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Significance of Antinuclear Antibody (ANA) Immunofluorescent Patterns and Titers in Systemic Lupus Erythematosus Nephritis

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Seventy-three patients with systemic lupus erythematosus (SLE) nephritis were studied for up to eight years using sequential serologic and renal function tests and renal biopsies. Antinuclear antibody (ANA) patterns and titers were classified into two systems: nonparticulate and particulate. We found a close relationship between disease activity and changes in titers of the nonparticulate peripheral homogeneous system. These changes predicted imminent flare-up or immunosuppressive induced remission of nephritis. Patients with the thready ANA pattern (part of the particulate system) as the main pattern showed a predominant association with membranous glomerulopathy and better renal function than those without threads. The association of the thready pattern with relatively benign disease suggests that patients with this pattern may represent a benign subset in the spectrum of renal SLE. (Henry Ford Hosp Med J 1988;36:121-9)

Various nuclear immunofluorescent patterns have been identified by indirect immunofluorescence employing human spleen imprints as substrate (1,2). Two systems of antinuclear antibody (ANA) patterns can be identified: nonparticulate and particulate (Fig 1, Table 1). The nonparticulate patterns consist of general ANA which is reactive with various different nuclei and leukocyte-specific ANA (LSANA) reactive only with granulocytic nuclei. The nonparticulate system, both general and leukocyte-specific, is further subdivided into the shrunken peripheral, peripheral, and homogeneous patterns. The particulate system, so-called because stained particles can be demonstrated (3), includes the thready and the speckle-like thready patterns. The patterns classified as particulate in this study were all of the general ANA class. A relationship between certain ANA patterns and specific connective tissue diseases has been shown previously (1). Subsequently, the correlation between the different patterns and the clinical manifestations of systemic lupus erythematosus (SLE) has been studied (4). Patterns were classified into those of poor, intermediate, or good prognostic significance with reference to the prevalence of renal disease. Patients with the shrunken peripheral pattern had a poor prognosis in that at least 60% had clinical renal involvement. In the intermediate prognostic group, which consisted of the peripheral, thready, and homogeneous patterns with titers of 160 or greater, approximately one third of the patients had renal disease. The good prognostic group was comprised of patients with large and small speckle-like threads. Only three of 73 SLE patients had large speckle-like threads as their main pattern. If these latter patterns were the only ones seen in the face of active disease, the likelihood of renal involvement was very small even in the presence of titers as high as 10,240 of the large speckle-like threads.

Special Note—This work is the culmination of the pioneer studies done by Thomas K.H. Burnham, MB, BS (London), and coworkers at Henry Ford Hospital over a period of 26 years. Highlights of this work included the discovery of the lupus band in 1963, now used in the "lupus band test," and the original finding and determination of the clinical significance of several nuclear immunofluorescent patterns in the connective tissue disease.

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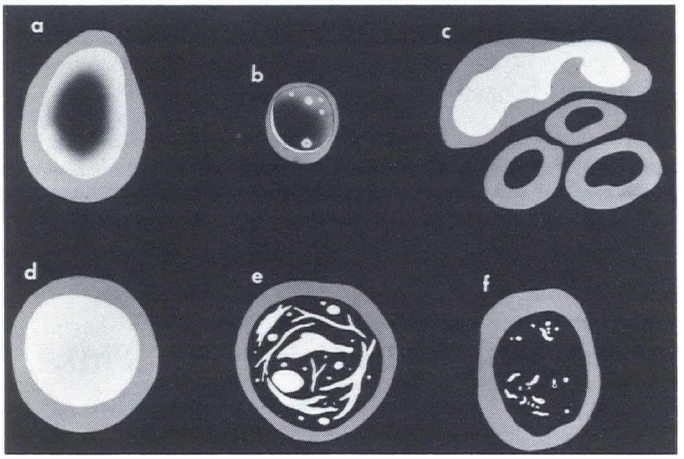

Fig 1—Diagrams of major ANA patterns. A. Peripheral general: a bright outer edge is seen with gradual darkening from the inner border to the dark center. B. Shrunken peripheral general: nucleus is only about one-third the usual size found with other patterns and consequently has a shrunken appearance. C. Homogeneous leukocyte-specific: one granulocytic nucleus is seen fluorescing intensely while the nongranulocytic nuclei are negative. D. Homogeneous general: diffuse fluorescence of the whole nucleus is present. E. Threads: irregularly shaped clumps, threads, and round structures of different sizes illustrate this pattern. F. Large speckle-like threads: note asymmetrically distributed small round and elongated thread-like structures.

Table 1
Classification of ANA Patterns*

Nonparticulate Patterns†
General ANA
Shrunken peripheral
Peripheral
Titer 160 or greater
Homogeneous
Titer less than 160
Leukocyte-specific ANA
Shrunken peripheral
Peripheral
Titer 640 or greater
Homogeneous
Titer less than 640
Particulate Patterns†
Threads
Large speckle-like threads
Small speckle-like threads
Other particulates: significance in SLE so far unknown
Nucleolar and speckles—not seen in SLE

*From References 1 and 4.
†Modified from Reference 3.

These findings suggested that certain ANA patterns may serve as immunological markers for different clinical subsets in the connective tissue diseases. This has been confirmed recently both in lupus erythematosus (LE) and scleroderma. In LE, the larger speckle-like thready pattern was found to be a marker for a benign subset (5). These patients have only generalized skin lesions with or without joint involvement. The large speckle-like thready pattern has been found to be closely related to, but possibly not actually produced by, antibodies to the cellular antigen RO (6). In scleroderma the "true speckled" ANA pattern which represents the anticentromere antibody (7,8) is a marker for a benign subset of scleroderma (9). These patients all had benign disease, the majority having acrosclerosis without pulmonary, cardiac, or renal involvement. As certain ANA patterns are therefore markers for relatively broad clinical subsets, we wished to determine if any ANA patterns could also serve as immunological markers for narrower clinical subsets such as different types of renal involvement in patients with SLE.

Various attempts have been made to correlate other laboratory data with the activity and severity of lupus nephritis (10). Studies have shown that circulating DNA-anti-DNA complexes disappear with remission of active SLE (11,12). Patients with IgG containing anti-DNA antibodies have renal disease of greater severity than those with IgM anti-DNA antibodies (13).

We have found that the nonparticulate system is more closely related to disease activity than is the particulate system. Most authors have not made such a differentiation which may be why they failed to recognize a relationship between ANA titers and disease activity in SLE (14-17). However, we have demonstrated relationships between the particulate system represented by the thready ANA pattern and specific histological diagnoses in patients with SLE nephritis.

In this study we correlated specific ANA patterns and titers with the clinical activity and severity of SLE as shown by histopathology and evaluation of renal function.

Materials and Methods

Patients

We studied 73 patients with SLE. Sera for ANA determinations were obtained when possible before immunosuppressive therapy and also 10 minutes after intravenous nitrogen mustard, when this was used, or 30 minutes after initiation of oral prednisone and/or oral azathioprine therapy and then two and four weeks later. ANA determinations were repeated if any change occurred in the clinical status or the therapeutic regimen. Simultaneous determinations were made of anti-DNA and anti-extractable nuclear antigen (anti-ENA) antibodies, C_3, creatinine clearance, and 24-hour urine protein excretion. The worst values recorded in a particular patient were established.

ANA testing

The immunofluorescent human spleen imprint technique was used (1,2,4,18). Touch imprints of surgically obtained spleens were employed as nuclear substrate to detect ANAs by indirect immunofluorescence using commercially obtained fluorescein conjugated goat, antihuman gamma globulin (Baltimore Biological Laboratories, Baltimore, MD). The slides were examined without cover slips on a fluorescent microscope (Leitz Ortholux) with a 95X fluorite oil immersion lens and 10X

oculars (1,2). All positive tests (other than weak homogeneous) were read by at least two observers, usually without knowledge of the patients' clinical status. Patients were grouped according to their most significant ANA pattern ever shown (4) (Table 2). This was classified as their "main" pattern. The degree of significance from most to least, based on previously defined clinical correlations regarding the likelihood of kidney involvement (4), was as follows: shrunken peripheral general, shrunken peripheral LSANA, peripheral general, peripheral LSANA, homogeneous general titer 160 or greater, homogeneous LSANA titer 640 or greater, threads, large speckle-like threads, and small speckle-like threads (Fig 1). Patients were classified as demonstrating threads, large and small speckle-like threads as their main pattern, only when unaccompanied by the peripheral or significantly titered homogeneous general (160 or greater) or homogeneous LSANA (640 or greater) patterns.

Testing for anti-DNA and anti-ENA antibodies

Antisingle-stranded DNA antibody determinations were performed serially using a solid phase radioimmunoassay technique as described previously (19). Only IgG antisingle-stranded DNA antibody results were used in our study. Anti-ENA antibody assays were performed similarly to the method of Nakamura et al (20).

Renal function tests

Each patient's creatinine clearance, serum C_3 concentrations, and 24-hour urine protein excretion were measured at the start of the study and when the disease was in remission or had stabilized.

Renal biopsies

Renal biopsies were performed before starting treatment in 63 patients. All biopsies were reviewed by one of us who had no knowledge of the patients' clinical information. The modified World Health Organization (WHO) classification (21) was used:

Class I: normal by light microscopy (NL).
Class II: mesangial nephritis (MES).
Class III: focal segmental glomerulonephritis (FSPGN).
Class IV: diffuse proliferative glomerulonephritis (DPGN).
Class V: diffuse membranous glomerulonephritis (MGN).

Glomerular activity was estimated based on the presence and extent of cellular proliferation, segmental necrosis, wire loop lesions, hyaline thrombi, and cellular and fibrocellular crescents and was assigned a grade on a scale of 0 to 10. The presence and degree of glomerular sclerosis was interpreted as evidence of chronic glomerular injury and was also assigned a grade on a scale of 0 to 10. A morphologic index (numerically representing the morphologic assessment of the biopsy) was obtained for each patient by multiplying the numerical values of glomerular activity and glomerular sclerosis in each histopathological class.

Statistical analysis

Student's *t* test and analysis of multiple variance (ANOVA) were used to examine statistical significance.

Table 2
Patients' ANA Profiles

Main Patterns (No. of Patients)	Nonparticulate System General, LSANA	Particulate System
Sh P Gen (17)		
5	Sh P LSANA	—
3	Sh P LSANA	SLT Lg
1	Sh P LSANA	OP
1	P LSANA	T
1	P LSANA	T
1	H LSANA*	—
2	H LSANA†	—
1	—	T
1	—	SLT Lg
1	—	OP
Sh P LSANA (1)	P Gen	—
P LSANA (10)		
3	H Gen‡	T
5	H Gen‡	—
2	H Gen§	—
P Gen (18)		
3	P LSANA	T
1	P LSANA	SLT Lg
1	P LSANA	OP
4	—	T
2	P LSANA	—
3	H LSANA*	—
2	H Gen‡	—
2	H Gen§	—
H Gen (11)		
4	H LSANA†	—
2	H Gen‡	—
5	H Gen§	—
T (13)		
8	H Gen§	—
5	—	—
SLT Lg (3)		
3	—	—

Sh P Gen: Shrunken peripheral general ANA.
Sh P LSANA: Shrunken peripheral leukocyte-specific ANA.
P LSANA: Peripheral leukocyte-specific ANA.
H LSANA: Homogeneous leukocyte-specific ANA.
P Gen: Peripheral general ANA.
H Gen: Homogeneous general ANA.
T: Thready ANA.
SLT Lg: Large speckle-like thready ANA.
OP: Other particulates.
*Significant titer 640 or greater.
†Nonsignificant titer less than 640.
‡Significant titer 160 or greater.
§Nonsignificant titer less than 160.

Results

Renal function tests and histopathology

Mean creatinine clearances, C_3 values, and 24-hour proteinuria results in the different groups are shown in Table 3. Analysis of the renal biopsies is shown in Table 4. The distribution in renal histopathology seen in this group of 63 patients was as follows: MES, 6 patients (9.5%); FSPGN, 11 patients (17.5%); DPGN, 31 patients (49.2%); and MGN, 15 patients (23.8%).

Anti-DNA and anti-ENA values

The results of the IgG antisingle-stranded DNA antibodies and anti-ENA (Smith) antibodies are shown in Tables 3 and 5. Only patients with the homogeneous general pattern with a titer of 160 or greater in the nonparticulate group had low levels of anti-DNA antibodies (Table 3). The group of patients with

threads had lower levels of the anti-DNA antibodies (Tables 3 and 5). All nine of the nine patients with threads that were tested were anti-ENA (Sm) antibody positive (Table 3). Also, ten of the 11 patients from the threads plus significant nonparticulate ANA patterns that were tested were anti-ENA (Sm) antibody positive (Tables 2, 3, and 5). The concomitant presence of threads in some patients with the peripheral patterns was probably responsible for the high incidence of positive anti-ENA (Sm) antibody tests in this group (Tables 3 and 5). These patients also had high levels of anti-DNA antibodies (Table 4).

Table 3
Means of the Most Abnormal Serological and Biochemical Values Recorded in Patients with Different ANA Patterns

ANA Pattern	Number of Patients	Ccr	C_3	Proteinuria	Anti-DNA (Pts Pos)	Anti-ENA (Sm) (Pts Pos)
Sh P Gen	17	58.2 ± 7.1	79.3 ± 10.9	2.9 ± 1.0	13.2 ± 2.4 (4/4)	11.0 ± 0.0 (4/4)
P Gen	18	44.7 ± 5.2	69.5 ± 9.0	4.6 ± 2.1	13.4 ± 2.4 (7/10)	7.5 ± 1.6 (7/10)
H Gen	11	45.0 ± 6.9	98.2 ± 12.1	4.4 ± 1.4	3.5 ± 3.5 (0/6)	2.7 ± 1.5 (1/6)
P LSANA	11	49.9 ± 10.5	73.7 ± 12.3	3.6 ± 0.9	10.4 ± 3.5 (4/7)	8.3 ± 1.5 (5/7)
T	13	85.0 ± 4.2	114.9 ± 10.3	4.2 ± 2.4	2.4 ± 1.0 (0/9)	9.3 ± 0.6 (9/9)

Sh P Gen: Shrunken peripheral general ANA.
P Gen: Peripheral general ANA.
H Gen: Homogeneous general ANA.
P LSANA: Peripheral leukocyte-specific ANA.
T: Thready ANA.
Ccr: Creatinine clearance in mL/min.
C_3: Complement-3 levels in U/dL (normal 80 to 200 U/dL).
Proteinuria: Urinary protein in g/24 hr.
Anti-DNA: IgG antisingle-stranded DNA antibodies in μg/mL, positive 6.9 μg/mL.
Anti-ENA: Anti-ENA (Smith) antibodies in μg/mL, positive 7.4 μg/mL.
Pts Pos: Number of patients positive out of number of patients tested.
Note: Mean values are recorded ± standard error of mean.

Table 4
Analysis of Renal Biopsies According to ANA Patterns

ANA Pattern (Number of Patients)	Histopathologic Classification (Number of Patients)	Mean Glomerular Activity	Mean Chronic Glomerular Injury and Sclerosis	Mean Patient Morphologic Indices
Sh P Gen (13)	MES (1) MGN (0) FSPGN (4) DPGN (8)	3.2	3.4	53.0
P Gen (17)	MES (2) MGN (1) FSPGN (4) DPGN (10)	3.4	3.4	41.9
P LSANA (11)	MES (0) MGN (2) FSPGN (2) DPGN (7)	3.0	2.5	48.6
H Gen (9)	MES (0) MGN (3) FSPGN (1) DPGN (5)	4.0	5.0	82.6
T (13)	MES (3) MGN (9) FSPGN (0) DPGN (1)	1.4	2.0	11.3
T plus other nonparticulates (13)	MES (0) MGN (0) FSPGN (4) DPGN (9)	3.4	3.1	48.1

Sh P Gen: Shrunken peripheral general ANA.
P Gen: Peripheral general ANA.
P LSANA: Peripheral leukocyte-specific ANA.
H Gen: Homogeneous general ANA.
T: Thready ANA.
T plus other nonparticulates: Thready ANA plus various nonparticulate patterns.
MES: Mesangial glomerulonephritis.
MGN: Membranous glomerulonephritis.
FSPGN: Focal segmental proliferative glomerulonephritis.
DPGN: Diffuse proliferative glomerulonephritis.
Number of renal biopsies: 63. Classification: Class I: Normal (0 patients [0%]), Class II: Mesangial GN (6 [9.5%]), Class III: Focal PGN (11 [17.5%]), Class IV: Diffuse GN (31 [49.2%]), Class V: Membranous GN (15 [23%]).

Specific ANA Patterns

Shrunken peripheral general and peripheral general (35 patients)

In those patients with the shrunken peripheral and peripheral general patterns, the majority also had other patterns present (Table 2) (Fig 1A and 1B). The homogeneous general and homogeneous LSANA patterns always coexisted with the shrunken peripheral and peripheral general and LSANA patterns, respectively, either undiluted or on dilution (1).

Of the 30 patients in these groups who had renal biopsies, 26 were found to have FSPGN or DPGN (Table 4). Patients in these groups generally had the more severe and active forms of the disease, which was evident from the higher levels of anti-DNA antibody titers and lower C_3 levels (Table 3). Analysis of renal biopsies showed a higher level of activity and greater proliferative changes (25/30) (Table 4). However, these patients responded well to appropriate therapy accompanied by changes in these nonparticulate ANA patterns (Figs 2 through 6).

LSANA group (11 patients)

This group included one patient with shrunken peripheral LSANA and ten patients with peripheral LSANA (Table 2) (Fig 1C). The mean creatinine clearance, C_3 levels, and 24-hour protein excretion were in the same range as in those patients with shrunken peripheral and peripheral general patterns (Table 3). Anti-DNA antibody concentrations tended to be lower. Histopathology examination revealed that nine of 11 patients had a proliferative glomerulonephritis. All patients had renal biopsies. The distribution of diagnosis is shown in Table 4. The glomerular activity and sclerosis as shown by the morphologic indices were comparable to the peripheral general group (Table 4). The clinical course of a patient with peripheral LSANA who had a marked increase in both creatinine clearance and C_3 levels after treatment with nitrogen mustard is depicted in Fig 2.

Homogeneous general ANA group (11 patients)

Only homogeneous patterns with titers of 160 or greater were considered to be significant (1) (Fig 1D). These patients had lower mean anti-DNA antibody levels (3.47 μg/mL) and near-normal C_3 levels (98.2 U/dL) (Table 3). Nine patients had renal biopsies. Analysis of renal biopsies showed that these patients had the highest amount of sclerosis or signs of chronic glomerular injury. The overall histopathologic picture was more advanced (morphologic index 82.6) as compared to patients with the peripheral patterns. These patients also showed an increased propensity to proliferative lesions (6/9) (Table 4).

Threads (13 patients)

These patients had the highest mean creatinine clearance (85.0 mL/min) (Fig 1E). They also showed less activity and severity of the disease as evidenced by low anti-DNA antibody levels (2.37 μg/mL) and high C_3 levels (115.0 U/dL). All these values were statistically significantly better than corresponding values for other groups of patients (Tables 3 and 5).

Table 5
Comparison of Means of the Most Abnormal Serologic and Biochemical Results Recorded in Patients with Threads and in Patients with Threads Plus Other ANA Patterns

	Threads	Threads Plus Others	P Value
Ccr	85.0 ± 4.2	50.0 ± 9.0	0.001
C_3	114.9 ± 10.3	60.3 ± 11.0	0.01
Proteinuria	4.2 ± 2.4	3.2 ± 0.7	NS
Anti-DNA	2.4 ± 1.0	13.4 ± 2.5	0.01
Anti-ENA (Sm)	9.3 ± 0.6	10.3 ± 0.5	NS
MI	11.3 ± 4.5	48.1 ± 9.1	0.01

Ccr: Creatinine clearance in mL/min.
C_3: Complement-3 level in U/dL.
Proteinuria: Urinary protein in g/24 hr.
Anti-DNA: IgG antisingle-stranded DNA antibodies in μg/mL.
Anti-ENA (Sm): Anti-ENA (Smith) antibodies in μg/mL.
MI: Morphologic index.
Note: Mean values are recorded ± standard error of mean.
See Table 3 for normal values of C_3 and for positive values of anti-DNA and anti-ENA.

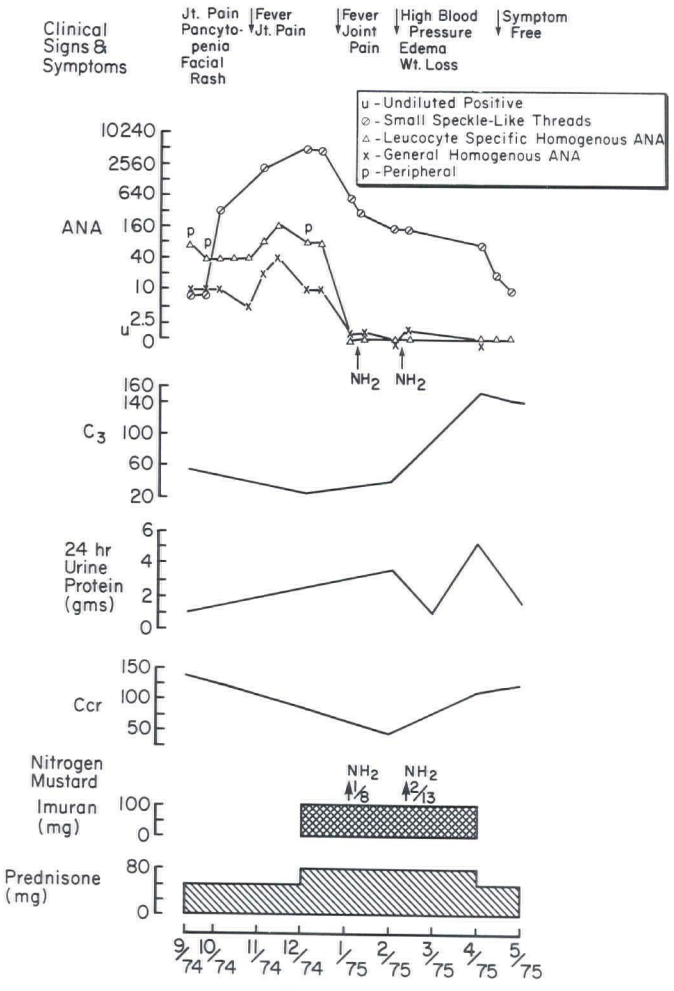

Fig 2—Correlations of clinical and laboratory findings.

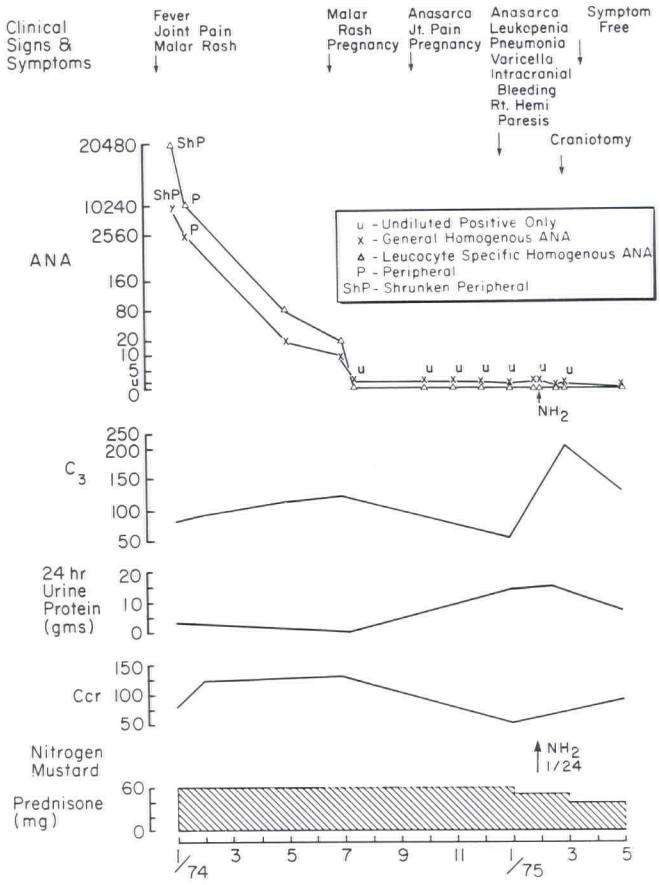

Fig 3—Correlations of clinical and laboratory findings.

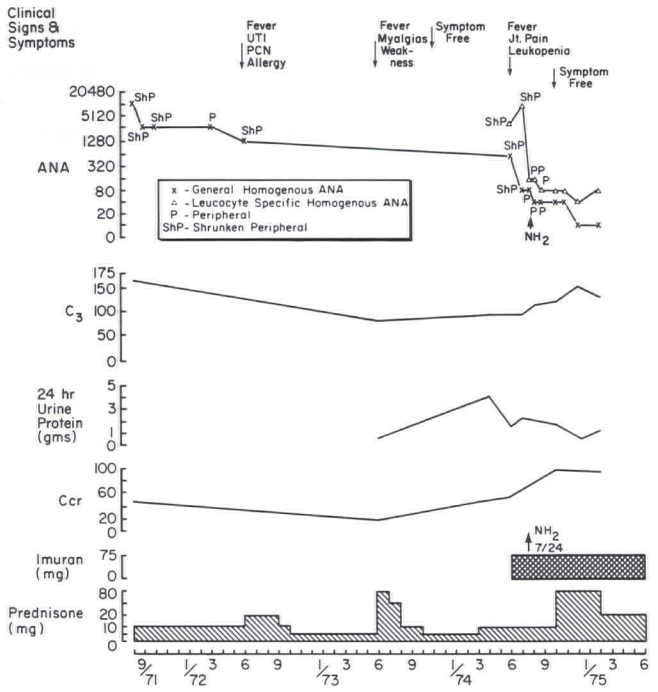

Fig 4—Correlations of clinical and laboratory findings.

A high incidence of the benign forms of histopathology (12 of 13 patients; MES, 3 patients, and MGN, 9 patients [Table 4]) was present in this group. Also, the activity or acute glomerular injury and the morphologic index were significantly lower ($P < 0.002$) than in other groups. These results clearly indicate less severe disease in patients with the thready pattern.

Thirteen patients had threads associated with significant nonparticulate ANA patterns (Table 2). These patients did not show any significant differences in the activity or severity of disease (Table 5) as compared to their counterparts in the nonparticulate pattern group without threads.

Large speckle-like threads

One patient had a FSGN and another MGN, but their biopsies were not fully analyzed and therefore not included in the tables. No conclusions can be made because of the small number of patients in this group. As discussed, patients with large speckle-like threads as their main pattern usually do not have renal involvement.

Changes in ANA patterns and titers with therapy

A fall in titer occurred in both the peripheral homogeneous and the particulate systems with therapy. However, two differences were noted in the behavior of the systems:

1. The mean titer of the peripheral homogeneous system was lower than that of the particulate system. Using the highest titers ever recorded in each patient, the mean homogeneous general ANA titer was 1,650 (40 to 10,240). These results included all patients in the peripheral homogeneous groups with or without concomitant particulate patterns. The mean highest titer of the patients with LSANA was 4,406 (40 to 20,480). In the particulate patterns the mean highest titer of the thready pattern was 70,976 (640 to 163,840), 13,344 (160 to 40,960) for large speckle-like threads, but only 322 (5 to 640) for small speckle-like threads.

2. The peripheral homogeneous system, both general and LSANA, was sensitive to therapy and to changes in disease activity in that with immunosuppressive therapy the peripheral patterns disappeared, leaving only the homogeneous patterns which in turn also could disappear (Figs 2 and 3). A common evolution, similar to that seen with serum dilution (1), was from shrunken peripheral to peripheral to homogeneous with progressive reduction in the titer of the homogeneous patterns when the disease became less active (Fig 4). Titers reported were those of the homogeneous patterns to which the peripheral patterns had converted. Conversely, particulate patterns such as threads tended to persist, although a fall in titers usually occurred (Figs 2 and 5). The only particulate patterns which disappeared were the small speckle-like threads in one patient, while two patients lost patterns in the "other particulates" group (Table 1). With reactivation of SLE, the reverse of this process was seen in the peripheral homogeneous system in that the general peripheral (Fig 5) and both the general peripheral and the LSANA pe-

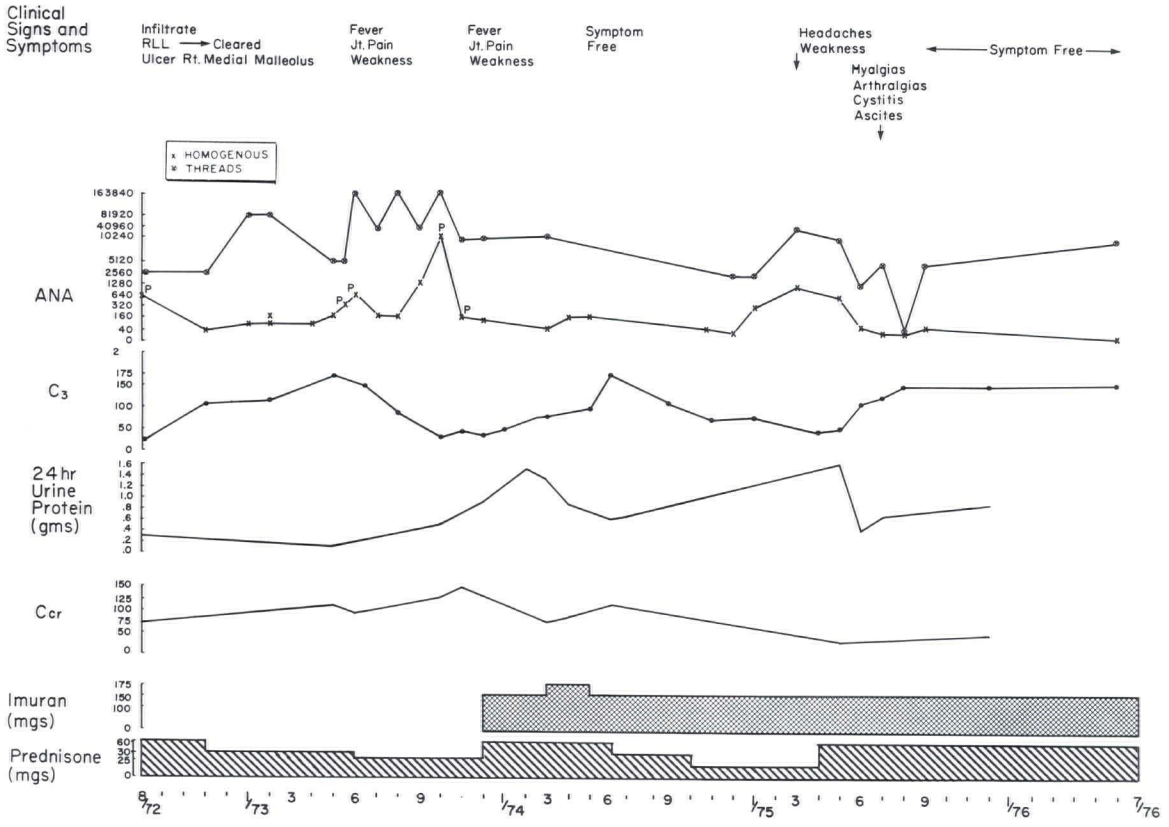

Fig 5—Correlations of clinical and laboratory findings.

ripheral patterns (Fig 6) reappeared (Figs 2, 5, and 6). In one patient the shrunken peripheral LSANA pattern appeared with a relapse (Fig 4). Reappearance of the general peripheral pattern was accompanied in one patient by elevation in the titer of the thready pattern (Fig 5). No significant changes occurred in ANA patterns and titers 10 minutes after intravenous injection of nitrogen mustard (Figs 2, 3, 4, and 6). IgG anti-DNA antibody concentrations were also noted to decrease from 12 μg/mL or greater to 4 μg/mL or less with improvement in the patients' condition.

Discussion

The various nuclear immunofluorescent patterns are associated with antinuclear antibodies which react with different nuclear antigens (18). The diagnostic and prognostic aspects of these patterns and titers can be appreciated only by accurate morphologic classification (1,4). Of equal importance in analyzing the relationship of ANA titer changes to changes in clinical status and treatment is that differentiation must be made between the two main ANA pattern systems: the peripheral homogeneous system and the particulate group as described earlier. Futhermore, the type of nuclear substrate and the technique employed affect the sensitivity of the ANA test using immunofluorescence (1). We have found that human spleen imprints have considerable advantages over other nuclear substrates regarding both sensitivity and ease with which the different patterns can be identified (1,2,4). If a less sensitive substrate is employed and if, in addition, accurate morphologic pattern identification is not practiced, the different nuclear immunofluorescent patterns cannot be distinguished from each other. This may explain why some authors' findings (16,17,22) have differed from ours (1,2,4). However, Nisengard et al (23) did find that the combination of the peripheral pattern accompanied by a titer of 160 or greater correlated with active disease in SLE. We have demonstrated that there is indeed a close correlation of ANA patterns with specific connective tissue diseases (1) and specifically of patterns and titers with activity and severity of SLE (4), especially when the titers of the two main ANA pattern systems are considered separately as in this study. An extreme example of the need to discriminate between the two ANA pattern systems in regard to titers is shown in Fig 5. Had such a differentiation not been made in this patient, an erroneous judgment of reactivation of the disease would have been reached even though the patient was in a clinical remission. In fact, the homogeneous titer had fallen to 40, correlating well with clinical improvement, whereas the thready titer was still 10,240.

In this report we have attempted to correlate ANA patterns and titers found before therapy with subsequent exacerbation or

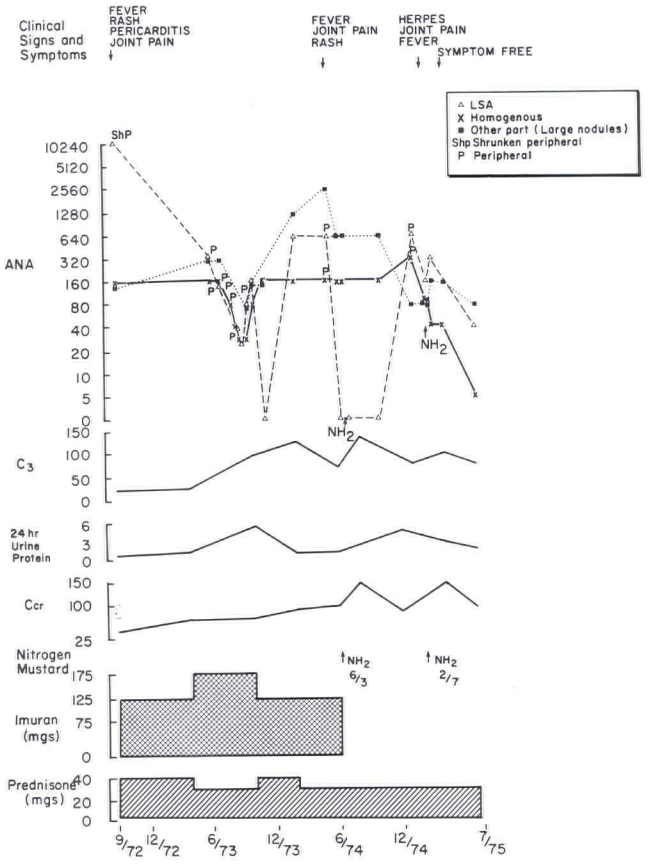

Fig 6—Correlations of clinical and laboratory findings.

improvement of the disease and the effect of the treatment. The shrunken peripheral general pattern can be seen early in SLE with active kidney involvement and is associated with high IgG anti-DNA antibody levels. This pattern is seen mainly in early or active forms of the disease and usually disappears with therapy. Even though the shrunken peripheral general pattern has been considered to be of poor prognostic significance, in the sense of its close association with renal involvement (4), it will confirm the diagnosis of SLE with presumptive renal disease at an early phase as shown by moderate changes in renal function and histopathology before irreversible damage has occurred (Figs 3, 4, and 6).

Patients with the thready ANA pattern as their main pattern seem to have a less severe form of SLE nephritis. This is reflected by the significantly better results of this group of patients (Tables 3, 4, and 5) as compared to all other groups of patients. We have found that the nuclear antigen with which the thready pattern reacts appears to be a large complex of protein and RNA which is associated with the nuclear membrane (24).

Clinicopathologic studies using the WHO classification have established that classes II and V (mesangial glomerulonephritis and membranous glomerulonephritis) have a much better prognosis (85% to 90% five-year renal function survival) than classes III and IV (FSPGN and DPGN) (60% five-year renal function survival). Thus, these results which show that 12 (92%) of 13 patients with threads had class II and V types of renal involvement are clearly of significance. Of the other 50 patients with renal biopsies (ANA patterns different than threads), only nine patients (18%) had class II and V disease; 41 patients (82%) showed proliferative glomerulonephritis (FSPGN and DPGN). The relative frequency of the different forms of histopathology seen in our group of patients was similar to the results of five series comprising over 300 patients that used the same WHO classification (25).

When the degree of activity and chronicity or sclerosis in the renal biopsies were quantitatively compared between patients with threads and those with other patterns, again a striking difference was noted. The renal biopsies of patients with threads showed much less glomerular activity, sclerosis, and a lower morphologic index when compared to the other group of patients (Table 4).

However, when patients have significant nonparticulate patterns along with the thready pattern, the benign implications of the thready pattern as the main pattern are no longer present. We found that all 13 such patients had a proliferative lesion (FSPGN and DPGN) on renal biopsy. The degree of activity and sclerosis was greater and the total morphology was worse than in those with the thready pattern only as evidenced by the morphologic index (Table 4).

Sharp et al (26) reported that 86% of patients with SLE nephritis who responded to therapy had antibodies to ENA, while only 8% of the patients with SLE nephritis who did not respond to therapy had anti-ENA antibodies. Sharp et al (27) suggested that anti-ENA antibodies might have a protective effect in patients with SLE. It has been postulated that anti-ENA antibodies are associated with the thready patterns seen with the fluorescent antibody technique (28). The thready pattern was found to have the highest correlation of anti-Sm antibodies (90%) compared to any other group (5). In our study this higher correlation was again noted in the threads plus other nonparticulate patterns group (Tables 2, 3, and 5) and was also found in the patients with only threads (Table 3). That patients with the thready pattern as their main pattern have less severe renal disease than patients with other patterns and that mesangial and membranous glomerulopathy are the types of renal involvement more commonly found in this group suggests that these patients may represent a different subset of renal SLE. The thready pattern is thus an immunologic marker for this narrow clinical subset of renal SLE. The findings of Winn et al (29), in which SLE patients with antibody to Sm antigen (frequently associated with the thready pattern) had a more benign form of renal disease, are intriguingly similar to ours. Sharp et al (26) reported that renal disease was associated with antidouble-stranded DNA antibodies. We found that patterns associated with high or intermediate IgG antisingle-stranded DNA antibody levels (shrunken peripheral and peripheral) also are among those that may frequently be associated with renal involvement.

Although long-term immunosuppressive therapy with clinical improvement was accompanied by changes in the peripheral homogeneous system, intravenous nitrogen mustard had no immediate effect on ANA titers (Figs 2, 3, 4, and 6), and results of immediate subsequent specimens are therefore valid

for evaluation of the clinical status. Possible reasons why the homogeneous pattern group (rather than the peripheral group) had greater degrees of sclerosis with the highest morphologic indices (Table 4) are: 1) since five patients had already been treated at the time of their first ANA specimen, they might have demonstrated the peripheral patterns prior to immunosuppressive therapy; and/or 2) they had received suboptimal immunosuppressive therapy early in their disease which nevertheless continued to progress slowly (Table 4). Improvement in the clinical status sometimes could have been predicted, based on the fall in titer in the peripheral homogeneous system (Figs 2, 4, 5, and 6). In a few patients the reverse could be observed, in that a pattern or titer higher in the peripheral homogeneous system reappeared in association with a relapse of the disease (Figs 2, 4, 5, and 6).

We wish to reemphasize that in the evaluation of titers it is important to determine the titers of each of the main pattern systems separately because the titers of the particulate patterns tend to be higher than those of the nonparticulate peripheral homogeneous system. Failure to make such a differentiation may explain the lack of correlation between titers and clinical presentation as found by most other authors.

Our results demonstrate that autoantibody profiles comprised of ANA immunofluorescent patterns and titers along with IgG antisingle-stranded DNA antibodies and to a lesser extent anti-ENA antibodies are useful in the evaluation of patients suspected of having SLE. Not only can the diagnosis of SLE be confirmed early, but prognostic data can also be obtained regarding the likelihood and severity of renal disease. Furthermore, therapeutic guidelines are available as shown by changes in patterns and titers in the peripheral homogeneous system.

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