The role of clinically significant antiphospholipid antibodies in systemic lupus erythematosus

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SUMMARY

The objective is to investigate the role of clinically significant antiphospholipid antibodies (aPL) in a cohort of systemic lupus erythematosus (SLE) patients.

All SLE patients followed for at least 5 years and with available aPL profile at the beginning of the follow-up in our center were studied. Clinically significant aPL were defined as: positive lupus anticoagulant test, anti-cardiolipin and/or anti-β2Glycoprotein I IgG/IgM >99th percentile on two or more occasions at least 12 weeks apart. Patients with and without clinically significant aPL were compared by univariate (Chi square or Fisher's exact test for categorical variables and Student's *t* or Mann-Whitney test for continuous variables) and multivariate analysis (logistic regression analysis). P values <0.05 were considered significant.

Among 317 SLE patients studied, 117 (37%) had a clinically significant aPL profile at baseline. Such patients showed at univariate analysis an increased prevalence of deep venous thrombosis, pulmonary embolism, cardiac valvular disease, cognitive dysfunction and antiphospholipid syndrome (APS), but a reduced prevalence of acute cutaneous lupus and anti-extractable nuclear antigens (ENA) when compared with patients without clinically significant aPL. Multivariate analysis confirmed the association between clinically significant aPL and reduced risk of acute cutaneous lupus [p=0.003, odds ratio (OR) 0.43] and ENA positivity (p<0.001, OR 0.37), with increased risk of cardiac valvular disease (p=0.024, OR 3.1) and APS (p<0.0001, OR 51.12). Triple positivity was the most frequent profile and was significantly associated to APS (p<0.0001, OR 28.43). Our study showed that one third of SLE patients had clinically significant aPL, and that this is associated with an increased risk, especially for triple positive, of APS, and to a different clinical and serological pattern of disease even in the absence of APS.

Key words: Systemic lupus erythematosus; antiphospholipid antibodies; antiphospholipid syndrome; thrombosis; valvulopathy.

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■ INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a heterogeneous spectrum of possible clinical and serological manifestations. Patients with SLE can produce a great variety of autoantibodies including antinuclear antibodies, anti-extractable nuclear antigen antibodies (ENA), anti-double stranded DNA antibodies (dsDNA), but also the so called antiphospholipid antibodies (aPL) such as anti-cardiolipin antibodies (aCL), anti-β2Glycoprotein I antibodies (aβ2GPI) or lupus anticoagulant (LA) (1). Antiphospholipid antibodies are the hallmark of antiphospholipid syndrome (APS), a condition that is characterized by pregnancy morbidity and/or thrombosis and that can be isolated (primary APS) or associated with other autoimmune diseases, in particular SLE (2). Antiphospholipid antibodies have been described in 20-40% of SLE patients, with 50-70% of patients with SLE and aPL showing the clinical features of APS after 20 years of follow-up (3).

We recently described in a multiethnic cohort of SLE patients how the presence of *clinically significant* (persistent medium to high titer) aPL is a risk factor for irreversible organ damage accrual during a fifteen-year follow-up (4). Anyway the collabora-

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tive nature of this retrospective study based on two Lupus registries did not allow us to analyze more deeply the differences between patients with and without significant aPL, in order to explain fully this different prognosis. Physicians dealing with SLE experience how patients with and without aPL show a different disease phenotype. Ünlü et al. (5) recently reviewed how SLE patients with aPL, compared with those without aPL, have a higher prevalence of thrombosis, pregnancy morbidity, but also cardiac valvular disease, pulmonary hypertension, livaedo reticularis, thrombocytopenia, hemolytic anemia, renal vascular lesions and moderate/severe cognitive impairment.

In that context we decided to investigate in a single center SLE cohort the role of *clinically significant* aPL beyond the risk of damage accrual.

■ **MATERIALS AND METHODS**

All the patients with a diagnosis of SLE, classified according to the 1997 American College of Rheumatology Criteria (6) and Systemic Lupus International Collaborating Clinics Criteria (7), who had been followed for at least 5 years and with complete aPL profiles available at the beginning of the follow-up (within ± 1 year of registry entry) in the Lupus registry of our center, were identified and included in the present analysis. Their demographical, clinical and immunological characteristics were retrospectively collected by medical charts. Disease activity was measured by the SLE disease activity index (SLEDAI) 2K (8) at the beginning of the follow-up in our center.

Clinically significant aPL were defined, according to the Updated Classification Criteria for APS (2), as: positive LA test, aCL IgG/IgM antibodies >99th percentile and/or aβ2GPI >99th percentile on two or more occasions at least 12 weeks apart. All the immunological tests were performed in a single referral laboratory and were considered positive if confirmed at least twice during the follow-up (at least 12 weeks apart for aPL). Antinuclear antibodies

were determined by indirect immunofluorescence on Hep-2 cell monolayers, ENA by counterimmunoelectrophoresis using calf and rabbit thymus and human spleen extracts, dsDNA by Farr's radioimmunological method or indirect immunofluorescence on Crithidia Luciliae substrate, total complement activity by the 50% complement hemolytic activity assay, C3 and C4 by nephelometry, aβ2GPI IgG and IgM by immunoenzymatic assay (medium-high titers, >99th percentile, defined as ≥0.5 optical density units), aCL IgG and IgM by immunoenzymatic assay (medium-high titers, >99th percentile, defined as ≥20 G or M antiphospholipid units), LA by coagulation assay. For aβ2GPI in patients followed before the test was available, the first determinations during the follow-up were used.

Categorical variables were reported as proportion and/or percentage. Continuous variables were reported as mean (±standard deviation, SD) or median (range) value. For the univariate analysis the characteristics of patients with and without clinically significant aPL, and of patients with and without single, double and triple aPL positivity were compared by the Chi square or Fisher's exact test for categorical variables and by Student's *t* test or Mann-Whitney-Wilcoxon test for continuous variables as appropriate. Variables that were found to be significantly associated with clinically significant aPL or triple aPL positivity at univariate analysis and that were considered relevant were included in the multivariate analysis by logistic regression analysis (StatView program version 5.1). P values <0.05 were considered significant. When significant, odds ratio (OR) with 95% confidence interval (95%CI) was indicated.

This study was performed according to the principles of the Declaration of Helsinki and the registry was approved by the local Ethics Committee.

■ **RESULTS**

Three hundred and seventeen SLE patients (95% female, 96% Caucasian), prospectively followed in our Unit from 1972 to

2014, were included in the analysis. The mean age at disease onset was 29 (±SD 11) years, the mean age at diagnosis 31 (±SD 11) years. The median follow-up was 14 (range 5-40) years with a median disease duration at the end of the follow-up of 19 (5-53) years.

One hundred and seventeen (37%) patients had a clinically significant aPL profile at baseline. In particular 34 patients (29%) had a single aPL positivity, 35 (30%) a double aPL positivity and 48 (41%) a triple positivity. Fifty-one of these patients (43%) developed an APS during the follow-up. The comparison (by univariate analysis) of demographical, clinical and immuno-logical characteristics during follow-up of patients with and without clinically signifi-cant aPL at baseline is shown in Tables I and II. Patients with clinically significant aPL showed a distinct clinical and se-rological profile. In particular, they had an increased prevalence of deep venous thrombosis (DVT), pulmonary embolism (PE), cardiac valvular disease, cognitive dysfunction and APS, but a reduced preva-lence of acute cutaneous lupus (ACLE) compared to patients without clinically significant aPL. From a serological point of view, they also had a reduced prevalence of ENA, in particular anti-Ro/SSA, anti-Smith and anti-U1RNP antibodies.

Multivariate analysis by logistic regression showed an association between clinically significant aPL and a reduced risk of ACLE (p=0.003, OR 0.43, 95%CI: 0.43-0.24), and ENA positivity (p<0.001, OR 0.37, 95%CI 0.21-0.66), while an increased risk of car-diac valvular disease (p=0.024, OR 3.1, 95%CI 1.16-8.36) and APS (p<0.0001, OR 51.12, 95%CI 12.47-209.5) was observed. The association with PE, DVT, cognitive dysfunction and specific ENA positivity (Ro, Sm, U1RNP) was not confirmed.

To understand better the role of clinically significant aPL, we compared the char-acteristics of patients with and without single, double and triple aPL positivity re-spectively. Univariate analysis showed an association between triple aPL positivity and PE (Fisher's exact test, p=0.012, OR 8.061, 95%CI 1.46-47.29), DVT (Fish-

er's exact test, p<0.001, OR 5.87, 95%CI 2.42-14.25), and APS (Fisher's exact test, p<0.001, OR 17.21, 95%CI 7.96-37.69), whereas a negative association between triple aPL positivity and ACLE was ob-served (Chi square test, p=0.002, OR 0.38, 95%CI 0.19-0.75). Multivariate analysis by logistic regression confirmed the posi-tive association between triple aPL positiv-ity and APS (p<0.0001, OR 28.43, 95%CI 9.71-83.21) and the negative association with ACLE (p=0.02, OR 0.39, 95%CI 0.18-0.86). We did not find any association between single or double aPL positivity and disease characteristics.

■ DISCUSSION AND CONCLUSIONS

This study was focused on a cohort of SLE patients with complete aPL testing at base-line, followed for a median follow-up of 15 years. In this cohort, we observed that around one-third of patients had clinically significant aPL and that such autoantibody positivity was associated with APS, but also with a different clinical and serologi-cal profile even in the absence of APS.

The prevalence of clinically significant aPL in this monocentric cohort (37%) is similar to that we recently described (33%) in a multicentric cohort of SLE, where we demonstrated an association with an in-creased risk of damage accrual during a 15-year follow-up (4). The prevalence of APS in our SLE cohort (19%) is consistent with that previously described in the literature (20%) (3).

The interest of our work was to identify any difference in SLE expression among patients with and without clinically signifi-cant aPL.

Antiphospholipid antibodies are well known to be associated with thrombotic events and adverse pregnancy outcome (2), and these events have been demonstrated to occur more frequently in SLE patients with aPL (9, 10). We were not able to docu-ment the pregnancy history of our patients as the information was not included in the registry. In any case, patients with clini-cally significant aPL had, as expected, an

Table I - Demographical and clinical characteristics during follow-up of patients with and without clinically significant antiphospholipid antibodies at baseline (univariate analysis).

Variable	All patients (n=317)	Patients with significant aPL (n=117)	Patients without significant aPL (n=200)	P value	OR (95%CI)
Female sex, n (%)	300/317 (95%)	112/117 (96%)	188/200 (94%)	0.510	NA
Caucasian ethnicity, n (%)	305/317 (96%)	113/117 (97%)	192/200 (96%)	0.794	NA
Age at onset (years), mean (SD)	29 (11)	29 (10)	30 (11)	0.857	NA
Age at diagnosis (years), mean (SD)	31 (11)	30 (10)	31 (12)	0.872	NA
Duration follow-up, median (range)	14 (5-40)	15 (5-39)	14 (5-40)	1.466	NA
Disease duration end of follow-up (years), median (range)	19 (5-53)	20 (5-53)	18 (5-49)	0.696	NA
SLEDAI-2K score at registry entry, mean (SD)	12 (6)	12 (6)	12 (6)	0.364	NA
Fever, n (%)	125/317 (39%)	50/117 (43%)	75/200 (37%)	0.357	NA
Fatigue, n (%)	246/317 (78%)	90/117 (77%)	156/200 (78%)	0.824	NA
Sicca syndrome, n (%)	176/317 (55%)	59/117 (50%)	117/200 (58%)	0.163	NA
Glomerulonephritis, n (%)	108/317 (34%)	37/117 (32%)	71/200 (35%)	0.482	NA
Arthritis, n (%)	185/317 (58%)	63/117 (54%)	122/200 (61%)	0.212	NA
Myositis, n (%)	2/317 (0.6%)	1/117 (0.8%)	1/200 (0,5%)	0.700	NA
Raynaud's phenomenon, n (%)	139/317 (44%)	50/117 (43%)	89/200 (44%)	0.760	NA
Photosensitivity, n (%)	150/317 (47%)	50/117 (43%)	100/200 (50%)	0.211	NA
Hair loss, n (%)	84/317 (26%)	31/117 (26%)	53/200 (26%)	0.999	NA
Oral ulcers, n (%)	113/317 (36%)	38/117 (32%)	75/200 (37%)	0.368	NA
Acute cutaneous lupus, n (%)	*176/317 (55%)*	*49/117 (42%)*	*127/200 (63%)*	*<0.001*	*0.41 (0.25-0.68)*
Subacute cutaneous lupus, n (%)	17/317 (5%)	3/117 (2%)	14/200 (7%)	0.091	NA
Chronic cutaneous lupus, n (%)	20/317 (6%)	4/117 (3%)	16/200 (8%)	0.105	NA
Purpura, n (%)	18/317 (6%)	6/117 (5%)	12/200 (6%)	0.746	NA
Pleurisy, n (%)	52/317 (16%)	18/117 (15%)	34/200 (17%)	0.708	NA
Lupic pneumonia, n (%)	9/317 (3%)	2/117 (2%)	7/200 (3%)	0.354	NA
Pulmonary embolism, n (%)	*7/317 (2%)*	*6/117 (5%)*	*1/200 (0.5%)*	*0.007*	*10.76 (1.26-240.20)*
Deep venous thrombosis, n (%)	*29/317 (9%)*	*19/117 (16%)*	*10/200 (5%)*	*0.001*	*3.68 (1.55-8.88)*
Pericarditis, n (%)	*41/317 (13%)*	*10/117 (9%)*	*31/200 (15%)*	*0.075*	*NA*
Cardiac valvular disease, n (%)	*28/317 (9%)*	*18/117 (15%)*	*10/200 (5%)*	*0.002*	*3.4 (1.44-8.40)*
Pulmonary Hypertension, n (%)	4/317 (1%)	2/117 (2%)	2/200 (1%)	0.585	NA
Myocardial infarction, n (%)	14/317 (4%)	6/117 (5%)	8/200 (4%)	0.637	NA
Stroke, n (%)	34/317 (11%)	17/117 (14%)	17/200 (8%)	0.094	NA
Epilepsy, n (%)	24/317 (8%)	13/117 (11%)	11/200 (5%)	0.068	NA
Psychosis, n (%)	12/317 (4%)	5/117 (4%)	7/200 (3%)	0.728	NA
Myelitis, n (%)	2/317 (0.6%)	1/117 (0.8%)	1/200 (0.5%)	0.700	NA
Mood disorders, n (%)	71/317 (22%)	29/117 (25%)	42/200 (21%)	0.435	NA
Cognitive dysfunction, n (%)	*38/317 (12%)*	*23/117 (20%)*	*15/200 (7%)*	*0.001*	*3.02 (1.43-6.41)*
Peripheral neuropathy, n (%)	23/317 (7%)	10/117 (9%)	13/200 (6%)	0.498	NA
Antiphospholipid Syndrome, n (%)	*60/317 (19%)*	*51/117 (44%)*	*9/117 (8%)*	*<0.001*	*16.39 (7.30-37.98)*
Leukopenia (<2000 cells/mm^3), n (%)	88/317 (28%)	27/117 (23%)	61/200 (30%)	0.154	NA
Lymphopenia (<1500 cells/mm^3), n (%)	47/317 (15%)	20/117 (17%)	27/200 (13%)	0.385	NA
Thrombocytopenia (100,000 cells/mm^3), n (%)	58/317 (18%)	23/117 (20%)	35/200 (17%)	0.632	NA
Haemolytic anaemia, n (%)	23/317 (7%)	9/117 (8%)	14/200 (7%)	0.132	NA

SLEDAI-2K, systemic lupus erythematosus disease activity index 2000; SD, standard deviation; aPL, antiphospholipid antibodies; OR, odds ratio; 95%CI, 95% confidence interval; NA, not applicable.

Table II - Serological characteristics of patients with and without clinically significant antiphospholipid antibodies at baseline (univariate analysis).

Variable	All patients (n=317)	Patients with significant aPL (n=117)	Patients without significant aPL (n=200)	P value	OR (95%CI)
Positivity for ANA, n (%)	314/317 (99%)	116/117 (99%)	198/200 (99%)	0.897	NA
Positivity for ENA, n (%)	*184/317 (58%)*	*54/117 (46%)*	*130/200 (65%)*	*0.001*	*0.46 (0.28-0.75)*
Positivity for Ro/SSA, n (%)	*138/317 (43%)*	*40/117 (34%)*	*98/200 (49%)*	*0.010*	*0.54 (0.33-0.89)*
Positivity for La/SSB, n (%)	34/317 (11%)	8/117 (7%)	26/200 (13%)	0.087	NA
Positivity for Sm, n (%)	*28/317 (9%)*	*7/117 (6%)*	*21/200 (10%)*	*0.001*	*0.24 (0.09-0.63)*
Positivity for U1RNP, n (%)	*49/317 (15%)*	*11/117 (9%)*	*38/200 (19%)*	*0.023*	*0.44 (0.20-0.95)*
Positivity for other ENA specificities, n (%)	24/317 (8%)	9/117 (8%)	15/200 (7%)	0.950	NA
Positivity for anti-dsDNA, n (%)	280/317 (88%)	103/117 (88%)	177/200 (88%)	0.901	NA
Reduced CH50, n (%)	126/309 (41%)	50/114 (44%)	76/195 (39%)	0.399	NA
Reduced C3, n (%)	144/317 (45%)	56/117 (48%)	88/200 (44%)	0.505	NA
Reduced C4, n (%)	101/317 (32%)	44/117 (38%)	57/200 (28%)	0.093	NA

ANA, antinuclear antibodies; ENA, anti-extractable nuclear antigen antibodies; Sm, anti-Smith antibodies; anti-dsDNA, anti double stranded DNA; CH50, 50% complement hemolytic activity assay; aPL, antiphospholipid antibodies; OR, odds ratio; 95%CI, 95% confidence interval; NA, not applicable.

increased prevalence of venous thrombosis (11). On the other hand, we did not observe an association with arterial events, such as myocardial infarction and stroke. This observation could be explained by the fact that other risk factors, such as traditional cardiovascular risk factors (hypercholesterolemia, hypertension, diabetes and metabolic syndrome) have been shown to be more prevalent in SLE patients and to participate, together with the inflammatory burden associated with disease activity, in the pathogenesis of premature atherosclerosis and arterial ischemic events (12-14).
Other clinical features have been associated with the presence of aPL and described in the clinical picture of systemic manifestations of APS (15). In our study, we confirmed the association with valvular heart disease, one of the possible manifestations of APS, which has been shown to be more prevalent in SLE patients with aPL compared to those without these autoantibodies (16, 17). We also found, as already described, that SLE with clinically significant aPL had more frequently cognitive dysfunction, even if a standardized cognitive examination was not routinely performed in our cohort, possibly limiting the diagnosis to more evident and severe

cases (18, 19). No association was found with other manifestations classically related to aPL, such as thrombocytopenia and hemolytic anemia, but other autoantibodies such as antiplatelet antibodies (directed against platelet membrane glycoproteins) and anti-red blood cell antibodies (mainly directed against Rh molecules) are known to be involved in the pathogenesis of these manifestations (20, 21). The prevalence of pulmonary hypertension in our cohort was probably too low (1%) to study any association with aPL (22, 23). The lack of association between venous thrombotic events, cognitive dysfunction and clinically significant aPL at multivariate analysis possibly suggests that these manifestations are not independent, but belong to the APS spectrum.
Acute cutaneous lupus is known to be associated with ENA, in particular anti-Ro and Sm (24). We were not expecting the inverse association between clinically significant aPL and ACLE or ENA, but we concluded that this observation reflects the fact that SLE patients with clinically significant aPL showed a different disease phenotype, possibly influenced by a different genetic background (25, 26).
Triple aPL positivity was the most frequent

scenario among patients with clinically significant aPL. Such a profile, which is known to be a strong predictor of thrombotic events (27) and pregnancy morbidity (28), was the only one that showed an independent association with APS.

The limitations of our study are the retrospective design and the lack of information about pregnancy outcome and renal non-glomerular disease. Its strengths are the long follow-up and the use of recommended aPL testing in a single referral laboratory.

In conclusion, our study showed that SLE patients with clinically significant aPL have an increased risk, especially if triple positive, of developing APS, but also show a different clinical and serological profile even in the absence of APS.

Conflict of interests: the authors declare no conflict of interest.

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