Antibodies against nuclear antigens: Association with lupus nephritis[1]

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The predictive value of serological markers for the presence of Class IV (diffuse proliferative) glomerulonephritis in systemic lupus erythematosus (SLE) was investigated in a group of 96 patients with SLE. All patients with proteinuria greater than 1 g/24 hr, and/or urine sediment containing cellular casts or more than 6 erythrocytes/high-power field, and/or serum creatinine greater than 1.5 mg/dL (51 patients) underwent renal biopsy. Sixteen patients had Class IV glomerulonephritis. The combined presence of anti-native DNA, anti-Sm, and anti-RNP had a positive predictive value of 50.0% for Class IV nephritis ($p = .0031$), while the predictive value of negative anti-native DNA for absence of Class IV nephritis was 97.4% ($p = .0019$). We conclude that serological markers can be helpful in determining the need for renal biopsy in SLE.

Index terms: Glomerulonephritis • Lupus erythematosus, systemic

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Systemic lupus erythematosus (SLE) is a disease whose severity varies greatly. Some patients deteriorate rapidly, eventually dying of renal, central nervous system, or other target-organ destruction, often despite aggressive therapy. Other patients have milder disease that requires minimal therapy and does not appear to shorten life. In most cases SLE is characterized by exacerbations and remissions. During exacerbations aggressive treatment may be employed in an attempt to prevent irreversible renal damage, whereas during remissions only minimal treatment may be required. Because of this variability, reliable predictors of outcome in a given patient would be extremely useful to determine

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the appropriate degree of vigilance and the necessity for potentially toxic treatment.

Many serological abnormalities have been described in SLE. The most characteristic of these are the antinuclear antibodies (ANA), of which the most specific for the diagnosis of SLE are anti-native DNA (anti-nDNA) and anti-Sm.[1] Anti-nDNA has been implicated in the pathogenesis of certain manifestations of SLE, particularly glomerulonephritis.[2] However, it has been suggested that the presence of anti-nDNA does not carry a high positive predictive value for severe lupus nephritis,[3,4] and our previous results,[5] as well as those presented here, confirm this. Studies of the effects of other ANAs on the likelihood of severe lupus nephritis have yielded conflicting results, and the prognostic value of determining the presence of these antibodies remains controversial.

The present study was undertaken in an attempt to determine the predictive values of testing for anti-nDNA, anti-ribonucleoprotein (RNP), anti-Sm, anti-SS-A (Ro), and anti-SS-B (La) for severe lupus nephritis in a cohort of patients who were followed at one institution for an adequate length of time and who underwent renal biopsies if there were any indications of active nephritis. We found that renal biopsy class had a close relationship to ultimate outcome and that the combined presence of anti-Sm, anti-nDNA, and anti-RNP had the highest positive predictive value for severe lupus nephritis (class IV biopsy, diffuse proliferative glomerulonephritis). We also found that the absence of anti-nDNA had a high predictive value for a benign renal course. Other serological markers had little relationship to the presence or absence of renal disease, its severity, or ultimate outcome.

Materials and methods

Patients

The patient population for this study was drawn from 103 individuals who fulfilled the American Rheumatism Association criteria for the diagnosis of SLE,[6] who were examined at the Cleveland Clinic between 1977 and 1981, and for whom complete serological data were available. Fifty-eight of these patients met the criteria for renal biopsy (proteinuria of at least 1.0 g/24 hr, and/or hematuria of at least 6 erythrocytes/high-power field, and/or cellular casts, and/or serum creatinine of 1.6 mg/dL or higher). Fifty-seven patients agreed to renal biopsy, and these biopsies were carried out by either open or closed (needle) technique. All biopsy materials were reviewed by one of us (GNG) without knowledge of the serological findings and were classified according to the World Health Organization classification scheme.[7] Biopsies in 51 patients were considered adequate for classification; the other six could not be classified with certainty. Thus, the final study population consisted of 96 patients, 45 of whom had no clinical or laboratory evidence of renal disease and therefore did not undergo biopsy, and 51 of whom had renal biopsy results that could be classified. There were 78 females and 18 males in the study population.

Serological testing

Anti-nDNA was measured using a modification of the Farr radioimmunoassay. Calf thymus DNA, labelled with I-125 by the thallium trichloride method,[8] was passed twice through nitrocellulose filters (0.45 μm pore size) to minimize single-strandedness. Duplicate reaction mixtures containing 1 μg I-125-labelled DNA and 0.05 mL heat-inactivated (56° C for 30 min) test serum in a total volume of 1.0 mL (0.02 M PBS, pH 7.4) were incubated overnight at 4° C. Bound I-125-labelled DNA was then precipitated by adding 1.0 mL cold saturated ammonium sulfate, pH 7.4, mixing, and incubating at 4° C for 1 hour. Precipitates were collected, washed twice with cold 50% saturated ammonium sulfate solution, redissolved in PBS, and counted in a gamma counter. For each batch of labelled DNA, the upper limit of normal (ULN) was defined as the mean + 2 standard deviations of values obtained on 50 normal subjects, and the following formula was used to calculate the normalized result:

$$\textit{Normalized nDNA binding}\ (\%) = 100 \times [(100 \times \textit{cpms/cpmt}) - \textit{ULN}]/(100 - \textit{ULN})$$

where *cpms* = sample counts per minute and *cpmt* = total counts per minute in the added DNA. Performed as described here, this assay has been compared with other standard anti-DNA assays,[9] a solid-phase radioimmunoassay for nDNA-binding immunoglobulins,[10] and quantitative assessments of suppressor-cell function in SLE.[11] In our laboratory the upper limit of normal for this assay is 10% binding, and values above this are considered strongly suggestive of the diagnosis of SLE.

Antibodies against ribonucleoprotein (RNP), Sm, SS-A, and SS-B were detected by double diffusion in agarose. An aqueous extract of rabbit thymus was used as antigen for detection of anti-RNP, and ribonuclease-treated rabbit thymus extract was used as antigen for detection of anti-Sm and anti-SS-B.[12] Human spleen extract was used as antigen for detection of anti-SS-A.[13] All sera that produced precipitin lines against these extracts were retested adjacent to monospecific standard sera, and antibody identification was made by observation of lines of identity. In some cases we noted lines that were not identical to any of the standard sera containing the specificities listed above; these were recorded as "anti-other".

Statistical analysis

Student's t test was used to compare mean anti-nDNA levels in various subgroups. The chi-square test was used to compare frequencies of occurrence of the qualitatively determined antibodies in the various subgroups. Predictive values were calculated as described by Galen and Gambino;[14] positive predictive value = 100 × (true positives/all positives); negative predictive value = 100 × (true negatives/all negatives); efficiency = 100 × (true positives + true negatives)/all tests performed.

Results

The patients were divided into six groups according to renal status. Group 0 consisted of 45 patients who exhibited no indications for renal biopsy and on whom no biopsy was done. The other 51 patients had renal biopsies, which were classified according to the World Health Organization nomenclature. Group 1 (6 patients) had normal biopsies (Class I: no abnormalities on light microscopy, no immunohistologically detectable glomerular deposits of immunoglobulins or complement, and no electron-dense deposits on electron microscopy). Group 2 (19 patients) had mesangial glomerulonephritis (Class II; variable mesangial proliferation on light microscopy, deposits limited to the mesangium on immunohistologic and electron microscopic examination). Group 3 (7 patients) had focal proliferative glomerulonephritis (Class III: similar to Class II except for the presence of segmental endothelial proliferation occluding glomerular capillary lumina, necrosis, and/or crescent formation). Group 4 (16 patients) had diffuse proliferative glomerulonephritis (Class IV: variable hypercellularity, usually with prominent mesangial/endothelial proliferation and reduplication of glomerular basement membrane, necrosis and/or wire loop formation on light microscopy, prominent immunohistologically detectable deposits in peripheral glomerular basement membrane as well as mesangium, and prominent subendothelial as well as mesangial dense deposits on electron microscopy). Group 5 (3 patients) had membranous glomerulonephritis (Class V: thickening of the glomerular basement membrane on light microscopy, immunohistologically detectable deposits in peripheral glomerular basement membrane, and prominent diffuse epimembranous dense deposits on electron microscopy).

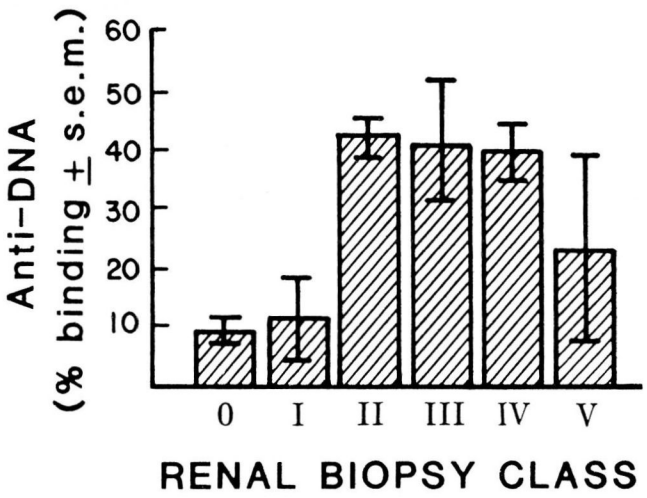

Figure. Comparison of mean anti-nDNA levels in SLE patients grouped according to renal biopsy results (0 = unbiopsied patients with no clinical evidence of renal disease; I = normal biopsy; II = mesangial glomerulonephritis; III = focal proliferative glomerulonephritis; IV = diffuse proliferative glomerulonephritis; V = membranous glomerulonephritis).

Serological testing was carried out on the study population. Anti-nDNA levels greater than 10% binding were found in 57.9% of the patients. For the precipitating antibodies positive tests were obtained in 34.3% of the patients for anti-RNP, 21.8% for anti-Sm, 37.9% for anti-SS-A, and 16.7% for anti-SS-B. Other precipitating antibodies were detected in 19.8% of the patients. Many patients had more than one antibody, and, as can be seen in *Table 1*, these were not randomly distributed. Positive associations were found between anti-RNP and anti-Sm as well as between

Table 1. Combinations of autoantibodies in SLE

Combinations	Frequencies (%)		p (chi-square)
	Expected	Actual	
RNP + Sm	7.5	21.7	.00005
RNP + SS-B	6.8	10.4	.009
RNP + SS-A	13.2	17.9	.05
RNP + nDNA	20.1	22.1	.4
Sm + SS-B	3.6	0	.02
Sm + SS-A	8.4	10.5	.3
Sm + nDNA	12.6	14.7	.4
SS-B + SS-A	9.3	8.4	.3
SS-B + nDNA	9.1	10.5	.5
SS-A + nDNA	22.4	25.5	.2

anti-RNP and anti-SS-B, and the positive association between anti-SS-A and anti-RNP approached significance. There was a significant negative association between anti-Sm and anti-SS-B. Of particular interest is the absence of a negative association between anti-nDNA and anti-RNP.

Comparison of mean anti-nDNA levels among the six groups of patients is shown graphically in the *Figure*. Clearly the patients in groups 0 and 1 (no renal disease) had significantly lower mean anti-DNA levels [9.4 ± 1.9% (s.e.m.)] than the patients in groups 2–5 [39 ± 3.1% ($p = 10^{-7}$)]. There were no significant differences between groups 0 and 1 or among groups 2, 3, 4, and 5.

The frequency of occurrence of precipitating antibodies in each of the groups is shown in *Table 2*. The prevalence of anti-Sm is significantly increased in patients with class III or IV renal biopsies (39.1% positive, compared with 16.4% positive in the remaining groups, $p = .02$). Thus, once the diagnosis of lupus is made, the predictive value of positive anti-Sm for a class III or IV biopsy is 42.9%, while the negative predictive value is 81.3% for a test efficiency of 72.9%. Since the odds in favor of a class III or IV biopsy simply from having made the diagnosis of SLE are about 1:4 (24.0%), the risk for the patients with positive anti-Sm of having a class III or IV biopsy is increased 1.8 times, or nearly doubled. As can be seen in *Table 3*, the positive predictive value of anti-Sm for a class IV biopsy, which carries the worst prognosis, is 28.6% with a negative predictive value of 86.7% and efficiency of 74.0%. Since the risk of a class IV biopsy in this study was about 1:6 (16.7%) overall, the presence of anti-Sm increases the likelihood of a class IV biopsy slightly over 1.7 times.

Table 2. Association of renal biopsy class with precipitating antibodies

Biopsy Class	Number	Positive Reactions to Precipitating Antibodies (%)				
		RNP	Sm	SS-A	SS-B	Other
0	45	24.4	17.8	35.6	15.6	17.8
I	6	16.7	16.7	20.0*	16.7	33.3
II	19	42.1	10.5	42.1	21.1	10.5
III	7	42.9	42.9	42.9	14.3	28.6
IV	16	43.8	37.5	37.5	12.5	31.2
V	3	100	33.3	66.7	33.3	0

* $n = 5$.

However, the combined effect of positive anti-Sm, anti-DNA, and anti-RNP provides the most powerful positive predictive value for a class IV biopsy (50.0%) with a negative predictive value of 87.1% and efficiency of 83.2%. With all three of these tests positive the risk of a class IV biopsy is increased 2.99 times ($p = .0031$). Although the negative predictive value (any or all of the tests negative) for this combination is not particularly strong, a negative anti-nDNA test reduces the likelihood of a class IV biopsy from 1:6 (16.7%) to 1:40 (2.5%).

Patient outcomes (*Table 4*) were determined by review of the clinical records. Outcome points were defined as (*a*) the date of the last follow-up visit for stable patients with preserved renal function, (*b*) the date of determination that a patient had end-stage renal failure, or (*c*) the date of death. Stable patients were divided into those with or without azotemia (not requiring dialysis). Mean duration of follow-up for patients not undergoing biopsy (from initial visit to outcome point) was 8.86 ± 0.9 (s.e.m.) years, and for those patients undergoing biopsy (from biopsy to outcome point) was 4.39 ± 0.4 years.

During the follow-up period 24 patients either died or reached end-stage renal failure, and three more had stable, mild-to-moderate azotemia, not requiring dialysis. Sixteen of the deaths were attributed to causes other than SLE nephritis.

Nine of the deaths were in group 0; the average age of these patients at death was 64 ± 4 (s.e.m.) years; five died of myocardial or cerebral infarctions thought to be atherosclerotic in origin. Causes of death in the other four patients included cardiac failure due to failed aortic valve replacement, pulmonary embolism, carcinoma of the bladder (in a patient treated several years previously with chlorambucil for central nervous

system lupus), and miliary tuberculosis (in a patient receiving corticosteroid therapy); the latter two deaths may have been treatment-related.

Among patients undergoing biopsy there were no occurrences of death or renal failure in group 1. In group 2 one patient reached end-stage renal failure 2 years after biopsy, and three other patients died of nonrenal causes (intractable central nervous system lupus, sudden unexplained death at home with no autopsy granted, cerebral infarction). In group 3 one patient reached end-stage renal failure within a few weeks of biopsy, and in another patient stable azotemia developed. In group 5 one patient had end-stage renal failure.

Group 4 patients fared worse than other patients in this study. Of the sixteen patients in this group, five had end-stage renal failure after a mean follow-up period of 2 years. Two other patients are being followed who had stable azotemia not requiring dialysis. Four additional patients have died of causes other than SLE nephritis (hepatic failure, perioperative anesthesia-related death, congestive heart failure due to myocardiopathy, pneumonitis). Thus, after a mean follow-up period of less than 4 years, over half the patients in this group were dead, receiving chronic dialysis, or had undergone renal transplantation, and two others had tenuous renal function. If we consider only those who reached end-stage renal failure or chronic azotemia as having had a "bad renal outcome," patients whose biopsy results were class IV did significantly ($p = 4 \times 10^{-6}$) worse than the other patients in this study. Within this group, however, serological markers were not predictive of outcome.

Discussion

The nature of the renal involvement in SLE largely determines the overall prognosis of the patient, and it is clear from this study and others that evaluation of an adequate renal biopsy specimen can give useful information pertaining to this.[15] Causes of death were unrelated to SLE in our patients who died but did not have glomerulonephritis. However, the majority of patients whose renal biopsies were class IV did poorly despite (or in some cases, perhaps, because of) aggressive therapy. The purpose of this study was to determine the nature and degree of correlation of serological findings with renal histopathologic findings (and, hence, prognosis).

Table 3. Predictive values for Class IV biopsy

Autoantibody Specificities	Predictive Values (%)		p	Risk Factor*	
	Positive	Negative	(chi-square)	Pos.	Neg.
Unknown	16.7	83.3	—	—	—
nDNA	26.8	97.4	.0019	1.60	.16
RNP	21.2	85.7	.39	1.27	.86
Sm	28.6	86.7	.098	1.71	.80
SS-A	16.7	83.1	.77	1.00	1.01
SS-B	12.5	82.5	.62	.75	1.05
Sm + nDNA	42.9	87.7†	.0049	2.57	.74
Sm + RNP	33.3	86.4	.059	1.99	.81
Sm + nDNA + RNP	50.0	87.1	.0031	2.99	.77
SS-A + SS-B	12.5	82.8	.73	.75	1.03

* Positive result, risk factor = positive predictive value/16.7. Negative result, risk factor = (100 − negative predictive value)/16.7.

† Negative result for a combination of tests = one or more results negative.

The diagnostic utility of antibodies against nDNA and Sm in SLE is well established;[16] these antibodies have the highest specificities and, therefore, the highest positive predictive values of all the antinuclear antibodies for the diagnosis of SLE.[17] Furthermore, a pathogenic role has been attributed to anti-nDNA in lupus nephritis, and this antibody is usually present in patients with active lupus nephritis.[2] The mechanism by which this is thought to occur is through formation of DNA:anti-DNA immune complexes that deposit or form *in situ* in the renal glomerulus, leading to destructive inflammation through complement activation.[18] Our study confirms the presence of anti-nDNA in the majority of SLE patients with nephritis, whether or not the nephritis is severe. However, anti-nDNA is also present in some patients with no evidence of nephritis. Thus, anti-nDNA has a high negative

Table 4. Outcome data

Group	Follow-up* (Yr ± s.d.)	End-stage Renal Disease	Stable Azotemia	Other Deaths	Total
0	8.86 ± 6.02	0/45	0/45	9/45	9/45
1	2.80 ± 1.30	0/6	0/6	0/6	0/6
2	4.36 ± 3.51	1/19	0/19	3/19	4/19
3	5.71 ± 2.50	1/7	1/7	0/7	2/7
4	3.74 ± 3.02	5/15	2/15	4/15	11/15
5	4.50 ± 4.95	1/3	0/3	0/3	1/3

* For patients who underwent biopsy, the overall mean follow-up period (from biopsy to outcome point, ie, death, dialysis, or the last follow-up visit in the case of patients not in end-stage renal failure) was 4.39 ± 3.18 years.

but low positive predictive value for severe glomerulonephritis in SLE.

Although other antinuclear antibodies, including anti-RNP, anti-Sm, anti-SS-A, and anti-SS-B, have been eluted from nephritic kidneys,[19] their role (if any) in pathogenesis is not so clear. Thus far, the presence of these antibodies has not been so closely associated with nephritis as has that of anti-nDNA. Indeed, anti-RNP and anti-Sm have been considered by some investigators to have benign prognostic significance,[20,21] though not all have concurred in this. Barada et al,[22] in a study of 30 patients, concluded that Sm antibody was not a marker for mild disease. Ginsburg et al[23] and Munves and Schur[24] found a tendency for patients with renal disease to have positive tests for anti-Sm but did not discuss renal biopsy data, so that the nature and severity of the renal disease are difficult to assess. Furthermore, in the latter study, not all patients had SLE, and the association of nephritis with anti-Sm could trivially be due to the association of both anti-Sm and nephritis with SLE, as opposed to the other diagnoses represented in the series. Possible reasons for conflicting results of various studies of this question have been suggested by Beaufils et al,[21] and include differences in criteria for patient selection and differences in methods of antibody detection.

Anti-RNP has its greatest value in the diagnosis of mixed connective tissue disease, a syndrome with benign renal prognosis compared with classical SLE.[25] Initially the presence of anti-RNP was considered to favor benign prognosis in SLE as well, principally because of an inverse relationship with anti-nDNA;[26] however, our study failed to reveal a negative association of anti-RNP with either anti-nDNA or SLE nephritis. Moreover, we detected no significant positive or negative relationship between severe nephritis and anti-SS-A and/or -SS-B.

This study clearly shows a significant association between diffuse proliferative (ie, WHO Class IV) glomerulonephritis in SLE and the combined presence of anti-nDNA, anti-Sm, and anti-RNP. The presence of this combination of antibodies is associated with a three-fold increase in the risk of diffuse proliferative glomerulonephritis. The reason for this, however, remains obscure. Anti-Sm and anti-RNP could participate in immune complex formation in a manner similar to anti-nDNA, and anti-Sm has been shown to have complement-activating capacity;[27] although these antibodies have been identified in renal eluates, RNP and Sm antigens have not. Alternatively, such antibodies, if they could gain entrance to cells, might disrupt cellular function by interfering with translation of genetic information through messenger RNA. This could cause a variety of problems, including dysregulation of immune function and possibly a more severe autoimmune response.

For practical purposes, these data help in assessment of the degree to which a patient with SLE is at risk for severe glomerulonephritis. The presence of the combination of anti-nDNA, anti-Sm, and anti-RNP or of anti-nDNA and anti-Sm should encourage greater vigilance in monitoring disease activity, and liberal use of renal biopsy in evaluation of such patients seems justified. On the other hand, absence of anti-nDNA is rarely associated with severe glomerulonephritis, and unless significant renal findings are present, biopsy is probably not indicated in anti-nDNA-negative patients. Nonetheless, it must be recognized that these are not all-or-none phenomena. Detailed knowledge of the antinuclear serologic status of a given patient allows a more intelligent approach to patient care through increased accuracy of risk assessment.

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