SLE. **a**, **b** Correlation between concentration of anti-Sm antibody and SLEDAI-2 K (**a**)/complement 3 (**b**) at diagnosis of SLE was assessed in total patients ($n=92$) and in patients with anti-Sm antibody ($n=38$). **c** Correlation between the changes of anti-Sm antibody (Δ anti-Sm antibody) and the changes of SLEDAI-2 K (Δ SLEDAI-2 K) at 12 months was analyzed in total patients ($n=67$) and in patients with anti-Sm antibody ($n=27$). A total of 67 patients were tested for anti-Sm antibody at 12 months, and 27 patients with anti-Sm antibodies were those who showed positive result for anti-Sm antibody at diagnosis of SLE. *SLE* systemic lupus erythematosus, *SLEDAI-2 K* systemic lupus erythematosus disease activity index-2000, *anti-Sm* anti-Smith antibody

between Δanti-Sm antibody titer and ΔBILAG showed no statistical significance. Unlike our study, the change in anti-Sm antibody titer and BILAG was determined by two different time points, regardless of the follow-up interval. The discrepancy in the results may be attributed to differences in disease activity index and follow-up intervals.

Interestingly, the longitudinal analysis between anti-Sm antibodies and disease activity showed no significant correlation at 6 months, whereas it revealed a significant correlation at 12 months. Although it is unclear whether the delayed change in anti-Sm antibodies is indeed more relevant to the disease activity in SLE, a previous study suggested that

Table 3 Association between changes of anti-Sm antibody titer and alterations of disease activity in patients with new-onset SLE

	At 6 months			At 12 months		
	vs. Δanti-Sm antibody (U/mL)			vs. Δanti-Sm antibody (U/mL)		
	Correlation coefficient (*r*)	95% CI	*P* value	Correlation coefficient (*r*)	95% CI	*P* value
Total patients		(*n* = 67)			(*n* = 67)	
ΔSLEDAI-2K	0.087	−0.157, 0.320	0.486	0.267	0.028, 0.477	0.029
Δanti-dsDNA antibody (IU/mL)	0.048	−0.195, 0.265	0.702	0.065	−0.178, 0.300	0.603
Patients with anti-Sm antibody at SLE diagnosis (*n* = 30)					(*n* = 27)	
ΔSLEDAI-2K	0.148	−0.225, 0.482	0.437	0.397	0.020, 0.675	0.040
Δanti-dsDNA antibody (IU/mL)	0.210	−0.132, 0.530	0.265	0.108	−0.284, 0.489	0.592

SLE systemic lupus erythematosus, *anti-Sm* anti-Smith antibody, *SLEDAI-2 K* systemic lupus erythematosus disease activity index-2000, *dsDNA* double-stranded DNA

anti-Sm antibodies showed a relatively static expression in peripheral blood [24]. Unlike anti-dsDNA antibodies, which undergo a dynamic change in relation to disease activity, anti-Sm antibodies may respond more slowly to changes in disease activity in SLE. Long-term studies with more patients would provide a better understanding of the delayed response of anti-Sm antibodies to disease activity.

This study has several limitations. First, this study was designed as a retrospective study, and we included only those patients with SLE who were followed up with anti-Sm antibody tests within 12 months. As monitoring of anti-Sm antibodies is not a routine clinical practice, there would be a selection bias. Second, this study included a relatively small number of patients with SLE. Third, the long-term effect of anti-Sm antibodies on disease activity was not assessed. Nonetheless, this study can suggest an association between anti-Sm antibodies and disease activity. Further studies involving long-term monitoring of anti-Sm antibodies in larger patient population would provide more information to elucidate the clinical significance of anti-Sm antibody in patients with SLE.

In conclusion, we have demonstrated that anti-Sm antibody is associated with disease activity at SLE diagnosis, and that its alterations could reflect changes of disease activity in patients with new-onset SLE. Thus, anti-Sm antibodies can be a serological marker to assess disease activity in patients with new-onset SLE.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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