Retroperitoneal fibrosis and membranous nephropathy. Improvement of both diseases after treatment with steroids and immunosuppressive agents

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Introduction

Recent studies [1] suggest that idiopathic retroperitoneal fibrosis belongs to a family of inflammatory diseases of similar morphological appearance (including inflammatory aneurysm, idiopathic mediastinal fibrosis and perianeurysmal fibrosis) now called chronic periaortitis. A common characteristic is represented by marked adventitial infiltration by lymphocytes, plasma cells and fibrosis around advanced aortic atherosclerotic plaques. These pathologic findings as well as the perivascular distribution suggest that the disease may be due to an immune reaction to a component of atherosclerotic plaques [1,2]. Likely candidates are ceroids, a complex of protein and oxidized LDL found in all atherosclerotic plaques. According to Parum et al. [3], the antibodies to ceroids would be produced when the aortic media surrounding the atherosclerotic plaques is breached so that the antigen can be recognized by lymphocytes. Immunoglobulins, mainly IgG, were detected by immunochemistry in close apposition to extracellular ceroids in the necrotic base of plaques with thinned media surrounded by local adventitial inflammation. This hypothesis is also supported by the finding of IgG antibodies to ceroids in the serum of patients with chronic periaortitis [4]. It is still debated, however, whether these antibodies have a pathogenetic role or rather represent an epiphenomenon. As a matter of fact, the same antibodies have been detected in the sera of old healthy individuals and in patients with atherosclerosis but without clinical disease. On the other hand, the described association with sclerod-
unchanged with the exception of a reduced size of the right kidney.

On admission to our unit the physical examination showed severe peripheral oedema and bilateral pleural effusions. The blood pressure was 140/90 with normal heart rate. Plasma creatinine was 1.6 mg/dl (140 μmol/l), plasma urea 68 mg/dl, total serum protein 4.2 g/dl, serum albumin 1.8 g/dl, serum cholesterol 403 mg/dl, triglycerides 444 mg/dl. Serum electrolytes were normal, haematocrit was 22%, white blood cell count was 5800/mm², platelet count was 231 000/mm³, erythrocyte sedimentation rate 82. C3 and C4 were normal. Antinuclear and anti-DNA antibodies were negative. The 24-h urinary protein excretion was 12.7 g, the urinary sediment contained five red blood cells and three white blood cells per high power field, granular and lipid casts were also present. A percutaneous renal biopsy of the left kidney was done. At light microscopy the kidney specimen contained 14 glomeruli one of which was completely sclerotic. There was a widespread thickening of the capillary walls of all glomeruli with subepithelial protein deposits identified in the trichromatic stain. A focal and segmental increase in the mesangial matrix and in mesangial cells was also observed. Hyalin droplets were present in the tubular epithelial cells. Interstitium and blood vessels were normal. Immunofluorescent study revealed diffuse granular type of fluorescence along the capillary walls with antisera against IgG (3+) and C3 (2+). Electron microscopy confirmed the presence of extensive subepithelial deposits with spikes formation. Many deposits were incorporated into a newly formed basement membrane, in some places fresh deposits were noted. The diagnosis was membranous glomerulonephritis. The patient was treated with intravenous methylprednisolone pulses, 1 g each, given every 24 h for three consecutive days followed by oral prednisone at a dose of 0.5 mg/kg/day in a single morning administration for 27 days. After the first month prednisone was stopped and the patient was given chlorambucil 0.2 mg/kg/day for 1 month. This treatment was repeated three times for a total of 6 months. At the end of the sixth month the patient was given prednisone 5 mg/day for maintenance. The treatment was well tolerated. Renal function rapidly improved, anaemia and nephrotic syndrome progressively improved. In August 1993 (after 5 months of therapy) protein excretion had diminished and was in the non-nephrotic range (2.2 g/24 h) and plasma creatinine was 1.3 mg/dl (117 μmol/l). Proteinuria diminished progressively and disappeared completely in April 1994. At the last follow-up visit in June 1998, the patient is still without any proteinuria with plasma creatinine of 1.3 mg/dl. The inflammatory indices, the lipid pattern, serum electrophoresis, haematocrit and blood pressure are normal. The patient was submitted to computer tomography of abdomen in 1994, 1996 and 1998 that showed a marked and progressive reduction of the inflammatory mass.

Discussion

The most frequent complication of retroperitoneal fibrosis is the obstruction of one or both the ureters with frequent hydronephrosis and a variable impairment of renal function. Although, some 40% of patients with retroperitoneal fibrosis have proteinuria [7], possibly as an expression of segmental glomerulosclerosis due to ureteral obstruction, the nephrotic syndrome is quite rare. For this reason we decided to submit our patient to renal biopsy that revealed a membranous nephropathy. To the best of our knowledge only three cases of retroperitoneal fibrosis associated with glomerulonephritis have been described. Lipman et al. [8] reported a patient with nephrotic syndrome and clinical signs and symptoms typical of systemic lupus erythematosus who developed a retroperitoneal fibrosis 5 years later. Renal biopsy revealed a proliferative glomerulonephritis. No other information is available as the renal tissue was examined only at light microscopy. Zabetakis et al. [10] described a patient with diffuse thickening of the glomerular basement membrane and diffuse electrodense intramembranous deposits. In addition, many glomeruli demonstrated capsular adhesions and organized crescents. An immunohistochemical study was not done. Of note, renal function and urinalysis were normal, while antinuclear and antismooth muscle antibodies were positive. Katz et al. [9] described a patient with similar histological findings at light and at electron microscopy and with positive staining for IgG and complement in a granular pattern along the glomerular capillary walls at immunofluorescence. No evidence of circulating autoantibodies was found.

The histological changes observed in the above mentioned cases as well as those seen in our patient are unlikely to be the consequence of obstruction but rather imply an immune complex aetiology. In particular, as in our patient, the glomerular lesions observed by Zabetakis et al. [9] and by Katz et al. [10] can be ascribed to a membranous nephropathy. Although the pathogenesis of membranous nephropathy remains unknown, experimental data suggest that it is an autoimmune disorder characterized by immune-complex deposits in the subepithelial space of glomerular capillary walls formed by the reaction of unbound antibodies with in situ antigens [12].

The optimal management of idiopathic retroperitoneal fibrosis is still unclear because of the paucity of the reports and the lack of controlled trials. At present, long-term administration of corticosteroids, alone or in association with ureterolysis, is recommended for the treatment of idiopathic retroperitoneal fibrosis [7,13]. Unfortunately, a number of patients relapse after discontinuing steroids and for this reason prolonged and close monitoring of the disease is recommended. In a few patients immunosuppressive agents such azathioprine and cyclophosphamide [6,14,15] have been administered either alone or in association with steroids with encouraging results.
Although the treatment of membranous nephropathy is still controversial, prospective controlled trials [11,16] showed that a 6-month regimen with steroids and chlorambucil can significantly improve the probability of remission of nephrotic syndrome and can prevent long-term deterioration of renal function in most patients.

To kill two birds with one stone, we decided to treat our patient with the schedule we are using for membranous nephropathy [11]. The patient eventually experienced a complete and stable remission of proteinuria and at the same time retroperitoneal fibrosis progressively regressed. No reactivation of retroperitoneal fibrosis was observed during the 5-year follow-up.

In conclusion, this case further documents the possible association between periaortic fibrosis and membranous nephropathy. The association between these two diseases, although infrequent, support the hypothesis that retroperitoneal fibrosis develops in patients with a disturbance of immune regulation. Moreover, an immunosuppressive treatment seems to be effective in the long-term not only for membranous nephropathy but also for preventing reactivation of retroperitoneal fibrosis. This last observation should be confirmed, however, by further experience.

References