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PAPER

Non-thromboembolic risk in systemic lupus erythematosus associated with antiphospholipid syndrome

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Objectives: We investigated the impact of secondary antiphospholipid syndrome (APS) and antiphospholipid antibody (aPL) positivity on the non-thromboembolic clinical manifestations of systemic lupus erythematosus (SLE). **Methods:** In total, 224 patients with SLE were studied, of whom 105 were aPL-positive; 52 fulfilled the criteria for APS. SLE- and APS-related clinical and laboratory features were assesed: SLE patients with aPL or APS were compared with those without these features. **Results:** Not only thromboembolic events, but also Coombs-positive haemolytic anaemia, thrombocytopenia and endocarditis occurred significantly more frequently in the aPL-positive than in the aPL-negative patients. In the APS + SLE subgroup, several non-thromboembolic symptoms occurred more often than in the absence of APS: pleuritis, interstitial lung disease, myocarditis, nephritis and organic brain syndrome. The mean number of major organ manifestations (1.2 vs. 0.5) and the overall number of organ manifestations (8.1 vs. 6.9) were higher in the APS + SLE patients than in those without APS ($p < 0.05$). The APS + SLE subgroup more frequently required intensive immunosuppressive treatment than did the APS-negative patients ($p < 0.05$). **Conclusions:** SLE patients with aPL positivity or secondary APS also have a higher risk to develop non-thromboembolic disease manifestations in addition to the aPL-related symptoms, and are predisposed to more severe SLE manifestations. *Lupus* (2014) **0,** 1–6.

Key words: Systemic lupus erythematosus; secondary antiphospholipid syndrome; non-thromboembolic risk; lupus anticoagulant; antiphospholipid autoantibodies

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous systemic autoimmune disease, characterized by immune-mediated inflammation in multiple organs. The course of the disease is tipified by exacerbations and remissions, and the severity of the clinical picture is greatly affected by the number and nature of the various organ manifestations. The mortality in patients with SLE is still considerable, and it may be due to lupus activity, when vital organs are involved; the complications of treatment, in particular infections; or to long-term complications, such as cardiovascular disorders.[1,2]

Typically, patients with SLE produce numerous autoantibodies. Some of the SLE-related autoantibodies, e.g. anti-dsDNA, correlate with disease activity, while others appear to be markers of specific disease subsets (e.g. anti-Ro/SSA); moreover, the presence of antiphospholipid antibodies (aPLs) is definitely pathogenic.[3,4] aPL positivity itself predisposes to accelerated atherosclerosis and to an increased thromboembolic risk.[5–7]

The aPLs form a heterogeneous group of autoantibodies, including lupus anticoagulant (LA), anti-cardiolipin (aCL) and anti-beta2-glycoprotein I (aβ2GPI). The latter two antibodies can be present in IgG, IgM and IgA isoforms, and are directed against anionic membrane phospholipids and associated proteins, and the IgG isotypes in particular are of clinical significance.[6,8,9] The reported prevalence of aPL in SLE varies between 15 and 35%.[10–13]

In the antiphospholipid syndrome (APS), the production of aPLs is accompanied by arterial or venous thrombotic events, or an adverse pregnancy outcome.[14–16] APS can be a primary, independent entity, but also presents as a secondary feature in malignant processes, autoimmune diseases or

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following infections. APS is frequently associated with SLE, and this association leads to hypercoagulability and specific vaso-occlusive, ischaemic lesions. In addition, particular clinical features, such as thrombocytopenia, Coombs-positive haemolitic anaemia, Raynaud's phenomenon, livedo reticularis and non-bacterial endocarditis have been found to be more common in SLE with secondary APS than in SLE without this association.[16,17] APS is also a major predictor of irreversible organ damage and death in patients with SLE,[17] in part because cardiovascular diseases cause a substantial morbidity.

Objectives

In view of the heterogeneity of SLE, it is important to identify prognostic clinical, demographic and laboratory parameters that would facilitate the prediction of the disease outcome in a condition in which an apporopriate early assessment and risk stratification are crucial to prevent life-threatening complications and to decide on the appropriate treatment, including immunosuppressive agents. Certain demographic parameters (e.g. age at onset, gender, etc.)[18–23] and specific autoantibody positivities[24–27] have been found useful in reaching prognostic conclusions. It is well known that the presence of aPLs is of strong predictive value in the development of various micro- and macrovascular organ involvements in which acute or chronic thrombotic mechanisms are key pathogenetic factors.[7,8,28] However, there are no data in the literature as to whether aPL-positive patients are predisposed to other non-thrombotic SLE-related morbidities.

Our present aim was therefore to study the impacts of aPL positivity alone and secondary APS on the clinical presentation of SLE. We investigated whether certain non-thrombotic SLE manifestations appear more frequently in the subgroups of patients with aPL production and definitive APS, and assessed the differences in disease severity and progression and the therapeutic requirements in these subgroups as compared with aPL-negative or APS-negative SLE patients, respectively.

Patients and methods

We performed a retrospective study on consecutive, unselected adult (age $>$ 18 years) patients with SLE attending the Department of Rheumatology, Faculty of Medicine at University of Szeged, Hungary. In total, 224 patients were enrolled, all of whom fulfilled the American College of Rheumatology criteria for the classification of SLE.[29,30] The proportion of female patients was 91% ($n = 204$), and the mean age of the patients at the time of inclusion was 49 (20–92) years, while the average length of time since the diagnosis was established was 13 (0–49) years.

The diagnosis of APS was based on the Sydney criteria.[31] aPL-s were considered positive when at least two determinations 12 weeks apart were positive for LA or aCL or aβ2GPI IgG and/or IgM. The diagnosis of APS required aPL positivity coexisting with documented obstetric and/or thrombotic complications.

Various SLE- and APS-related clinical and laboratory features were compared between patients without or with aPL positivity. The data on the SLE + APS patients were also compared with those on the SLE patients without APS. The parameters were studied in three categories, relating to organ involvement, laboratory parameters and immunosuppressive therapy.

Organ involvement

In this study 31 types of organ involvements of SLE were included. The manifestations involving the heart, the lungs, the kidneys and the central nervous system were regarded as major organ manifestations, as these have a profound impact on the outcome of the disease. The diagnosis of the various lupus-related organ involvements was established on standard clinical methods, radiological or histological signs. Other causes of organ damage or any other pathological condition, e.g. drug- or infection-related symptoms, were excluded. The definitions of selected organ manifestations were as follows.

Nephritis was recorded in the event of biopsy-proven lupus glomerulonephritis exhibiting a characteristic histological picture (class I–V lupus nephritis) or, if a biopsy was not performed, the presence of proteinuria ≥ 0.5 g/d and/or microscopic hematuria and/or cylindruria not explained by any condition other than active SLE.

Pulmonary involvement was diagnosed when specific signs of parenchymal lung disease, including interstitial pneumonitis, chronic fibrosing alveolitis (pulmonary fibrosis) or acute alveolitis were demonstrated by radiological examination.

Organic brain syndrome denoted diffuse brain tissue damage with psycho-organic syndrome.

Skin vasculitis included the clinical presence of cutaneous vasculitis including periungual vasculitis, digital vasculitis, nodular vasculitis, livedo vasculitis, urticaria vasculitis, purpura or crural ulcers, in selected cases verified by histological examination.

Neuropathy comprised cranial and peripheral inflammatory neuropathies.

Secondary Sjögren's syndrome was regarded in the presence of objective and subjective sicca symptoms affecting the eyes and/or the mouth, with decreased tear and/or saliva production, meeting the American-European Consensus Criteria for Sjögren's syndrome.[32]

Laboratory tests

Laboratory variables related to SLE were evaluated, including haemolytic and non-haemolytic anaemia (haematocrit < 35%), leukopenia (WBC < 4.0 G/l), lymphopenia (Ly < 1.5 G/l) and thrombocytopenia (Thr < 100 G/l). Haemolysis was verified with Coombs test and increased reticulocyte count, whereas non-haemolytic anaemia comprised anaemia due to chronic inflammation or lupus-related myelopathy, but other causes, including occult gastrointestinal blood loss, anticoagulation-related gynaecological blood loss, chronic renal failure, etc. were not recorded as lupus-related anaemia. The immunoserological profile of the patients was also assessed: antinuclear antibody (ANA), anti-dsDNA, anti-SSA, anti-SSB, anti-Sm, anti-RNP, aCL, aβ2GPI, LA and hypocomplementaemia (C3 and C4) were examined. The tests were performed at the Department of Laboratory Medicine of our University by means of routine diagnostic methods (ELISA, nephelometry, LA-sensitive coagulation tests, etc.).

Immunosuppressive therapy

Depending on the severity of the disease, milder (e.g. chloroquine) or more potent immunomodulatory agents (eg. cyclophosphamide) were administered based upon the decision of the treating physician. Treatment with oral or i.v. corticosteroid, chloroquine, azathioprine, methotrexate, cyclosporine or i.v. cyclophosphamide was recorded in detail.

Statistical methods

The differences between the occurrence of the various organ manifestations, the immunoserological variables and the different treatment modes in the various subgroups were calculated with the chi^2 test. Levels $p < 0.05$ were regarded as statistically significant.

Results

The most common clinical manifestations, immunoserological abnormalities and immunosuppressive therapies in the overall cohort can be seen in Table 1. The frequency of the distinct aPLs ranged between 20 and 33%. Of the patients, 105 (47%) were found to produce at least one type of aPL, according to the Sidney criteria, and 52 of these aPL-positive patients (23% of the total) fulfilled the criteria for APS (Figure 1). The APS-related clinical manifestations were venous thromboembolism (39 patients), stroke (eight patients), and repeated spontaneous abortion or intrauterine death (nine patients).

The impact of antiphospholipid antibody positivity

Several clinical differences were detected between the aPL-positive ($n = 105$) and negative patients ($n = 119$). The data in Table 2 reveal that not only venous thromboembolism, but also endocarditis, haemolytic anaemia and thrombocytopenia were observed nearly three times more often in the aPL-positive patients than in those without aPLs. Although endocarditis is a relatively rare manifestation of SLE, it occurred exclusively in the aPL-positive patients, supporting the role of aPL positivity as a risk factor in the development of non-bacterial endocarditis. The aPL-positive patients exhibited a significantly higher morbidity than that for the aPL-negative patients, as indicated by the significantly higher total number of organ involvements detected during the course of the disease.

The clinical presentation of SLE with secondary antiphospholipid syndrome

The frequency of APS among our patients is in accord with the literature findings that 15–30% of SLE cases are associated with APS.[14,15,33]

The disease course of the patients in whom SLE was accompanied by secondary APS displayed significant clinical differences as compared with the APS-negative SLE subgroup (Table 3). Patients with APS exhibited major SLE manifestations more frequently than did those patients without secondary APS (average numbers per patient: 1.2 vs. 0.5; $p < 0.05$). Stroke, as a thrombotic event

Table 1 Prevalences of the most common and the major clinical manifestations, the immunoserological abnormalities and the immunosuppressive therapies in the studied SLE patients

	%
Arthritis	89.3
Photosensitivity	65.2
Non-haemolytic anaemia	56.3
Raynaud's phenomenon	54.9
Leukopenia	54.0
Lymphopenia	46.0
Other skin manifestations	32.1
Lymphadenomegaly	31.3
Pleuritis	30.4
Pericarditis	24.1
Butterfly erythema	20.5
Thromboembolism	19.2
Skin vasculitis	18.8
Thrombocytopenia	17.9
Secondary Sjögren's syndrome	17.9
Haemolytic anaemia	14.7
Oral ulceration	10.3
Repeated spontaneous abortion	5.2*
Nephritis	**35.3**
Pulmonary involvement	**8.9**
Organic brain syndrome	**7.1**
Stroke	**4.5**
Myocarditis	**3.6**
Convulsion	**3.6**
Psychosis	**2.7**
Endocarditis	**1.3**
ANA	87.1
anti-dsDNA	76.3
anti-SSA	46.0
anti-SSB	33.9
anti-Sm	21.4
anti-RNP	16.1
anti-CL	35.3
anti-ß2GPI	23.2
LA	24.6
low C3	62.9
low C4	46.4
oral corticosteroid	90.2
i.v. corticosteroid	37.5
chloroquin	62.9
azathioprin	34.4
i.v. cyclophosphamide	25.9
methotrexate	21.0
cyclosporin A	9.8

SLE: systemic lupus erythematosus, aCL: anti-cardiolipin, anti-ß2GPI: anti-beta2-glycoprotein I, LA: lupus anticoagulant, ANA: anti-nuclear antibodies, anti-dsDNA: anti-double stranded DNA, anti-SSA: anti-Sjögren's syndrome A, anti-SSB: anti-Sjögren's syndrome B, iv.: intravenous,
Numbers indicate percentages. *in female patients
The major manifastations are written in bold.

typically present in APS, was excluded from the major manifestations in this comparison. APS also proved to be accompanied by a higher total number of organ involvements in comparison

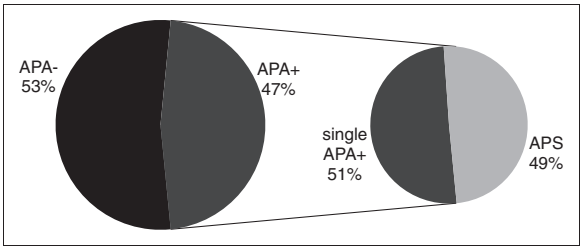

Figure 1 Proportions of aPL-positive, aPL-negative and APS patient subgroups. aPL: antiphospholipid antibody, APS: antiphospholipid syndrome.

Table 2 Clinical differences between the APA + and the APA- SLE patients

	Mean number of total organ involvements	*Endocarditis %*	*Thrombo-embolism %*	*Haemolytic anaemia %*	*Thrombo-cytopenia %*
APA+	7.6	2.8	29.5	21.9	25.7
APA−	6.8	0	10.1	8.4	10.9
p	<0.05	0.101	0.000	0.007	0.005

APA: antiphospholipid antibody, SLE: systemic lupus erythematosus.

with the aPL-negative patients (8.1 vs. 6.9; $p < 0.05$), similarly to that seen in the cases with aPL positivity alone. However, aPL positivity alone did not lead to an increased incidence of major SLE manifestations.

As is to be expected in APS, stroke, thromboembolism and spontaneous abortion were more common in this patient subgroup than in the absence of APS. In addition, a significantly higher proportion of the APS cases than in the non-APS group developed myocarditis, pleuritis, nephritis, interstitial pulmonary involvement, organic brain syndrome or thrombocytopenia (Table 3). Lupus glomerulonephritis was present in more than half of the SLE + APS cases, and renal involvement is known to be crucial in determining the outcome of the disease.

The more severe disease course in APS implies the need for more aggressive therapy. When SLE was complicated by APS, the patients required i.v. corticosteroid, cyclophosphamide, or azathioprine medication significantly more often (Table 3).

Discussion

SLE can present a wide variety of organ involvements. The burden of the disease is even greater

Table 3 Differences in the frequency of selected organ involvements and in the therapeutical requirements between the SLE + APS and SLE + non-APS patients ($p < 0.05$)

	SLE + APS	*SLE + non-APS*
Stroke	15.4%	1.2%
Thromboembolism	75.0%	2.3%
Spontaneous abortion	17.3%	1.25%
Pleuritis	40.4%	24.3 %
Nephritis	53.9%	29.4%
Myocarditis	7.7%	2.3%
Pulmonary involvement	17.3%	6.4%
Organic brain syndrome	13.5%	5.2%
Thrombocytopenia	26.9%	17.8%
Total number of organ involvements per patient	8.1	6.9
Total number of major organ involvements per patient	1.2	0.5
iv. corticosteroid	56%	32%
azathioprine	52%	29%
cyclophosphamide	39%	22%

APS: antiphospholipid syndrome, SLE: systemic lupus erythematosus, i.v: intravenous.

when major manifestations occur, e.g. exhibiting central nervous system, cardiac, pulmonary and renal symptoms. As the disease course is highly variable, ranging from mild, intermittent symptoms to life-endangering flares or a frequently relapsing clinical course, any parameter of predictive value with regard to the severity of the disease is highly informative for both the patient and the treating physician. The presence of certain autoantibodies can indicate an increased likelihood of various organ manifestations. As examples, anti-C1q antibodies are associated with the development of nephritis,[25] and anti-ribosomal-P antibodies with neuropsychiatric SLE,[26,27] and if these autoantibodies are detected, close attention to the early recognition of the development of these serious manifestations may help prevent irreversible organ damage. aPLs are particularly useful in the prediction of thromboembolic events, and treatment guidelines advocate preventive platelet aggregation inhibitor therapy even without previous such events.[33,34] The presence of aPLs not only enhances the thromboembolic risk and accelerates atherosclerosis,[35] but has also been verified to be associated with higher lupus-related organ damage[17] and a poorer survival.[2,17]

Although the contribution of secondary APS to the clinical picture of SLE with regard to APS-specific symptoms has been extensively studied, we have not found any detailed analysis in the literature as concerns the impact of secondary APS on other lupus-related clinical events. Our study has revealed novel aspects of the disease course of SLE combined with secondary APS. The results highlighted several non-thromboembolic SLE manifestations that present more frequently in relation to secondary APS. In accordance with earlier literature data, a significantly higher proportion of the aPL-positive than of the aPL-negative SLE patients developed Coombs-positive haemolytic anaemia, thrombocytopenia or endocarditis. Moreover, we found significant differences in the clinical presentation ofSLE when it was complicated by APS, since various non-thromboembolic symptoms, including pleuritis, interstitial lung disease, myocarditis, nephritis and organic brain syndrome, occurred more often than in the absence of APS.

The presented results also proved that patients with secondary APS are more predisposed to a more severe SLE disease course. The total number of major organ manifestations and the total number of organ manifestations that had ever occurred in an individual patient were both higher in the SLE + APS patients than in those without APS. In contrast, aPL positivity alone was only accompanied by an increased incidence of organ involvements.

The treatment of active SLE itself is a challenge, but the situation is further complicated by secondary APS. Our results confirmed that in the presence of APS, patients with SLE have a need not only for long-term anticoagulant treatment, but also more frequently require powerful immunosuppressive therapy including i.v. corticosteroid, i.v. cyclophosphamide and azathioprine than the non-APS patients ($p < 0.05$).

In conclusion, SLE patients with aPL positivity or with secondary APS are at a higher risk of the development of non-thromboembolic disease manifestations in addition to the aPL-related symptoms. APS usually presents in young or middle-aged SLE patients, and this is followed by a longer disease course and enhanced disease severity, with a predisposition to more extensive organ damage. These results indicate that early screening for aPLs, at the time of the diagnosis in SLE patients, is essential. The higher morbidity and mortality of these patients requires extremely close control with the aim of the early detection of potential nephritis, interstitial lung disease or neuropsychiatric manifestations, with the provision of appropriate, often intense immunosuppressive therapy that can prevent life-threatening organ involvements and complications.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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