Renal Amyloidosis Associated with Antiglomerular Basement Membrane Disease

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Dear Sir,

Amyloidosis is a systemic disease characterized by the presence of extracellular deposits of insoluble fibrillar proteins. There are several varieties of amyloid, identified by the nature of the proteins involved; among them, we found the secondary amyloidosis, associated with chronic diseases. The involvement of several organs depends on the type of amyloidosis. Renal involvement occurs in a 75–100% in secondary amyloidosis. Renal amyloidosis is diagnosed observing amyloid deposits especially in glomerular mesangium, although they can also be found in capillaries, vessels and interstitium. These deposits are characterized by their Congo red and/or thioflavine T stain positiveness [1].

Rapidly progressive glomerulonephritis (RPGN) is characterized by a rapid deterioration of renal function and cellular proliferation of the parietal epithelium of Bowman capsule. Without treatment, 80–90% of the patients develop terminal renal failure in less than 6 months.

Immunofluorescence allows to differentiate this disease in three types: type I with linear deposits of immunoglobulins (Ig) IgG often accompanied by C3 deposition, type II with granular deposits of Ig, and type III with no deposits. RPGN can be divided into primary or secondary. Secondary RPGN may be associated with other glomerulopathies, infections or systemic diseases [2]; however, association of RPGN and renal amyloidosis is rare.

We report the case of a 71-year-old woman with chronic rheumatoid arthritis (RA) and rapidly progressive renal failure. Renal biopsy showed amyloid deposition and RPGN, with the particularity of the presence of anti-glomerular basement membrane (anti-GBM) antibodies (lineal IgG) that, as far as we know, has not been reported previously.

A 71-year-old female was admitted to our department because of oligoanuria and acute renal failure. She had been suffering from RA since she was 15. She had been treated with several nonsteroid anti-inflammatory drugs (NSAID). No antecedents such as hypertension, diabetes mellitus, hematuria or hemoptysis were referred to. Four months prior to hospitalization pretibial edema and mild proteinuria were noted, with normal renal function. Three months before

admission, piroxicam was prescribed. At the time of admission physical examination revealed pretibial edema and deformities on the fingers as well as restriction of movement in almost all joints. The rest of the examination was normal. Laboratory data were: plasma creatinine 661 $\mu\text{mol/l}$, plasma urea 38 mmol/l , K 6 mmol/l , pH (venous blood) 7.29, HCO_3^- 14.8 mmol/l ; 24-hour urinary protein was 1.5 g. Urinary sediment contained 60–80 red cells/high-power field. Chest X ray was normal. Renal echography showed normal size kidneys; gallium renal scintigraphy was negative; biopsy of the rectum gave no evidence of amyloidosis. Eosinophiluria was 5%. Immunoglobulins, complement, latex, Waaler-Rose, ANA, anti-DNA and cryoglobulins were normal.

Renal biopsy was performed showing extensive amyloid deposition in mesangium, with extensive cellular proliferation in Bowman's space in 90% of the glomeruli, with severe interstitial fibrosis, focal destruction of tubular epithelium and scattered infiltration of mononuclear cells. Immunofluorescence studies revealed linear deposition of IgG in glomerular basement membrane and fibrin in crescents. On electronic microscopic examination numerous fine fibrils defined as amyloid fibrils were found.

Treatment with anticoagulants (Ancrod) was started; nevertheless renal function did not improve and the patient started hemodialysis.

Renal involvement in patients with long-standing RA is either secondary to amyloidosis or nephrotoxicity. In some cases, unspecific glomerular lesions have been found not associated with any of the former causes. Amyloid deposition appears in 15% of the renal biopsies of RA patients, 75–100% of whom develop renal insufficiency [2].

Our patient had not been treated with D-penicillamine or gold salts; these drugs were implicated as a cause of membranous glomerulonephritis, which reverts after

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stopping the treatment [3, 4]. D-penicillamine was also involved in the appearance of anti-GBM and Goodpasture diseases [5], but this etiology can be discarded because there was not prior antecedent of this drug administration.

The only treatment administered to our patient was NSAID. Several mechanisms of NSAID nephrotoxicity have been described: hemodynamic acute renal failure, papillary necrosis, interstitial nephritis, nephrotic syndrome, vasculitis, hydrosaline metabolism disturbances and hyperkalemia [6]. In our case, the anuria and eosinophiluria focused on an immunoallergic etiology, although eosinophiluria is not a pathognomonic feature [7].

The association of renal amyloidosis with other glomerulopathies is not frequent; one case of membranoproliferative glomerulonephritis and 4 of Lupus nephritis associated with amyloid deposition were reported [8–10]. The occurrence of crescents in renal amyloidosis has rarely been mentioned. A review of the literature shows 5 cases [11–14]. Panner [11] in 1980 described 2 cases of possible amyloidosis associated with RPGN; however, the presence of amyloid fibers could not be visualized in electronic microscopy in the first case and in the other Congo red and thioflavine T stains were negative. In 1984, 2 new cases were reported [12, 13]; Waranabe et al. [13] reported the possibility of the relationship between extracapillary reaction and amyloid glomerular basal membrane lesion, which made the fibrin disruption into the urinary space possible, with the consequent crescent proliferation. In all these reports immunofluorescence was negative.

Anti-GBM disease is characterized by the linear pattern of Ig deposition along the GBM in the context of a RPGN. The pathophysiology of this disease has been studied in experimental models. Complement activation attracts and activates polymorphonuclear leukocytes which synthesize proteolytic enzymes producing glomerular capillary injury. When the complement is not activated, macrophages, which are attracted by activated lymphocytes or by Fc fraction of anti-GBM antibodies, synthesize enzymes which contribute to glomerular injury [2]. The development of anti-GBM antibodies in the context of an amyloidosis secondary to RA could be explained by three mechanisms: first, the modification of the GBM antigenicity due to direct amyloid injury; second, the production of autoantibody anti-GBM in the context of an autoimmune disease such as RA, and third, the drugs received by the patient could have been involved in the anti-GBM antibody development in two ways: one as haptens, responsible for the autoantibody synthesis and the other by the modification of the GBM in a similar way as the amyloid deposition.

In conclusion, we report the first case of renal amyloidosis associated with anti-GBM disease. Although both of them are secondary to an immune process, the relationship between them is difficult to establish, not without discarding the participation of either NSAID or RA in the development of anti-GBM antibodies.

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