Nephrotic Syndrome in Scleroderma

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The renal affection is infrequent in scleroderma, unlike other collagen diseases. The appearance of nephrotic syndrome has been related to the drug use, especially the D-penicilamine, or rarely as a manifestation of secondary amylodosis, quite infrequent in scleroderma. We report a case of nephrotic syndrome in a patient with systemic scleroderma, produced by a membranous glomerulonephritis, exceptionally described in literature.

Key words: Diffuse scleroderma. Nephrotic syndrome. Membranous glomerulonephritis.

Síndrome nefrótico en esclerodermia

La afección renal es infrecuente en la esclerosis sistémica, a diferencia de otras colagenosis. La aparición de síndrome nefrótico se ha relacionado con el uso de fármacos, especialmente la D-penicilamina, o raramente como manifestación de amiloidosis secundaria, bastante infrecuente en la esclerosis sistémica. Presentamos un caso de síndrome nefrótico en una paciente con esclerosis sistémica, producido por una glomerulonefritis membranosa, descrito de forma excepcional en la literatura.

Palabras clave: Esclerodermia difusa. Síndrome nefrótico. Glomerulonefritis membranosa.

Introduction

Though membranous glomerulonephritis can be present in a primary form or a secondary one to other diseases, it is not common in patients who have been diagnosed with systemic sclerosis (SS), in whom renal affection is rare, though something characteristic of the disease.[1] Our case corresponds to the appearance of membranous glomerulonephritis in a patient with SS with aggressive characteristics. We will go over the onset and progression of the case and present a review of literature.

Case Report

A 51-year-old woman without any history of exposure to toxins, was diagnosed with systemic sclerosis 10 years before, presenting, at the moment of her diagnosis, interstitial lung disease, constrictive pericarditis, esophageal, joint, and diffuse skin affection. She was initially treated with D-penicilamine with a good skin and respiratory response. Afterwards she was switched to oral cyclophosphamide due to the unfavorable progression of the lung disease. After 3 years of treatment with cyclophosphamide she presented hemorrhagic cystitis as a complication, leading to the suspension of the drug and a transurethral resection 1 year after its appearance. During the progression of the disease she has presented finger ulcers on multiple occasions due to severe Reynaud's phenomenon, which had been treated with intravenous prostaglandins and inhibition of the stellate and axillar ganglia, with a good response.

After 3 years without any relevant systemic events, proteinuria in the nephritic range and hematuria without renal function affection or hypertension were seen during a routine, outpatient visit. She responded initially to angiotensin converting enzyme (ACE) inhibitors, but the signs reappeared after 3 months, this time with hypoproteinemia and lower limb edema, making it necessary to hospitalize the patient for adequate study and treatment. The patient did not have any other symptoms indicating the activity of the baseline disease or any associated constitutional signs.

Upon hospitalization, the physical examination showed acceptable general conditions, blood pressure of 110/50; normal respiratory rate. She had scleroderma skin lesions on the face, neck, and upper thorax. Heart sounds were rhythmical, without any murmurs, heart rate was 70 bpm, and she had bilateral dry rales. Abdominal examination

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Manuscript received February 3, 2006; accepted for publication June 7, 2006.

was normal. No synovitis nor swelling, or limitation in joint mobility was present. She had pitting edema in both legs.

Complementary testing showed positive ANA >1/320 in a speckled pattern with negative anti-DNA and ENA (including anti-RNP), negative ANCA, an elevated ESR (53); total protein, 6.3; CRP, 26; a normal complete blood count; the 24 hour urine analysis showed: volume, 1000 mL; proteins, 6462 mg/L; and creatinine clearance of 93 mL/min; 280 red blood cells in the elemental urine test. The rest of the parameters were normal. An abdominal ultrasound found no interesting data. Based on the compatibility of this information with glomerular affection we proceeded to perform a diagnostic percutaneous renal biopsy. The Congo red stain was negative for amyloidosis. Direct immunofluoresence showed diffuse, intense granular deposits of IgG and, in a lesser quantity, of C3, in the glomerular capillaries. Negative IgA, IgM, and fibrinogen were documented. Upon examination with the optical microscope showed a renal cortex with 19 glomeruli, 1 of them with irregular sclerosis of the capillary walls, associated to mild local mesangial hypertrophy mild interstitial fibrosis in a diffuse distribution, discrete intima hyperplasia of 1 artery. All of these findings, as well as those of the electron microscope (Figure), are compatible with the diagnosis of membranous glomerulonephritis.

Regarding the evolution, proteinuria has partially responded to treatment with mycophenolate mofetil at a dose of 2 g/day installed approximately 1 year ago; with the usual measures she is currently treated with ACE inhibitors and antiotensin II receptor antagonists, aspirin, and clopidogrel as antiplatelet therapy, loop diuretics, and potassium savers. In spite of treatment, she was recently hospitalized due to a bout of massive proteinuria, hypoalbuminemia, and edema, which was treated with intravenous albumin and an intensification of the baseline treatment. To discard the possibility that this worsening was the complication of a renal vein thrombosis an abdominal ultrasound was performed.

Our patient currently continues presenting proteinuria in non-nephrotic ranges and, from a clinical standpoint, has controlled hypertension and barely presents edema. Momentarily, the parameters of renal function are within normal ranges.

Figure. *Glomerular capillary with granular, electron-dense deposits in the subepithelial space and a minor, spiculated response, leading to the diagnosis of membranous glomerulonephritis in its initial stage.*

Discussion

There are very few cases described of nephrotic syndrome associated to SS, most of them in relation to the use of D-penicillamine treatment. There are indications that a relationship might exist with P2 antiribosomal antibodies, detected in a patient with SS who developed nephritic syndrome and improved after the administration of steroids, reducing the titers of these antibodies in the patients serum. It is uncommon that renal amyloidosis appears as secondary to SS, though some cases have also been described.[3]

The largest described series of patients with systemic sclerosis and membranous glomerulonephritis includes 5 patients.[4] Most of them had positive ANA, a positive lupus band test in addition to leukopenia, and/or thrombocytopenia; the authors described these findings as risk factors for the development of kidney disease in these patients. They demonstrated that proteinuria during the course of the disease of the patients in their series predisposed them to an early appearance of systemic sclerosis manifestations such as lung fibrosis, serositis, or alterations in esophageal motility; this coincides with another case of a woman with SS who developed a nephritic syndrome in the postpartum,[5] accompanied by renal failure and the late appearance of pericarditis, and respiratory insufficiency. In this patient, the renal biopsy was inconclusive

Our case represents an exceptional form of nephropathy in a patient with SS, which was not related to the medications usually associated to this and which has seldom been described in the literature.[6] Its association with D-penicillamine treatment is well known, a circumstance that in our case was discarded due to the time that had passed since treatment, more than 6 years. This patient also had severe manifestations of systemic sclerosis such as lung fibrosis, pericarditis, and esophageal hypomotility; however, she did not have any of the characteristics described in the Japanese series of patients as risk factors for the development of kidney affection. On the other hand neither the clinical data nor the analytic characteristics allowed for the suspicion of a case of overlap.

The prognosis of membranous glomerulonephritis is unfavorable; it leads to irreversible renal damage almost in all of the cases and progresses to renal failure in an important percentage of cases, requiring hemodyalisis and, in some cases, kidney transplant.

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