Correlations between antinucleosome antibodies and anti-double-stranded DNA antibodies, C3, C4, and clinical activity in lupus patients

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Abstract

Objective

To examine the correlations between antinucleosome antibodies and anti-double-stranded (ds) DNA antibodies, complement (C) 3 and 4 levels, and clinical activities in SLE patients.

Methods

Antinucleosome antibodies and anti-dsDNA antibodies were detected by enzyme-linked immunosorbent assays (ELISA). The levels of C3 and C4 were measured by nephelometry. Clinical activities were determined by SLE Disease Activity Index (SLEDAI).

Results

Of 65 SLE patients, the prevalence of antinucleosome antibodies were higher than anti-ds DNA antibodies (52.3 vs 36.9%, respectively, p < 0.05). Similar results were obtained in 45 active SLE patients, 64.4% for antinucleosome antibodies and 46.7% for anti-ds DNA antibodies. Of 34 patients lacking anti-ds DNA antibodies, 16 (47.1%) were shown antinucleosome antibodies. Activity of antinucleosome antibodies was significantly correlated with the SLEDAI scores and inversely correlated with the C3 levels but not with the C4 levels.

Conclusion

Antinucleosome antibodies could be one of the earliest and most sensitive markers in diagnosis of SLE, particularly in anti-dsDNA antibodies-negative patients. More importantly, antinucleosome antibodies is correlated with clinical activities and C3 levels.

Key words

SLE, antinucleosome antibodies, anti-dsDNA antibodies, SLEDAI, C3, C4.
Introduction

Systemic lupus erythematosus (SLE) is a non-organ specific autoimmune disease characterized by widespread inflammation, affecting virtually every organs and/or systems in the body, and by the production of various autoantibodies, in particular, antinuclear autoantibodies (ANA). The ANA are autoantibodies directed against chromatin and its individual components including double-stranded DNA (dsDNA) and histones, and some ribonucleoproteins. Therefore, anti-double-stranded DNA (anti-dsDNA) antibodies have been considered to be the serological hallmark that is disease specific and would participate in the development of various lesions in SLE (1-3). The primary event inducing the formation of anti-dsDNA, however, has always been obscured, since it has been very difficult to demonstrate the presence of free DNA in the sera of SLE patients (4). Furthermore, native DNA is usually considered non-immunogenic (5, 6); immunization with mammalian DNA could not induce pathogenic anti-dsDNA antibodies (7).

Currently, nucleosome, released by internucleosomal clearance of the chromatin during cell apoptosis, has been demonstrated in experimental as well as clinical levels to be the most reactive substrate among the nuclear antigens and plays a central role in both induction and pathogenicity of SLE including lupus nephritis (8-16). Antinucleosome antibodies are specifically induced by and react with only nucleosomes but not with its constituents DNA, and histones (2, 8). Furthermore, antinucleosome antibodies occur before the development of anti-dsDNA and anti-histone antibodies. Following studies have shown that antinucleosome antibodies possess high specificity for the disease (12, 13, 15) and could be positively detected in SLE patients lacking anti-dsDNA antibodies (17, 18). Of interest, the titers of antinucleosome antibodies excellently correlated with the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score (14, 19-21).

The correlation between antinucleosome antibodies and each serological markers as well as clinical activities, however, have been separately studied in several previous studies (4, 5, 7, 14, 15, 17-23). As such, the present study was carried out to assess, in the same study, the correlation between antinucleosome antibodies and anti-dsDNA, C3 as well as C4 components of complement, and the SLEDAI score.

Materials and methods

Patients and controls

The study was approved by the Ethics Research Committee of the Faculty of Medicine, Chulalongkorn University Hospital, Bangkok, Thailand. Each participating patient gave informed consent. Sixty-five patients from the outpatient and inpatient services of King Chulalongkorn Memorial Hospital, who fulfilled at least 4 of the American College of Rheumatology (ACR) revised criteria for SLE, were studied. To circumvent the drug effect on the levels of serologic markers (24), all the patients were newly diagnosed and did not receive corticosteroids and immunosuppressive drugs prior to the study. At each patient visit, clinical as well as biologic information was obtained and used to determine the SLEDAI score by the physicians. A blinded study, thus, the laboratory technician had no any information in disease activity of each individual patient before evaluating the correlation between serologic markers and disease activity. Active lupus was defined when the SLEDAI score was above 5 as previously described (25).

One hundred and eighty healthy blood donors (101 women, age range 17-53 years; mean 32 years; and 79 men, age range 19-58 years; mean 34 years) from the National Blood Bank Center; Thai Red Cross Society were collected and constituted as the control group. Five milliliters (mL) of blood sample from each patient were collected, and stored at -80°C until used.

Preparation of nucleosomes

Nucleosomes were basically prepared as previously described (12). Chicken erythrocytes were prepared from 1-2 mL of chicken blood by centrifuging at 800 g for 10 minutes at room tempera-
ture and the buffy coat was removed by suction. The erythrocyte pellet was washed 3 times with 10-fold excess, in a 15 mM Tris buffer containing 15 mM NaCl, 60 mM KCl, 2mM EDTA, 0.5 mM EGTA, 0.15 mg/ml spermine, 0.5 mM spermidine, 0.34 M saccharose, 15 mM 2-mercaptoethanol, and 0.2 mM phenylmethylsulfonyl fluoride (PMSF), for 10 minutes, 2,000 rpm at 4°C. The cells were lysed in washing buffer containing 0.5% Triton X-100, using 10 mL of buffer/ml of red blood cells, incubated 5 minutes, 4°C, and centrifuged for 10 minutes, 2,500 g at 4°C. The pellets were washed 2 times in a digestion buffer containing 50 mM Tris, 25 mM KCl, 4 mM MgCl$_2$, 1 mM CaCl$_2$, and 0.2 mM PMSF, using 10 mL of buffer/ml of red blood cells for 10 minutes, 2,000 rpm at 4°C. The pellets containing the nuclei were resuspended approximately in 1 mL of washing buffer/ml of starting volume of red blood cells and measured the concentration of DNA at OD 260 nm. Micrococcal nuclease (Sigma, USA) was added at the concentration of 40 IU/mg DNA and incubated at 37°C for 30 minutes and the reaction was terminated by addition of 0.2 M Na$_2$EDTA to a final concentration of 2mM.

The nuclei were pelleted at 2,500 g for 10 minutes, 4°C, resuspended in 1 mL of an extraction buffer/ml of starting volume of red blood cells, and, then homogenized in a tight-fitting dounce homogenizer. The homogenate was dialyzed against extraction buffer overnight at 4°C and centrifuged for 10 minutes, 27,000 g at 4°C. The supernatant was subjected to a gel filtration column (Sephacryl S-300; Pharmacia, Freiburg, Germany) equilibrated in 50 mM Tris, 0.25 mM EDTA, 0.02% NaN$_3$, and 0.2 mM PMSF, the volume should be in the range of 1-4% of the total bed volume of the column at a flow rate of 12 ml/h and collected the samples at 3 ml/fraction. Nucleosome fractions were collected by spectrophotometry after determination of the OD$_{260}$.

The fractions corresponding to pure mononucleosomes were concentrated on Amicon PM-30 filters (Amicon, Lexington, MA), and were stored at 4°C for no longer than 2 weeks.

Analysis by means of sodium dodecyl sulfate-polyacrylamide gel electrophoresis demonstrated the presence of core histones composing H2A, H2B, H3 and H4. Furthermore, nucleosomal DNA was monitored by agarose gel electrophoresis showing the presence of nucleosomal DNA at 154 bp.

**Determination of antinucleosome and anti-dsDNA antibody**

Antinucleosome and anti-dsDNA antibody determination were assessed by indirect enzyme-linked immunosorbent assay (ELISA) as previously described. Briefly, antigen-coated plates (5 ug/ml for each antigen) were washed with phosphate buffered saline (PBS)-0.05% Tween 20, pH 7.4 and blocked with PBS-0.05% Tween 20 (PBST) and 10% fetal calf bovine serum (FBS) for 2 hours at room temperature. The sera to be tested in dilution of 1:100 in PBST-10% FBS were added to the plates and then allowed to react for 2 hours. The plates were washed with PBST and incubated with dilution of 1:4000 peroxidase-conjugated anti-human IgG for 2 hours at room temperature. Binding was measured by adding peroxidase substrate (o-phenylenediamine) and OD was read at 492 nm. Since standard serum expressing as international unit was not available in our laboratory, in the present study, the cut off values for discriminating positive and negative antinucleosome and anti-dsDNA antibodies were set at the mean OD of healthy control+3SD. Positive and negative control for both antibodies were included in each run of the assay.

The intra- and interassay coefficients of variation were 8.2% and 9.4%, respectively for antinucleosome antibodies and were 5.4% and 8.8%, respectively, for anti-dsDNA antibodies.

**Detection of antinuclear antibodies**

Antinuclear antibodies were detected by indirect immunofluorescence assay using HEp-2 cell (Diasorin, Stillwater, MN, USA) as the substrate. Antibody titer equal to or greater than 1:40 was considered positive.

**Complement assays**

The levels of C3 and C4 complements were measured by nephelometry using the diagnostic kit (Behring AG, Marburg, Germany). The results were evaluated by comparison with a standard of known concentrations and the normal values for C3 and C4 were 76-171 and 10-40 mg%, respectively. CH50 was measured by standard hemolytic assay (normal 19-40 unit/mL).

**Statistical analysis**

Student’s t-test was used for comparisons of the means. The chi-square test was used to determine the significant levels of correlations. The correlation analysis was analysed by linear regression. Statistical significance was considered when p < 0.05.

**Results**

**Characterization of nucleosome preparations**

Preparation of nucleosomes was analyzed by gel electrophoresis. Nucleosomes were composed of DNA at 154 bp (Fig. 1A) and core histone bands at 16.5 kDa, 15 kDa, 13.5 kDa and 12 kDa for H3, H2A, H2B, and H4, respectively (Fig. 1B).

**Demographic data**

Of 65 participating patients, 63 were women (age range 16-62 years, mean ± SE 33 ± 4 years) and 2 were men (19 and 28 years). Forty-five patients had active SLE, the SLEDAI score above 5, while the remaining 20 subjects were inactive. Clinical presentations, according to the SLEDAI score, in patients with active SLE included alopecia (40%), new rash (22%), arthritis (20%), lupus headache (11%), mucosal ulcer (9%), pleurisy (9%), visual disturbance (7%), myositis (7%), fever (7%), organic brain syndrome (2%), and cerebrovascular accident (2%). By ACR criteria, lupus nephritis was identified in 36 patients.

**Detection and prevalence of antinucleosome and anti-dsDNA antibodies in SLE patients**

The activities of antinucleosome and anti-dsDNA antibodies were determined in 65 SLE patients and 180 healthy controls. The values of mean±SD of antinucleosome antibody activity, re-
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revealed as optical density, were significantly higher in SLE patients than normal controls (SLE patients 0.451 ± 0.447, controls 0.138 ± 0.031; p < 0.0001). The similar results were also noted in the case of anti-dsDNA antibodies (SLE patients 0.378 ± 0.364, controls 0.152 ± 0.044, p < 0.0001).

Of 65 SLE patients, 34 (52.3%) were positive for antinucleosome antibodies and 24 (36.9%) were positive for anti-dsDNA antibodies (p < 0.05). In contrast, none of the healthy controls were found to have these antibodies in their sera (Table I).

Next, the association between antinucleosome antibody activity and the disease activity were assessed. The levels of both antibodies, expressed as optical density, were depicted in Figure 2. Of 45 active SLE, 29 patient sera (64.4%) were positive for antinucleosome antibodies. In inactive SLE patients, 5 of 20 (25%) had antinucleosome antibody activities, indicating that active SLE patients had significantly higher positivity of these antibodies (p = 0.008).

Table I also illustrates the results of antinuclear antibodies, which were present in almost all (63/65; 96.9%) of SLE patients (100% in the active and 90% in the inactive group, respectively).

Complement assays in SLE patients

As demonstrated in Table I, 19 of 65 SLE patients (29.2%) were shown to have low C3 levels (range 22.9 – 74 mg%). Of these SLE patients with low C3 levels, 18 were in active SLE while the remaining one was inactive. Low C4 levels (range 6.0-8.7 mg%) were noted in 9 patients (13.9%), all of whom were active. CH50 levels were decreased in 27 SLE patients (41.5%), 24 of whom were active while the remaining three were in inactive state.

Association of antinucleosome antibodies with anti-dsDNA antibodies and complement C3, C4 levels

Of the 65 SLE patients, 18 (27.7%) exhibited both antinucleosome and anti-dsDNA antibodies. 16 (24.6%) were positive for only antinucleosome antibodies, 6 (9.2%) were positive for only anti-dsDNA, while the remainder 25 (38.5%) were all negative (Table I). It was interesting that the 16 patients who had only antinucleosome antibodies, 13 (81.3%) were in active state of SLE.

Table I. Prevalence of antinuclear, anti-dsDNA, antinucleosome antibodies, and complement assays (C3, C4, and CH50) in SLE patients.

<table>
<thead>
<tr>
<th>Presence of autoantibody</th>
<th>No. (%)</th>
<th>Decreased level of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. tested</td>
<td>ANA</td>
</tr>
<tr>
<td>SLE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>Inactive</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>63</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>180</td>
<td>ND</td>
</tr>
</tbody>
</table>

*ANA-antinuclear antibodies were detected by indirect immunofluorescence on HEp-2 cell, anti-dsDNA and antinucleosome antibodies were detected by ELISA, C3 and C4 levels was determined by nephelometry, *p < 0.01 when compared with inactive patients, **p < 0.001, †p < 0.05 when compared with anti-dsDNA.
DNA-positive sera had low C3 and C4 levels, respectively. In contrast to inactive SLE, none of the 3 anti-dsDNA-positive sera were found to have low complement C3 as well as C4 levels.

**Correlation between antinucleosome antibody activity and anti-dsDNA antibody activity**

In further examining the correlation between these 2 antibodies, the data demonstrated that the antinucleosome antibodies were significantly correlated with the anti-dsDNA antibodies in SLE patients ($r = 0.82$, $P < 0.0001$) (Fig. 3). The discrepancies of the results of these 2 antibodies were clearly observed in most of these patients, only very few were shown weakly positive (as indicated by OD) for antinucleosome antibodies with negative anti-dsDNA antibodies or vice versa.

**Correlation between antinucleosome, anti-dsDNA antibody activity and SLEDAI**

The simple regression analysis was used to identify the correlation between antinucleosome and anti-dsDNA antibody activity, expressed as OD unit, and the SLEDAI score. Antinucleosome antibody activity in SLE was significantly correlated with SLEDAI ($r = 0.33$, $P = 0.007$) (Fig. 4A). Similar results were also noted between anti-dsDNA antibody activity and SLEDAI ($r = 0.37$, $P = 0.002$) (Figure 4B).

**Detection of antinucleosome, anti-dsDNA antibodies, C3, C4, and CH50 levels in SLE patients with and without lupus nephritis**

From the 65 SLE patients studied, 36 (55.38%) were found to have lupus nephritis. As shown in Table III, the presence of antinucleosome antibodies was significantly higher in lupus nephritis when compared to non-lupus nephritis patients (63.9% vs. 37.9%, $p < 0.05$). No significant difference was noted in the presence of anti-dsDNA antibodies in both lupus nephritis and non-lupus nephritis patients. The levels of C3, C4, and CH50 were not significantly different between the both groups although the low levels of CH50 seemed to be a more sensitive marker in lupus nephritis than in non-lupus nephritis group (47.2% vs. 34.5%, NS).

**Discussion**

Nucleosome is a large macromolecular complex comprised of a 154 base-pair DNA, wrapping around a core histone octamer, with a relative molecular mass of 250 kDa. Recent evidence obtained in murine models of SLE suggests that nucleosome is a preferential target for lupus autoantibodies and a putative autoantigen triggering the production of antibodies against its components, dsDNA and histones (22). This nucleosome is emerging as the most reactive substrate among the nuclear antigens in SLE, since 48-80% of SLE patients are found to have antibody response to nucleosomes (12-15).

For a long time, “naked” dsDNA has been believed to be the major autoantigen in SLE. As a consequence, most of the studies on sensitivity and specificity have focused on anti-dsDNA antibodies. Nevertheless, dsDNA does not behave as such in vivo and also has poor immunogenicity in animal models (4-7). Indeed, DNA outside the cell is generally present in the form of nucleosomes generated by apoptosis (10, 16, 22). Thus, nucleosomes appear to be the particles that provide DNA in vivo, possibly making the DNA immunogenic when is not properly eliminated. Apoptosis defects are well known to be

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**Table II.** Number (percentage) of antinucleosome and anti-dsDNA antibodies in 65 SLE patients.

<table>
<thead>
<tr>
<th>Antinucleosome Antibodies</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>18 (27.7)</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>16 (24.6)</td>
<td>25 (38.5)</td>
</tr>
</tbody>
</table>
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In the present study, the nucleosomes, prepared from the chicken erythrocyte nuclei, consisted of nucleosomal DNA banding at 154 base pairs and the core histone bands at molecular masses of 16.5k (H3), 15k (H2A), 13.5k (H2B), and 12k (H4) without the presence of H1 linker protein (31k) or any other contaminant proteins. This indicates that this preparation yielded “intact” and highly purified mononucleosome core particles.

In this report, the correlation between antinucleosome antibodies, anti-dsDNA antibodies, C3, C4, and the SLEDAI score were simultaneously evaluated in 65 SLE patients and compared with 180 healthy controls. Antinucleosome antibodies were presented in 34 patients (52.3%). The results were similar to that of the previous works in which the figure of 48-80% had been reported (12-15). The frequency was lower for anti-dsDNA, 24 patients (36.9%) were found to be positive by the anti-dsDNA ELISA. Of the 180 healthy controls, none was revealed for antinucleosome as well as anti-dsDNA positivity.

The present data also suggest that the production of anti-dsDNA antibodies would be associated with that of antinucleosome antibodies (Fig. 3). One reason for this circumstance could be that most anti-dsDNA antibodies will also react with nucleosomes. Indeed, in the 24 anti-dsDNA positive SLE sera tested, anti-dsDNA activity was detected in concomitant with antinucleosome antibody activity in 75% (18/24) of patients. Interestingly, in SLE patients with anti-dsDNA negative sera, it had been reported that 60-65% of this group showed antinucleosome antibody activity (16,23). In the present study, 16 of 34 sera (47.1%) were shown to react with nucleosomes detected by ELISA without positivity for anti-dsDNA antibodies, supporting the view that the antinucleosome antibodies could be a reliable and accurate marker for anti-dsDNA negative SLE. However, 6 of 24 SLE patient sera (25%), which had anti-dsDNA antibody activity without exhibiting activity to nucleosomes, were present. According to the kinetic analysis of autoantibody production in lupus-prone mice, it had been demonstrated that the nucleosome-specific antibodies occurred early in the disease and preceded the formation of anti-dsDNA and anti-histone antibodies (11). In human SLE, of interest, changes in levels of anti-dsDNA, rather than absolute levels, have been shown to reflect new disease activity (2, 26, 27). It might be possible that the levels of these antibodies may fluctuate and convert from positive to negative and vice versa during the disease course. Further longitudinal studies are required.

Recent accumulating evidence suggests that antinucleosome antibodies are related to the SLE pathogenic pro-
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Table III. Results of antinucleosome antibodies, anti-dsDNA antibodies, levels of C3, C4 and CH50 in SLE patients with and without lupus nephritis.

<table>
<thead>
<tr>
<th></th>
<th>Lupus nephritis (n = 36)</th>
<th>Non-lupus nephritis (n = 29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinucleosome antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>23 (63.9%)</td>
<td>11 (37.9%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Negative</td>
<td>13 (36.1%)</td>
<td>18 (62.1%)</td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>13 (36.1%)</td>
<td>11 (37.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Negative</td>
<td>23 (63.9%)</td>
<td>18 (62.1%)</td>
<td></td>
</tr>
<tr>
<td>C3 level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>11 (30.6%)</td>
<td>8 (27.6%)</td>
<td>NS</td>
</tr>
<tr>
<td>Normal</td>
<td>25 (69.4%)</td>
<td>21 (72.4%)</td>
<td></td>
</tr>
<tr>
<td>C4 level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>5 (13.9%)</td>
<td>4 (13.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Normal</td>
<td>31 (86.1%)</td>
<td>25 (86.2%)</td>
<td></td>
</tr>
<tr>
<td>CH50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>17 (47.2%)</td>
<td>10 (34.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Normal</td>
<td>19 (52.8%)</td>
<td>19 (65.5%)</td>
<td></td>
</tr>
</tbody>
</table>

P values are lupus nephritis versus non-lupus nephritis patients. NS = not significant.

In this regard, we found that, in 45 active SLE patients, 29 (64.4%) were positive for antinucleosome antibodies. Further analysis in inactive SLE patients revealed that only 5 of 20 (25%) patient sera showed antinucleosome antibody positivity. A previous study showed much higher occurrences of antinucleosome antibodies in active (100%) than inactive SLE patients (25%) (7). The higher frequency of active SLE than the present study might be explained by the much smaller sample size (n = 12 in active SLE group used in the previous report). The evidence of participating in the pathogenic process of antinucleosome antibodies was emphasized by the higher frequency of this antibody found in lupus nephritis patients when compared to non-lupus nephritis group. The percentage of antinucleosome antibodies were also higher than other serologic markers (anti-dsDNA, C3, C4 and CH50 levels) in this study. The results suggested that detection of antinucleosome antibodies is superior to other markers in lupus nephritis. Further analysis for the isotype of antibody might be more meaningful, since it has been demonstrated that the antinucleosome IgG3 subclass is present at high levels in patients with active SLE but undetectable in inactive patients (15). The levels of IgG3 antinucleosome also exerted a positive correlation with disease activity and were found to be closely associated with lupus nephritis. On the contrary, no significant correlation was observed between the disease activity and IgG3 anti-dsDNA (15).

In the present study, by using SLE Disease Activity Index (SLEDAI), both antinucleosome and anti-dsDNA antibody activities in SLE patients were comparable to have correlation to disease activity, (r = 0.33, P = 0.007 and r = 0.37, P = 0.002 respectively). In this regard, strong correlation was also noted between antinucleosome and anti-dsDNA antibody activities (r = 0.82, P < 0.0001). The present data are in agreement with many previous studies in which antinucleosome antibodies were found to correlate with the disease activity and anti-dsDNA antibodies (4, 5, 14, 17, 18, 22).

Recent studies have reported that only few connective tissue diseases in which antinucleosome antibodies are detected are bound to histone. This includes SLE, especially in those that anti-dsDNA antibodies are undetectable. In the present study, except antinuclear antibodies, antinucleosome antibodies were the most sensitive marker in SLE patients when compared with other markers. Of more importance, their detection was significantly correlated with the disease activity. The use of antinucleosome antibody measurement as a marker of disease activity deserves further large-scale evaluation.

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