Autoantibodies Against C-Reactive Protein: Clinical Associations in Systemic Lupus Erythematosus and Primary Antiphospholipid Syndrome

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ABSTRACT. ***Objective.*** To investigate the prevalence of anti-C-reactive protein (CRP) autoantibodies in patients with systemic lupus erythematosus (SLE) and non-SLE patients with persistent antiphospholipid antibodies (aPL) and their association with clinical manifestations.

Methods. Sera of 137 patients with SLE, 127 with persistent aPL and 30 with idiopathic venous thromboembolic disease, were assayed for the presence of anti-CRP reactivity by ELISA. Associations of anti-CRP reactivity with clinical features, with other autoantibodies, and with serum concentrations of C3 and CRP were assessed.

Results. Antibodies against CRP were seen in 51% (n = 137) of patients with SLE and in 54% (n = 127) of patients with aPL. SLE patients with anti-CRP antibodies showed increased frequencies of anti-dsDNA and aPL antibodies compared to those without anti-CRP (52% vs 26% and 68% vs 31%, respectively). Mean serum C3 levels were lower in the subgroup of patients with SLE positive for anti-CRP antibodies (79 ± 25 vs 92 ± 25 mg/dl; p = 0.004) and mean serum CRP levels were significantly higher (13 ± 17 vs 5 ± 8 mg/l; p = 0.01). The frequency of nephritis was higher in SLE patients with anti-CRP antibodies, than in those without (27% vs 13%; p = 0.058). In patients with clinical and serological evidence of antiphospholipid syndrome (APS) the frequency of anti-CRP antibodies was significantly higher than in asymptomatic aPL carriers, in both SLE patients [85% (23 of 27) vs 59% (19 of 32); p = 0.021] and non-SLE patients [76% (38 of 50) vs 19% (9 of 47); p < 0.001]. Among patients with APS with or without SLE, 26 had arterial events, 31 had venous events, 6 had combined arterial and venous events, and 14 had fetal loss. Mean titers of IgG anti-CRP (29 ± 21, 30 ± 19, 60 ± 37, and 26 ± 12 AU/ml) and frequencies of anti-CRP antibodies (88%, 71%, 50%, and 71%) in these subgroups of patients were comparable.

Conclusion. We confirmed the high prevalence of anti-CRP autoantibodies both in patients with SLE and in non-SLE and aPL-positive patients. We observed that the presence of these antibodies was associated with lupus nephritis and with clinical features of the APS in patients with lupus and non-lupus patients. (J Rheumatol 2006;33:1980–6)

Key Indexing Terms:
AUTOANTIBODIES C-REACTIVE PROTEIN SYSTEMIC LUPUS ERYTHEMATOSUS
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Systemic lupus erythematosus (SLE) is the prototype human autoimmune disease. The presence of a great variety of autoantibodies is the hallmark of the disease[1], and the deposit of antigen-antibody complexes within tissues, leading to local inflammation, its pathogenic paradigm[2]. The relationships between different autoantibodies and clinical manifestations have been a matter of intensive study and debate. Despite substantial advances, numerous issues remain to be clarified in order to understand how autoantibodies or subpopulations of autoantibodies are involved in the pathogenesis and manifestations of the disease. Presently it is not possible to predict a particular patient's clinical outcome on the basis of the autoantibody profile alone[3].

Circulating antibodies against C-reactive protein (CRP) have been found in patients with SLE[4,5], and antibody levels were associated with disease activity[6], indicating that these autoantibodies may have biological functions of pathogenic interest.

We assessed the anti-CRP reactivity in sera from 137 patients with SLE. Since the presence of these antibodies was

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significantly increased in the subgroup of SLE patients with antiphospholipid antibodies (aPL), 127 non-SLE patients with documented persistent aPL antibodies were also studied. Our purpose was to identify significant associations between the presence of these antibodies and relevant clinical manifestations of SLE.

MATERIALS AND METHODS

IgG anti–CRP reactivity was retrospectively assayed in serum from 137 patients with definite SLE by American College of Rheumatology criteria[7] and in 127 non-SLE patients with persistent aPL antibodies [defined as a positive IgG/IgM anticardiolipin (aCL) and/or positive lupus anticoagulant (LAC) confirmed at least 6–8 weeks later[8]]; serum samples had been collected between 1994 and 2003. Serum samples were kept frozen in separate aliquots at –70°C until tested. Serum from 80 healthy volunteers (65 women, 15 men) served as the control. Patients with SLE were 119 women, 18 men, aged 15 to 69 years; non-SLE aPL-positive patients were 68 women, 59 men, aged 18 to 75 years. Thirty patients, 18 women, 12 men aged 25 to 68 years, with idiopathic venous thromboembolic disease (VTE) but without antiphospholipid syndrome (APS) were included as a non-APS, VTE control group.

Medical histories of all patients were reviewed for documented evidence of skin disease (malar rash, oral ulcers, photosensitivity, discoid rash), pleuritis/pericarditis, arthritis, cytopenias, arterial or venous thrombotic event, and late-term fetal loss (> 10 weeks of gestation) at any time between disease onset and study entry. Renal status was recorded as either active nephritis (manifested by proteinuria > 500 mg/day, microscopic hematuria, red cell casts and other cell or granular casts, and increased serum creatinine) or inactive kidney disease in remission of previously active nephritis (absence of urinary pathological features) at the time each serum sample was collected. Serological features refer to the same serum in which anti-CRP antibody was measured. Arterial thrombotic events were classified as peripheral arterial thrombosis, cerebrovascular accident, multiinfarct dementia, transverse myelopathy, myocardial infarction, and/or angioplasty. Venous events were classified as deep vein thrombosis, pulmonary embolism, cerebral venous thrombosis, or other sites of venous thrombosis. Patients with any confirmed thrombotic event by positive diagnostic test (Doppler studies, phlebography, arteriography, computed tomography, magnetic resonance scans) were categorized as patients with thrombosis. Diagnosis of lupus nephritis was by histopathology examination of renal biopsies in 25 patients and on clinical grounds in 3 other patients, with similar urinary abnormalities, decreased renal function (creatinine), and low serum C3 concentrations. Disease activity was assessed by retrospective Systemic Lupus Activity Measure[9] result.

The study was approved by the Ethics Committee of the hospital and followed the Declaration of Helsinki principles.

ELISA for anti-CRP and serological assays. Anti-CRP assay was performed by in-house ELISA as described[5] with modifications. Briefly, microtiter plates (Maxisorp; Nunc, Roskilde, Denmark) were coated overnight at room temperature with 100 μl human CRP (Sigma, St. Louis, MO, USA) in carbonate/bicarbonate buffer (pH 9.6) at 1 μg/ml. The plates were washed 4 times with phosphate buffered saline (PBS, pH 7.4) containing 1% bovine serum albumin (BSA). Serum samples were diluted 1/20 in PBS-BSA and added to the plates (100 μl) in duplicates. After 60 min incubation, the plates were washed 4 times with PBS-BSA. Then 100 μl horseradish-peroxidase conjugated goat anti-human IgG (Nordic Immunology, Tilbury, The Netherlands) diluted 1/2000 in PBS-BSA was added to each well. After 1 h incubation at room temperature and washing in PBS-BSA, 100 μl of peroxidase substrate solution (o-phenylenediamine dihydrochloride; Sigma) diluted in PBS containing H_2O_2 was added to each well. Plates were incubated 10 min at room temperature. Optical densities were measured at 490 nm. The value for each serum sample was calculated as the mean of the 2 measurements. The serum with the highest OD level was defined as 100% anti-CRP reactivity. This OD value was identical to that obtained with 1/5000 diluted rabbit peroxidaxe-conjugated anti-human CRP antibody (Dako, Glostrup, Denmark). This serum sample and anti-CRP antibody at the indicated dilution were always included as positive reference in every microtiter plate. Expression of results (percentage of positive control) and calculation of positive cutoff values (95th percentile of OD values in 80 healthy volunteer controls) were as described[10]. Antibodies to double-stranded DNA (anti-dsDNA) were determined by ELISA[12]. Antibodies to extractable nuclear antigens, anti-Sm, anti-RNP, anti-Ro/SSA, and anti-La/SSB were determined by counter-immunoelectrophoresis and ELISA. C3, C4, and high sensitivity CRP (hsCRP) were measured by nephelometric assay (Beckman Instruments, La Brea, CA, USA). IgG and IgM isotypes of aCL were measured by a $ß_2$-glycoprotein I ($ß_2$-GPI)-dependent ELISA[11]. Data were expressed as GPL or MPL units using international reference data. Upper normal values for IgG aCL were 20 GPL units, and for IgM aCL 15 MPL units. Determination of LAC used 2 different screening tests (activated partial thromboplastin time and dilute Russell viper venom time), a confirmatory test (shortening or correction of the prolonged coagulation time by addition of excess phospholipid), and exclusion of other coagulopathies, according to the proposed criteria[13]. All patients with titers of GPL/MPL units > 20 and/or LAC-positive in 2 tests performed at least 6 weeks apart were classified as aPL-positive.

Absorption of serum on CRP and cardiolipin-$ß_2$-GPI substrates. Sera of 10 patients with dual reactivity for CL and CRP diluted 1/20 were incubated in microtiter plates coated with CRP or cardiolipin-$ß_2$-GPI for 1 h at room temperature. Then samples absorbed on the cardiolipin-$ß_2$-GPI substrate were tested for reactivity toward CRP, and samples absorbed on the CRP coated surface were tested for reactivity to cardiolipin-$ß_2$-GPI. Nonabsorbed samples were tested in parallel in the same microtiter ELISA plate. Results are expressed as percentage of binding before absorption.

Statistics. Chi–square test or Fisher exact test was performed for frequency comparison among groups. Correlation between variables was assessed by Spearman's correlation coefficient. Continuous variables were compared by Student's t test. The effect of IgG anti-CRP antibodies on frequency of APS features was evaluated by logistic regression analysis adjusted for sex, age, and time from diagnosis to study entry. CRP values were log-transformed to allow parametric tests. Calculations were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

RESULTS

IgG antibodies to CRP were found in sera from 70 of 137 patients with SLE (51%; $p < 0.0001$), compared to 4 of 80 (5%) controls. The prevalence of serological and clinical features of patients with SLE, subclassified according to anti-CRP reactivity, is given in Table 1. In patients positive for IgG anti-CRP there was a significantly greater frequency of anti-dsDNA and aPL antibodies (52% vs 26%, $p < 0.01$, and 68% vs 31%, $p = 0.008$, respectively); however, serum levels of IgG anti-CRP showed no significant correlation with serum levels of IgG anti-dsDNA antibodies ($r = –0.0432$) or with serum aCL values (GPL units) ($r = –0.0781$) (Figure 1). The possibility of crossreactivity between IgG aCL antibodies and anti-CRP antibodies was excluded by measuring aCL reactivity in 10 double-reactive sera after incubation with CRP coated plates, and vice-versa, anti-CRP reactivity was measured after absorption on the cardiolipin-$ß_2$-GPI substrate (Figure 2). There was no reduction in reactivity to CRP or cardiolipin-$ß_2$-GPI after absorption in any tested sera.

Mean serum C3 levels were significantly lower in SLE patients positive for anti-CRP antibodies, but the frequency of clinically significant hypocomplementemia (serum C3 < 80 mg/dl) was similar in both groups of patients (50% vs 46%;

Table 1. Demographic, serologic, and clinical features of patients with SLE (n = 137), according to presence or absence of anti-CRP autoantibodies. Data are number (%) or mean ± SD.

	Without Anti-CRP Antibodies, n = 67	With Anti-CRP Antibodies, n = 70	p
Female sex	60 (93)	58 (83)	NS
Age at study entry, yrs	32 ± 10	31 ± 8	NS
Time from diagnosis to study entry, yrs	5.5 ± 3	6 ± 4	NS
Serological features			
Anti-dsDNA	17 (26)	37 (52)	0.01
Anti-Ro	22 (34)	31 (44)	0.01
Anti-RNP	17 (26)	21 (30)	NS
Anti-La	11 (17)	9 (13)	NS
Anti-Sm	9 (14)	12 (17)	NS
aCL and/or LAC	21 (31)	48 (68)	0.008
Hypocomplementemia (C3 < 80 mg/dl)	30 (46)	35 (50)	NS
C3, mg/dl	92 ± 25	79 ± 25	0.004
CRP, mg/l	12 ± 17	5 ± 8	0.01
Clinical features			
Skin disease	18 (28)	30 (42)	NS
Serositis	25 (39)	35 (50)	NS
Arthritis/arthralgia	12 (19)	14 (20)	NS
Neuropenia	18 (28)	25 (35)	NS
Renal disease	21 (32)	18 (26)	NS
Active nephritis*	2 (3)	10 (14)	0.03
Inactive kidney disease	7 (11)	9 (13)	NS
aPL-positive			
Thrombosis/fetal loss	4 (6)	23 (31)	0.005
Other aPL associated conditions**	6 (9)	4 (6)	NS
aPL carriers†	13 (11)	19 (13)	NS

* Proteinuria > 500 mg/l, microscopic hematuria, red cell casts and other cell and granular casts, and increased serum creatinine. ** Patients with thrombocytopenia (n = 4), Coombs positivity (1), optic neuropathy (2), transverse myelitis (2), livedo reticularis (1). † Patients with persistent aPL antibodies but without clinical manifestation associated with APS. NS:nonsignificant.

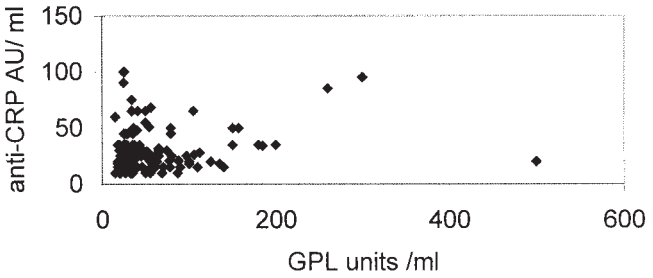

Figure 1. Relation between serum levels of anti-CRP antibodies and titers of aCL antibodies (GPL units/ml). Only anti-CRP-positive sera data are shown. Sixty-one patients had APS, 15 had other aPL-associated conditions, and 19 had lupus nephritis. No significant correlation was observed.

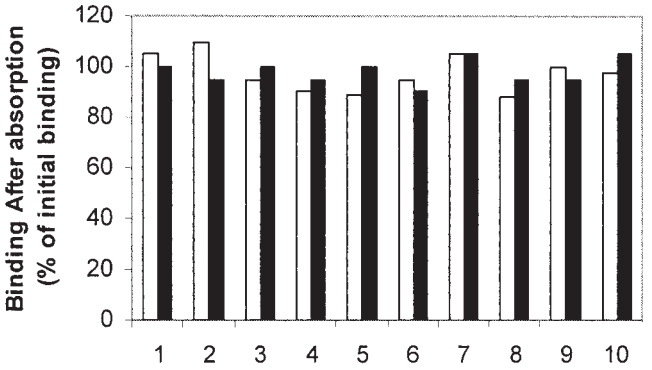

Figure 2. Effect of absorption of double-positive anti-CRP/aCL sera with CRP or cardiolipin-$ß_2$-GPI coated surfaces. Serum was absorbed with coated surface and tested for reactivity to CRP (white bars) or with CRP substrate and tested for reactivity to cardiolipin-$ß_2$-GPI (black bars). Results are expressed as percentage of binding before absorption.

Table 1). Similar results were observed when patients with renal disease were excluded from the analysis. The mean level of serum C3 was significantly lower in patients with anti-CRP antibodies (79 ± 26 vs 92 ± 25 AU/ml; p < 0.01) and no difference was observed in frequency of hypocomplementemia [27 of 52 (52%) vs 24 of 57 (42%); p = 0.56]. In this subgroup of SLE patients without nephritis, multivariate linear regression analysis revealed that presence of anti-CRP antibodies, but not of anti-DNA antibodies, was significantly and inversely associated with serum C3 levels, (anti-CRP: ß = –0.2, t = –2.04, p = 0.04; anti-DNA: ß = –1.6, t = –1.7, p = 0.09; R^2 = 0.08, F = 4.14, p = 0.018). In non–SLE aPL-positive patients mean serum C3 levels did not differ significantly between those with and those without anti-CRP antibodies (Table 2). Significantly higher levels of hsCRP were observed

Table 2. Demographic and clinical features of non-SLE, aPL-positive patients with and without anti-CRP antibodies. Data are number (%) or mean ± SD.

	Without Anti-CRP Antibodies, n = 59	With Anti-CRP Antibodies, n = 68	p
Female sex	31 (52)	38 (54)	NS
Age at study entry, yrs	46 ± 15	47 ± 17	NS
Time from diagnosis to study entry, yrs	2.5 ± 1.5	2.3 ± 1.2	NS
Thrombosis/fetal loss	12 (20)	38 (55)	0.005
Other aPL associated conditions*	9 (15)	11 (20)	NS
Asymptomatic aPL carriers	38 (64)	9 (13)	0.001
C3 < 80 mg/dl	8 (13)	9 (13)	NS
C3, mg/dl	109 ± 32	108 ± 26	NS
CRP, mg/l	4 ± 3	8.4 ± 11	0.006

* Patients with thrombocytopenia (n = 6), Coombs positivity (1), valvular heart lesion (2), seizures (1), cutaneous ulcer (1), livedo reticularis (3), transient ischemic attack (1), transverse myelitis (2), optic neuropathy (1), migraine (2). NS: nonsignificant.

in patients with anti-CRP antibodies among SLE patients (Table 1) and non-SLE patients (Table 2).

Clinical associations of anti-CRP autoantibodies in patients with SLE. The frequency of kidney disease in patients with anti-CRP antibodies was 27% (19 of 70), compared with 13% in those without (9 of 68; p = 0.057). This difference increased significantly when patients with active nephritis were compared with those in remission from previous active nephritis (14% vs 3%; p = 0.03; Table 1).

Clinical thrombosis and/or fetal loss occurred in 37 patients: 27 were aPL-positive (i.e., APS) and 10 were aPL-negative. In the anti-CRP-positive group the frequency of APS was significantly higher compared with those that were anti-CRP-negative (31% vs 6%; p < 0.005). However, the frequency of other clinical features associated with aPL was not different between patients with and those without anti-CRP antibodies (9% vs 6%). The proportion of patients with persistent aPL antibodies but without antiphospholipid associated features (aPL carriers) was similar in those with (13%) and those without anti-CRP antibodies (11%).

Clinical associations of anti-CRP autoantibodies in non-SLE aPL-positive patients. Sixty-eight of 127 (53%) non-SLE aPL-positive patients were positive for anti-CRP antibodies. Thrombosis/fetal loss occurred in 38 of 68 (55%) patients that were anti-CRP-positive, and in 12 of 59 (20%) that were anti-CRP-negative (p < 0.005; Table 2). The frequency of other aPL associated conditions was similar in both groups of patients. Asymptomatic aPL carriers were predominantly anti-CRP-negative (64% vs 13%; p < 0.001).

Anti-CRP antibodies, APS, and idiopathic thrombosis. Sixty-seven patients with SLE were aPL-positive; 27 of these patients had one or more episodes of thrombosis/fetal loss, and 23 (85%) were also positive for anti-CRP antibodies compared with 19 of 32 (59%) of those with no clinical evidence of thrombosis/fetal loss (p < 0.01; Figure 3). In aPL-positive non-SLE patients, the frequency of anti-CRP reactivity in

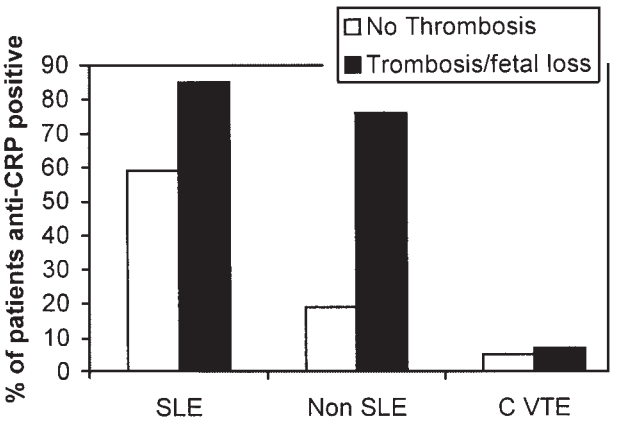

Figure 3. Prevalence of anti-CRP antibodies in aPL-positive patients with and without clinical features of APS and in those with idiopathic venous thromboembolic disease (VTE). C: healthy controls.

those with thrombosis/fetal loss was 76% (38 of 50), as compared with 19% (9 of 47) in asymptomatic aPL carriers (p < 0.001). In 30 aPL-negative patients with deep venous thrombosis and/or pulmonary embolism (control VTE) the prevalence of anti-CRP antibodies was 7% (2 of 30). Among patients with APS with or without SLE, 26 had arterial events, 31 had venous events, 6 had combined arterial and venous events, and 14 had experienced fetal loss. The mean titer of IgG anti-CRP and the frequency of anti-CRP antibodies in these subgroups of patients were comparable (Table 3). As shown, mean serum levels of hsCRP were significantly higher in patients with anti-CRP antibodies compared to those without; therefore we analyzed the interaction between the presence of anti-CRP antibodies, serum levels of hsCRP, and thrombosis. Multivariate regression analysis showed that hsCRP levels were not an independent factor for thrombosis in lupus or non-lupus patients with aPL antibodies (Table 4).

Table 3. Anti-CRP reactivity in subgroups of patients with APS with or without SLE.

	Arterial Events, n = 26	Venous Events, n = 31	Combined Events, n = 6	Fetal Loss, n = 14
Titer of anti-CRP, AU/ml, mean ± SD	29 ± 21	30 + 19	61 ± 37	26 ± 12
Frequency of anti-CRP, n (%)	23 (88)	23 (74)	4 (66)	11 (78)

Table 4. Effect of anti-CRP reactivity and serum levels of CRP on the frequency of APS clinical features in aPL-positive patients with and without SLE; logistic multivariate analysis (adjusted for age, sex, and time from diagnosis to study entry).

Variable	SLE aPL-Positive Patients			Non-SLE aPL-Positive Patients		
	OR	(95% CI)	p	OR	(95% CI)	p
Log CRP, mg/l	1.7	(0.4–7)	0.4	1.5	(0.57–4.8)	0.37
Anti-CRP (yes/no)	4.7	(1.7–12)	0.03	2.6	(1.06–5.9)	0.038

DISCUSSION

Antibodies against CRP have been reported in patients with SLE[4-6], particularly in those with ongoing kidney involvement[6]. We found a high prevalence of these autoantibodies in patients with active nephritis at the time of sampling, and surprisingly, also in those with documented serological and clinical features (thrombosis/fetal loss) of the antiphospholipid syndrome. A similar strong association was observed in patients with primary APS and no evidence of SLE. In patients with persistent aPL antibodies, but with no associated clinical features of the APS, the prevalence of anti-CRP antibodies was higher than in the control population, but significantly lower than in those with the clinical features of the syndrome. In patients with idiopathic venous thromboembolic disease the frequency of the anti-CRP antibodies was similar to that of controls. Levels of high-sensitivity CRP were significantly higher in patients with anti-CRP antibodies compared to those without, in both SLE and non-SLE patients, but only the presence of anti-CRP antibodies was independently associated with thrombosis in patients with aPL antibodies. However, interpretation of these data is not easy. Due to the retrospective design of the study, subclinical active infection at the time of sampling in some patients cannot be completely excluded. Recent studies have shown that hsCRP is often moderately elevated in patients with SLE (as in our patients); however, serum levels were not associated with either disease activity or any particular organ involvement[14,15]. Other investigators have found elevated mean serum levels of CRP in non-SLE patients with LAC, but association with thrombosis was lacking[10]. However, the prospective LUMINA study has shown that the presence of any aPL antibody and serum levels of CRP were significant predictors of future vascular events[16]. Compared with patients without anti-CRP antibodies, those positive for anti-CRP antibodies had a similar prevalence of low C3, in both the SLE and non-SLE aPL-positive patients. The lower mean C3 serum levels observed in the group of SLE patients with anti-CRP antibodies might be due to the higher prevalence of anti-dsDNA and active kidney disease observed in these patients.

The association between the presence of antibodies against CRP and the clinical manifestations that we observed appears to be more than circumstantial, which makes it tempting to suggest that anti-CRP antibodies may contribute to their pathogenesis. Recent investigations have provided evidence of the presence of CRP in lupus nephritis, in both animal models[17,18] and human disease[19]. Experimental evidence points to an antiinflammatory role for CRP. It is conceivable that the mechanisms of protection may be disrupted by the presence of these autoantibodies. Complement-mediated tissue damage is a well known mechanism of glomerular injury in lupus nephritis. Anti-CRP antibodies may bind to their antigen *in situ* in the glomerulus, and contribute to complement-dependent injury by amplifying a classical pathway activation through a synergistic effect with other glomerular-targeting autoantibodies[20]. In addition, anti-CRP antibodies may impair the control of the alternative pathway amplification by CRP that is critical to prevent the formation of the membrane attack complex[21]. Mean serum C3 levels were significantly lower in nephritic and non-nephritic patients with anti-CRP antibodies, and their presence was significantly and inversely associated with serum C3 levels in patients without kidney disease — this association was independent of anti-dsDNA antibodies. These findings suggest increased C3 consumption in SLE patients with anti-CRP antibodies. Regarding APS, the role of CRP in the syndrome, if any, remains unknown. Recent observations point to a possible role for complement activation in the pathogenesis of APS[22]. It is now accepted that the majority of pathogenic aPL antibodies are those that react with the phospholipid-binding protein $ß_2$-GPI[23]. CRP is also a phos-

pholipid-binding protein, but ß$_2$-GPI and CRP bind to distinct anionic phospholipid ligands that might be present in phospholipid-containing surfaces such as apoptotic cells, activated endothelial cells, or oxidized low-density lipoprotein in atherosclerotic lesions[24-26]. Antiphospholipid antibodies alone, or together with anti-CRP antibodies, might react with lipid-binding proteins on endothelial cells to trigger local complement activation, which in turn damages cells, leading to a procoagulant state and eventually to thrombosis. Loss of upregulation of complement inhibitors induced by CRP, as a consequence of the binding of anti-CRP antibodies to CRP, may also be a significant factor in cell damage[27]. Thus, it is theoretically possible that in APS, anti-CRP antibodies may contribute to excessive complement activation occurring in self-tissue. In this regard, we found no significant differences in serum C3 levels among our non-SLE aPL-positive patients, with or without anti-CRP antibodies. However, another study revealed that hypocomplementemia was present in nearly half of patients with primary APS[28]. On the other hand, measurements of concentrations of individual components are of limited value to detect *in situ* local complement activation[29]. Evaluation of soluble terminal complex and/or other split products of complement components is a more reliable indicator of complement activation *in vivo*[30]. This method should be applied to measure *in vivo* complement activation in patients with APS. Theoretically, the potentially damaging presence of these antibodies would not only be reduced to amplify local complement-dependent injury, but would impair other important physiological functions of CRP such as recognition and clearance of apoptotic cells[31], and/or nuclear antigens that may be prominent autoantigens[32].

The mechanism of induction of anti-CRP antibodies remains unknown. Apoptotic cells and blebs are considered the source of autoantigens targeted by the autoantibodies that characterize SLE. Because CRP binds to apoptotic cells, the production of anti-CRP antibodies may result from a general autoimmune response against the autoantigen complex of the apoptotic material[33].

We have demonstrated the high prevalence of anti-CRP autoantibodies in SLE and in patients with primary APS. We also observed strong significant associations of anti-CRP reactivity with nephritis and thrombosis. The retrospective design of our study limits the value of its findings. Additional prospective and pathogenic/experimental studies are needed to clarify whether the presence of these antibodies might be a contributory factor for development of nephritis and/or thrombosis in patients with SLE and in those with primary APS.

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