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Original

Clinical significance of antiphospholipid syndrome nephropathy (APSN) in patients with systemic lupus erythematosus (SLE)

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A B S T R A C T

Antiphospholipid syndrome nephropathy (APSN) is now a well recognized vaso-occlusive renal lesion associated with acute thrombosis and chronic arterial and arteriolar lesions, leading to zones of cortical ischemic atrophy. Our objective was to evaluate the prevalence and clinical significance of APSN in patients with Systemic Lupus Erythematosus (SLE).

Methods: Kidney biopsy specimens obtained from 162 patients with lupus glomerulonephritis were retrospectively examined for the presence of APSN. Clinical and laboratory data obtained at the time of kidney biopsy and during a mean follow-up of 7 years were recorded. In cases for which serial kidney biopsy specimens were available, the evolution of APSN was examined.

Results: We found APSN in 17 (10.4%) patients with lupus glomerulonephritis (GN), 12 with focal or proliferative lesions. Both activity and chronicity indexes were higher in patients with APSN when compared with lupus nephritis without APSN. Patients with APSN had a higher frequency of hypertension and elevated serum creatinine levels at the time or kidney biopsy, as well as a higher frequency of rapidly progressive GN, nephrotic syndrome and death at the end of the follow-up. Anticardiolipin antibodies were found in 52% of those with APSN and in 27% of those without APSN. Serial kidney biopsy specimens were available from 18 patients. An increase of glomerular sclerosis was found in the second biopsy particularly in those patients with APSN in the first biopsy.

Conclusions: APSN is a risk factor that contributes to an elevated prevalence of hypertension, elevated serum creatinine, nephrotic syndrome and increased glomerular sclerosis. APSN should be included in the classification criteria of APS, and the use of appropriate anticoagulant therapy should be tested.

Significado clínico de la nefropatía del síndrome antifosfolípido en pacientes con lupus eritematoso sistémico (LES)

Palabras clave:
Lupus eritematoso sistémico
Nefritis lúpica
Nefropatía anti fosfolípido

R E S U M E N

La nefropatía del síndrome anti fosfolípido (NSAF) es actualmente una alteración patológica bien definida, caracterizada por la presencia de lesiones renales vaso-oclusivas, trombosis aguda arterial y arteriolar, y que ocasiona zonas de atrofia isquémica cortical. El objetivo del presente trabajo fue analizar la prevalencia y el significado clínico de la NSAF en pacientes con glomerulonefritis (GN) secundaria a Lupus Eritematoso Sistémico (LES). Se analizaron retrospectivamente las biopsias renales de 162 pacientes con GN secundaria a LES, buscando intencionadamente los datos histopatológicos de la NSAF. Se registraron los datos clínicos y serológicos al momento de la biopsia renal y durante el período de seguimiento promedio de 7 años. En los casos en que se obtuvo una biopsia renal subsecuente se analizó el desarrollo de la NASF.

Resultados: Encontramos datos de NSAF en 17 pacientes (10.4%); 12 de ellos tenían lesiones proliferativas focales o difusas. Los índices histopatológicos de actividad y de cronicidad fueron más altos en los pacientes con la NSAF cuando se compararon con los pacientes sin NSAF. Los pacientes con nefropatía anti fosfolípido tuvieron con mayor frecuencia hipertensión arterial, creatinina sérica elevada, síndrome nefrótico, GN rápidamente progresiva y muerte, en comparación con los pacientes con GN lúpica sin NSAF. Se detectaron anticuerpos anticardiolipina en 52% de los pacientes con NSAF en quienes se realizó el examen al momento de la biopsia, en comparación con 27% de los pacientes sin NSAF. Se realizó biopsia renal subsecuente en 18 pacientes; quienes tuvieron NSAF en la primera biopsia tuvieron mayor incremento en la esclerosis glomerular en la segunda biopsia, al compararlo con quienes no tuvieron NSAF en la biopsia inicial.

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Conclusiones: La nefropatía del antifosfolípido es un factor de riesgo para hipertensión arterial, síndrome nefrótico y GN rápidamente progresiva en los pacientes con GN lúpica. La NSAF debiera considerarse en los criterios de clasificación del síndrome anti fosfolípido, y sería recomendable realizar estudios con tratamiento anticoagulante en estos pacientes.

Introduction

The antiphospholipid syndrome (APS) is defined by the presence of antiphospholipid antibodies, recognized as anticardiolipin antibodies (aCL) and/or circulating lupus anticoagulant associated with thrombosis, particularly of the large arteries or veins and/or obstetrical fetal loss (repeated miscarriages or fetal death *in utero*).[1] New clinical and laboratory insights had been addressed at a workshop in Sidney, Australia, before the Eleven International Congress on antiphospholipid antibodies. Based on this, a recent publication[2] suggests the inclusion of anti β_2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma, present on two or more occasions, to the classification criteria.

This syndrome may be primary or secondary, particularly in association with systemic lupus erythematosus (SLE). The frequency of thrombotic complications and the presence of antiphospholipd antibodies was first described in SLE.[3–5] In a compilation of several series, including more than 1000 lupus patients, a prevalence of 34% for lupus anticoagulant and 44% for aCL was found in these patients.[6] Thrombotic events occurred in nearly 30% of lupus patients demonstrating these antibodies. Although renal involvement is often not prominent, numerous observations show its implication in the course of APS, in which it may worsen the prognosis.[7,8]

In a retrospective study[9] 16 cases of primary APS were found and followed for at least 5 years. There was a vascular nephropathy in all patients, characterized by small vessel vasooclussive lesions associated with fibrous intimal hyperplasia of interlobular arteries, recanalizing thrombi in arteries and arterioles, and focal cortical atrophy. The clinical hallmark of this vascular nephropathy was systemic hypertension, variably associated with renal insufficiency, proteinuria or hematuria. In a subsequent retrospective study of 114 patients, Daugas et al[10] reported the presence of APSN in 32% renal biopsies of lupus patients, independently of lupus nephritis findings; those patients with APSN had association with lupus anticoagulant but not with anticardiolipin antibodies, association with extrarenal APS and with a worse prognosis.

We have previously reported[11] the presence of glomerular thrombosis in 36 of 108 lupus nephritis patients, associated with systemic hypertension, nephrotic syndrome and bad prognosis for both renal function and survival. We are now reporting our studies to evaluate the prevalence and prognostic significance of APSN in lupus nephritis patients.

Patients and methods

The present study included 162 patients followed at the Department of Rheumatology, Centro Medico Nacional La Raza, Mexico City. All patients met the American College of Rheumatology criteria for Systemic Lupus Erythematosus (SLE)[12,13] and in all cases renal biopsy was performed due to renal function abnormalities. Patients with vascular lesions probably due to other causes, such as systemic sclerosis, malignant hypertension, hemolytic uremic syndrome, thrombotic thromocytopenic purpura, postpartum renal failure, preeclampsia, diabetic nephropathy, human immunodeficiency virus infection, chemotherapy or patients with previous cyclosporine treatment were not included.

For each patient the following demographic data was obtained: age, gender, duration of SLE and duration of lupus nephritis. We also documented clinical and laboratory data relative to SLE: arthritis, malar or discoid rash, mouth ulcers, photosensitivity, serositis, systemic hypertension (systolic blood pressure >140 mmHg, diastoli blood pressure >90 mmHg), raised srum creatinine levels (>1.4 mg/dl), proteinuria, nephrotic syndrome (urinary protein concentration >3 g/24 hs), leukopenia (white blood cell count $<4000/mm^3$), thrombocytopenia (platelet count $<100{,}000/mm^3$), autoimmune hemolytic anemia, and hyperlipidemia. We also recorded aCL, antinuclear and anti DNA antibodies, and complement levels (C3, C4). Patients were considered to be hypertensive with a systemic blood preassure >160 mmHg and/or diastolic blood preassure >95 mmHg and/or if taking antihypertensive medication.

The renal tissues obtained by needle biopsy were fixed in 10% neutral buffered formalin, gradually dehydrated, and embedded in paraffin. Paraffin sections were stained with eosin and hematoxilin, periodic acid Schiff (PAS), silver methenamine, Masson's trichrome stain, and elastic-Van Gieson stain. In the cases in which TMA was demonstrated on light microscopy, additional paraffin sections were studied for fibrinogen deposits by immunohistochemistry. After dewaxing and dehydration, paraffin sections were transfered to Tris beffered saline (TBS) and subjected to antigen retrieval in a microwave.

The following histologic data were recorded for each renal biopsy: Lupus Nephritis according with the WHO classification.[14] Semiquantitative evaluation of the activity and chronicity indexes.[15] According with previously published reports,[9,10] APS nephropathy was diagnosed when at least one of the following lesions were detected: thrombotic microangiopathy (TMA), characterized for the presence of fibrin thrombi in arterioles and/or glomeruli (acute lesion), or miofibroblastic intimal cellular proliferation leading to intimal thickening of interlobular arteries (FIH), organized thrombi with or without recanalization, fibrous arterial and arteriolar oclussion and subcapsular zone with focal cortical atrophy (FCA) (chronic lesions). In cases of APSN for which serial kidney biopsy specimens were available, the evolution of histologic lesions was examined.

Results

We studied 162 patients, 144 female, with mean age of 27.6 ± 8.1 years and mean disease evolution of 3.5 ± 1.9 years. The mean follow up of these patients was 7.0 ± 4.4 years. The kidney biopsy specimens obtained from patients with lupus nephritis were classified according to WHO criteria as follows: 13 patients with mesangial lupus nephritis, 30 with focal proliferative, 86 with diffuse proliferative, 22 with membranous and 11 with the sclerosing form.

We searched for vascular lesions in all biopsies ($n = 162$) and found vascular abnormalities in 132 cases (81.4%). The most frequent alteration in vesseles was fibrosis in 93 patients (70.4%). Necrosis was noted in 6 patients (4.5%), leukocycoclastic vasculitis in 4 (4.0%), thrombosis in 43 (32.5%) and necrotizing vasculitis in