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PAPER

Rare autoantibodies to cellular antigens in systemic lupus erythematosus

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Objective: A high number of antinuclear antibody specificities can be detected in systemic lupus erythematosus (SLE). Some of them are related to a distinct clinical subset of disease, independently of their frequency. The aim of our study was to investigate, in a cohort of SLE patients, the prevalence and the clinical relevance of autoantibodies to cellular antigens less frequently found in SLE. **Methods:** Antinuclear antibodies were detected by indirect immunofluorescence on HEp-2 cells while counterimmunoelectrophoresis was used to detect anti-ENA antibodies in 540 patients with SLE, classified according to ACR and SLICC criteria. Clinical and serological features were collected from clinical charts. **Results:** A total of 319 (58.9%) out of 540 sera were positive for anti-ENA antibodies. Anti-Ro/SSA was found in 235 sera, 50 of which also contained anti-La/SSB. Anti-U1RNP were detected in 67, anti-Sm in 46 and anti-ribosomal P protein in 13 sera. In a multivariate analysis anti-Sm was associated with discoid lupus ($p = 0.045$) and photosensitivity ($p = 0.037$), anti-U1RNP with malar rash and Raynaud's phenomenon ($p = 0.01$ and $p = 0.0004$, respectively) and anti-Ro/SSA with malar rash, oral ulcers, xerostomia, xerophthalmia and rheumatoid factor ($p = 0.029$, $p = 0.01$, $p = 0.031$, $p = 0.002$ and $p = 0.028$, respectively). Other anti-ENA antibodies were found in 50 positive sera (15.6%). Anti-Ki antibodies were detected in 31, anti-Ku in 8, anti-centromere in 5, isolated anti-La/SSB, anti-PCNA and anti-Topo I in 3 each and anti-Jo-1 in 2 sera. About half of these antibodies (27 out of 50) were detected as the single anti-ENA specificity in serum. At multivariate analysis anti-Ki was significantly associated with male gender while anti-Ku with African ethnicity ($p = 0.017$ and $p < 0.0001$, respectively). No sign of muscular or pulmonary involvement was found in anti-Jo-1-positive patients whilst features of systemic sclerosis were detectable in two out of three anti-Topo I. **Conclusions:** Our study shows that antibodies to cellular antigens more rarely found in SLE are detectable in more than 15% of patients with anti-ENA antibodies. Most of them are found as single anti-ENA specificity. Anti-Ki and anti-Ku are found in a subset of disease, characterized by male gender and African origin, respectively. Clinical features of scleroderma were found only in patients with anti-Topo I. *Lupus* (2014) **23,** 672–677.

Key words: Rare antibodies; subset disease; anti-Ki; anti-Ku; anti-ENA; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multiorgan autoimmune disease that involves almost all the organs in the human body and is accompanied by the production of numerous autoantibodies.[1] These autoantibodies not only have diagnostic relevance but they can also be associated with peculiar clinical subsets.[2] The revised American College of Rheumatology (ACR) criteria for SLE,[3] as well as the most recent Systemic Lupus International Collaborating Clinics (SLICC) classification,[4] includes several autoantibodies: antinuclear (ANA), anti-Smith (Sm), anti-double-stranded DNA (dsDNA), antiphospholipid and anti-red blood cells antibodies. Other autoantibodies directed against other nuclear, cytoplasmic and cell membrane antigens have also been identified in SLE although their role in pathogenesis is less clear.[1] Antibodies to U1RNP associated with anti-Sm as well as the highly specific anti-ribosomal

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P protein can be considered somewhat diagnostic for SLE. Other autoantibodies to ENA (extractable nuclear antigens) are reported with low prevalence in SLE,[5,6] and they are not exclusively found in SLE but are also detected in other connective tissue diseases. Therefore they should be considered non-diagnostic for SLE. Frequency of these autoantibodies reported in the literature varies widely also depending on the method used for their detection. Anti-topoisomerase I (anti-Topo I), a specific marker for systemic sclerosis, has been reported in SLE as high as 25%.[7] Similarly, anti-proliferating cell nuclear antigen (PCNA) was reported for a long time in less than 5%, even if exclusively detected in SLE patients,[8] but recent reports did not confirm these data.[6,9]

The present study aims to investigate the prevalence of more rare (non-diagnostic) autoantibodies using counterimmunoelectrophoresis (CIE) as a single method for detection, trying to correlate them with specific patterns of the disease.

Methods

A cohort of 540 patients affected by SLE, attending the Rheumatology Unit of Brescia Hospital between 1976 and 2008, was retrospectively evaluated. The diagnoses were confirmed based on the ACR criteria revised in 1997[3] and the more recent SLICC criteria.[4]

The following clinical and laboratory data were collected from medical records: fatigue, arthritis, arthralgias, Jaccoud, myalgias, malar rash, sub-acute cutaneous or discoid lupus, photosensitivity, Raynaud's phenomenon, myositis, purpura, oral ulcers, xerostomia, xerophthalmia, pleuritis, pericarditis, peritonitis, cerebral ischemia, epilepsy, glomerulonephritis, and thromboembolic events. The occurrence of clinical features was considered during the follow-up. Data recorded in clinical charts were collected and organized in a database.

The laboratory and immunological assessment included: complete blood cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complement (C3, C4, CH50), rheumatoid factor (RF), ANA, anti-dsDNA, anti-ENA, anticardiolipin antibody (aCL), anti-$\beta_2$glycoprotein I (anti-β2GPI) and lupus anticoagulant (LA).

ANA, including anti-centromere, were detected by indirect immunofluorescence (IIF) test on HEp-2 cells (BioRad, Hercules, CA, USA) and considered positive at titre $\geq$1:160, while anti-ENA antibodies were analysed by CIE using rabbit thymus extract.[10,11] Human or porcine spleen extract was used as substrates for anti-Ro/SSA detection,[12] without differentiating the response to Ro-52 and Ro-60. Reference sera for anti Topo-I, anti-Jo-1 and anti-centromere antibodies were obtained from the Centers for Disease Control in Atlanta, Georgia, United States (US).[13] Anti-Ku, anti-Ki and anti-PCNA were originally identified by Immunoblot analysis using cell nuclear extracts as the antigens source: single antibody specificity was recognized based on their known molecular weights. These positivities were subsequently confirmed using European Consensus sera. Anti-dsDNA antibodies were detected by radioimmunological assay (Farr assay, Kodak Clinical Diagnostics, Amersham, UK) and considered positive when >7 IU/ml. aCL (immunoglobulin IgG and IgM) were measured by home-made enzyme-linked immunosorbent assay (ELISA) following the methods suggested by the International Standardization Workshop[14] and levels >10 IgG phospholipid units (GPL) and/or IgM phospholipid units (MPL) were considered positive. Anti-β2GPI antibodies (IgG and IgM) were detected by ELISA, as previously described.[15] Patients were considered antiphospholipid antibody positive if at least one of the three laboratory criteria was persistently positive (i.e. LA, aCL, anti-β2GPI). Serositis included at least one among pleuritis, pericarditis and peritonitis.

Clinical and laboratory data were identified from clinical records. Autoantibodies profile was obtained at the time of diagnosis and routinely at least every three years during follow-up; only persistent positivity for autoantibodies was considered. This study was approved by the local ethics review board.

Statistical analysis

All the variables were expressed as mean ± standard deviation (SD). Two-tailed Student's *t*-test for continuous variables and Fisher's exact test or Yates's χ^2 test for categorical variables were used. A multivariate analysis was conducted by a logistical regression model (Statview). $P < 0.05$ was considered statistically significant. Odds ratio (OR) and 95% confidence interval (CI 95%) were calculated.

Results

Demographic data

The analysed cohort (540 SLE cases) included 498 females and 42 males (female to male ratio of 12:1) with a mean age at onset of 34.01 years (SD: 12.8 years) and a mean follow-up 9.6 years (SD: 7.2 years). Most patients were Caucasians (512 (94.8%)), while 28 patients were of different origin, namely African (13 cases, 2.4%), south-Asian (10 cases; 1.85%) and Chinese (5 cases; 0.92%). The main clinical features recorded are reported in Table 1. In addition, thrombocytopenia (9.62%), haemolytic anaemia (8.1%), discoid lupus (7.3%), Jaccoud's arthritis (6.9%), lymphopaenia (6.66%), epilepsy (5.7%), sub-acute cutaneous lupus (5.4%), and purpura (5.3%) were less frequently recorded.

Autoantibodies prevalence

Prevalence of autoantibodies is summarized in Table 2. Anti-ENA antibodies were detected in 59% of cases, most of them represented by anti-Ro/SSA or U1RNP. Isolated anti-ENA antibodies were detected in more than 60% of sera (202/319), represented by 137 anti-Ro/SSA (137/185: 74.0%), one anti-La/SSB (one of three: 33.3%), nine anti-Sm (nine of 46: 19.5%), 24 anti-U1RNP (24/67: 35.8%), 13 anti-Ki (13/31: 41.9%), four anti-ribosomal P protein (four of 13: 30.7%), five anti-Ku positive (five of eight: 62.5%), two anti-Topo I (two of three: 66.7%), three anti-PCNA (100%) and two anti-Jo-1 (100%). Isolated anti-centromere was found in two of five anti-centromere-positive sera (40%).

Autoantibodies and clinical associations

At the univariate analysis anti-Sm antibodies were associated with photosensitivity ($p = 0.0010$, OR 3.09, CI 95% = 1.58–6.03), malar rash ($p = 0.031$, OR 2.07, CI 95% = 1.10–3.87), discoid lupus ($p = 0.036$, OR 2.62, CI 95% = 1.08–6.33) and leucopenia ($p = 0.0196$, OR 2.16, CI 95% = 1.52–4.23). Anti-U1RNP antibodies show a significant association with Raynaud's phenomenon ($p = 0.0002$, OR 2.77, CI 95% = 1.63–4.23), malar rash ($p = 0.0021$, OR 2.31, CI 95% = 1.37–3.91), leucopenia ($p = 0.0005$, OR 2.54, CI 95% = 1.52–4.23). Anti-Ro/SSA was associated with malar rash ($p = 0.034$, OR 1.47, CI 95% = 1.03–2.11), oral ulcers ($p = 0.004$, OR 1.73, CI 95% = 1.19–2.51), xerostomia ($p = 0.021$, OR 1.59, CI 95% = 1.10–2.30), xerophthalmia ($p = 0.004$, OR 1.72, CI 95% = 1.19–2.49), leucopenia ($p = 0.038$, OR 1.48, CI 95% = 1.02–2.15), and positive rheumatoid factor ($p = 0.031$ OR 1.70, CI 95% = 1.04–2.77) Anti-Ro/SSA + anti-La/SSB antibodies were associated with xerophthalmia ($p = 0.045$, OR 1.81, CI 95% = 1.01–3.25) and rheumatoid factor ($p = 0.00001$, OR 4.87, CI 95% = 2.6–9.14). Anti-P antibodies were associated with leucopenia ($p = 0.036$, OR 3.15, CI 95% = 1.02–9.78), while anti-Ki antibodies were

Table 1 Clinical features of 540 patients with SLE. We reported clinical and serological features that were present at least in 10% of our SLE patients

	n	*Percentage*
F/M	12/1	
Arthralgias	488	90.53
Fatigue	386	71.61
Photosensitivity	248	46.01
Malar rash	245	45.45
Raynaud's phenomenon	242	44.89
Xerostomia	202	37.47
Xerophthalmia	189	35.06
Leucopenia	185	34.32
Oral ulcers	178	33.02
Glomerulonephritis	162	30.00
Serositis	106	19.66
Deep venous thrombosis	65	12.05
Cerebral ischemia	64	11.87

SLE: systemic lupus erythematosus; F: female; M: male.

Table 2 Immunological findings of 540 SLE patients

	N	*Percentage*
Antinuclear antibodies	527	97.77
Anti-centromere	5	0.92
Anti-dsDNA antibodies	437	81.07
Antiphospholipid antibodies	290	53.80
Rheumatoid factor	78	14.47
Anti-ENA	319	58.99
Ro/SSA	185	34.25
U1RNP	67	12.43
Ro/SSA+La/SSB	50	9.27
Sm	46	8.53
Ki	31	5.75
Ribosomal P protein	13	2.41
Ku	8	1.48
La/SSB	3	0.55
PCNA	3	0.55
Topoisomerase I	3	0.55
Jo-1	2	0.37

SLE: systemic lupus erythematosus; Anti-dsDNA: anti-double-stranded DNA; Anti-ENA: anti-extractable nuclear antigens; PCNA: proliferating cell nuclear antigen.

associated with male gender ($p = 0.0054$, OR 3.88, CI 95% = 1.56–9.64) and anti-Ku antibodies were associated with African race ($p = 0.00056$, OR 31.2, CI 95% = 6.5–149.1).

In a multivariate analysis most of the associations at univariate analysis persisted; anti-Sm antibodies were associated with photosensitivity ($p = 0.037$, OR 2.68, CI 95% = 1.05–6.78) and discoid lupus ($p = 0.045$, OR 2.92, CI 95% = 1.02–8.33). In addition, the associations between anti-U1RNP and Raynaud's phenomenon ($p = 0.0004$, OR 3.02, CI 95% = 1.63–5.59) and malar rash ($p = 0.010$, OR = 2.11, CI 95% = 1.19–3.72) were present. Anti-Ro/SSA were still associated with malar rash ($p = 0.029$, OR = 1.48, CI 95% = 1.04–2.10), oral ulcers ($p = 0.01$, OR 1.55, CI 95% = 1.11–2.75), xerostomia ($p = 0.031$, OR 1.75, CI 95% = 1.20–2.54), xerophthalmia ($p = 0.02$, OR 1.80, CI 95% = 1.20–2.61) and positive rheumatoid factor ($p = 0.028$ OR 1.60, CI 95% = 1.11–2.65). In addition, there was association between anti-Ro/SSA + anti-La/SSB antibodies and rheumatoid factor ($p = 0.0001$, OR 4.50, CI 95% = 2.45–9.35). Finally, the associations with anti-Ki and male gender ($p = 0.017$, OR 3.24, CI 95% = 1.22–8.55) and with anti-Ku and African race ($p < 0.0001$, OR 76.5, CI 95% = 11.5–150.1) also persisted.

Rare SLE autoantibodies

Uncommon (not diagnostic for SLE) autoantibodies to ENA were found in 50 patients (9.25%): 27 of them as single anti-ENA specificity, representing 8.4% of anti-ENA-positive SLE patients ($n = 319$). Anti-Ki was detected in 13 out of 31 sera (41.9%) as single anti-ENA antibody, while 18 sera showed multiple anti-ENA, namely anti-Ki+Ro/SSA+La/SSB (13 cases), anti-Ki+Sm (two cases), anti-Ki+U1RNP (one case), anti-Ki+PCNA (one case), anti-Ki+Ro/SSA+La/SSB+Ku (one case).

Anti-centromere was the unique specificity in two out of five patients (25%), while two cases were associated with anti-Ro/SSA+La/SSB and one with anti-Ro/SSA+La/SSB+Sm+U1RNP antibodies.

Isolated anti-Ku was found in five out eight sera (62.5%), while one was also associated with anti-Ro/SSA+La/SSB, one with anti-Ro/SSA+La/SSB+U1RNP and one with anti-Ro/SSA+La/SSb+Ki. Anti-Topo I was the single specificity in two out of three (66%) positive patients while the other one was associated with anti-Ro/SSA+La/SSB antibodies.

None of the two anti-Jo-1-positive patients showed any signs of inflammatory myopathies or anti-synthetase syndrome, after a mean of 9.8 years of follow-up. By contrast, two out of the three anti-Topo I-positive patients showed an overlap of SLE-systemic sclerosis, characterized by a scleroderma pattern at nailfold, capillaroscopy and Raynaud's phenomenon, interstitial lung disease and skin ulcers after a mean follow-up of 10.3 years. Only one out of five anti-centromere-positive patients showed Raynaud's phenomenon, but they did not present any other features related to systemic sclerosis or Sjögren's syndrome after a mean follow-up of 13.6 years.

Discussion

To our knowledge, the cumulative prevalence of anti-ENA antibodies in SLE not limited to the six more frequently searched specificities (Sm, U1RNP, Ro/SSA, La/SSB, Jo-1 and Topo-I) is not detectable in recent literature. Some investigations were directed to study both prevalence and clinical associations of single anti-ENA specificity, such as anti-Topo I or anti-ribosomal P protein[7,16] with highly sensitive methods.

In our study CIE, a relatively insensitive but highly specific method was used allowing the detection of different precipitating antibodies to ENA that were found in about 60% of sera. Anti-Sm, anti-U1RNP and anti-Ro/SSA were the more frequent specificities in our cohort. They were found in association with mucocutaneous and vascular features confirming previous reports,[1] and most of these associations persisted after multivariate analysis. No association between anti-ribosomal P protein and neuropsychiatric SLE was found.

Anti-ENA antibodies not specific for SLE were detected in more than 9% of all SLE patients and in more than 15% of anti-ENA-positive patients. Moreover, about half of those antibodies were the only anti-ENA specificity found in our cohort.

Some of these rare anti-ENA antibodies seem to be associated with specific patterns of the disease. Anti-Ki was the most frequently encountered antibody representing 59% of the total rare anti-ENA detected in SLE. It is significantly associated with male gender, thus confirming previous Italian studies using CIE as the detecting method.[17,18] In contrast with other reports in which anti-Ki were frequently found associated with other anti-ENA antibodies,[19] particularly anti-PCNA,[16] more than 40% of anti-Ki were found isolated in the present study. Even if other methods have been employed to detect anti-Ki (such as ELISA using

recombinant antigen or immunoblotting),[20,21] this antibody is rarely routinely searched for in SLE because these methods are not currently commercially available.

Although our cohort was mostly represented by Caucasians, anti-Ku was detected significantly more often in African patients ($p < 0.0001$). This is in line with the high prevalence of anti-Ku in African Americans with genuine SLE as previously reported.[22] By contrast, in our cohort, anti-Ku was detected in 25% of SLE patients in overlap with myositis as reported in other Japanese[23] and European studies.[24] Furthermore, anti-Ku antibodies were detected as a single anti-ENA specificity in 62.5% of our patients while in other systemic autoimmune disease they were frequently found associated with other anti-ENA,[22] particularly anti-SSA/Ro, as previously reported.[25] Along with anti-Ku, antibodies to Sm and U1RNP are more commonly reported in African American patients with SLE than in Caucasians.[22,26] While anti-Sm was generally associated with more severe disease,[27] anti-Ku was not correlated with a specific clinical profile. Nevertheless it is remarkable that none of our anti-Ku-positive patients developed lupus nephritis.

The majority of rare anti-ENA antibodies (anti-PCNA, anti-Topo I, anti-Jo-1) were not associated with other anti-ENA specificity, with the exception of anti-centromere, detected with anti- Ro/SSA and anti-LA/SSB in three out of five cases.

However, anti-PCNA, anti-centromere, anti-Jo-1 and anti-Topo-I were detected with a very low prevalence in our cohort and they do not appear to be associated with any specific disease manifestation after long follow-up of patients, except for anti-Topo I. This is in contrast with other reports that found very high prevalence of anti-Topo I[7,9] and anti-PCNA[6] in SLE or a significant association between anti-Jo-1 with lupus pericarditis[28] or uncommon features.[29]

Anti-Jo-1 and anti-Topo I are serologic markers of inflammatory idiopathic myositis and systemic sclerosis, respectively. While anti-Jo-1 SLE patients did not exhibit any features of myositis or anti-synthetase syndrome, two out of three anti-Topo I presented systemic sclerosis in overlap with SLE. This is in contrast with the previous study by Gussin at al.[7] that reported a high prevalence of anti-Topo I antibodies in a genuine SLE without concomitant systemic sclerosis.

Anti-centromere antibodies were detected in 0.92% of our patients, a result that is lower than the one found in other studies using different assays.[30,31] In agreement with previous studies,[30] none of our patients presented clinical features of systemic sclerosis except Raynaud's phenomenon despite being followed for at least five and up to 30 years. Furthermore, though anti-centromere were detected in associations with anti-Ro/SSA+anti-La/SSB in three out of five cases, no clinical signs of Sjögren's syndrome were found in our series as well as in another study.[31]

In conclusion, we reported a high prevalence of anti-ENA antibodies in our cohort, detectable in about 60% of patients. Rare anti-ENA were detectable in more than 15% of patients with anti-ENA positivity. The majority of them are found as a single anti-ENA specificity. Anti-Ki and anti-Ku appear to characterize a subset of disease with a prevalence in males and patients of African origin, respectively. By contrast, except for anti-Topo I, autoantibodies considered markers of systemic sclerosis or myositis did not define any overlap features in our SLE cohort.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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