Membranous glomerulonephritis with monoclonal immune deposits and crescents

Sir,

Membranous glomerulonephritis is most often idiopathic. However, membranous nephropathy can be secondary to other conditions. In this report, we present an unusual cause of secondary membranous glomerulonephritis. The pattern of injury was unusual in that the membranous nephropathy was associated with crescents. The primary disease was detected following the renal biopsy.

A 29-year-old man presented with generalized malaise, shortness of breath and oedema. At admission, the patient had the following laboratory values: serum creatinine 4.4 mg/dl, blood urea nitrogen 110 mg/dl, white blood cell count 4 × 10^9/l, haemoglobin 7.6 gm/dl, haematocrit 26%, platelet count 367 × 10^9/l, total protein 6.1 mg/dl, serum calcium 8.8 mg/dl. Complements were within normal range. ANA and ANCA titers were negative. Urinalysis was positive for 3+ albumin, 3+ red blood cells and protein: creatinine ratio was 8. Renal biopsy was done to determine the cause of renal failure.

Renal biopsy showed glomeruli with thickened peripheral capillary walls and fine spike like projections. Eleven out of 21 glomeruli were sclerosed. Three glomeruli showed cellular crescents (Figure 1A). Fibrinoid necrosis, inflammatory cells or proliferative features were not present. The interstitium showed moderate interstitial fibrosis and tubular atrophy. On immunofluorescence microscopy, there was diffuse granular deposition of IgA (+] and C3 (+) along the peripheral capillary walls. The deposits were positive for κ light chains (Figure 1C), but negative for IgG, IgM and λ light chains. On electron microscopy, the glomerular capillary walls showed subepithelial deposits that were separated by basement membrane spikes (Figure 1D). The deposits showed fine tubular substructures. Subendothelial and mesangial deposits were not seen.

The renal biopsy diagnosis was: (i) membranous glomerulonephritis, secondary to monoclonal paraprotein deposition; and (ii) crescentic glomerulonephritis.

Follow up was as follows: serum IFE showed monoclonal IgA κ with depressed IgM and IgG. Bone marrow biopsy showed <5% plasma cells. Treatment with prednisone, anti-hypertensive and diuretic agents was initiated. However, the renal function continued to decline and after 1 year the serum creatinine was 6.4 mg/dl. Two small lytic lesions were noted on skeletal survey. Six cycles of chemotherapy were given.

The patient continues to have monoclonal IgA κ on serum IFE. At present, the patient is on dialysis and is being considered for transplant.

Typically patients with lymphoproliferative diseases that present with severe proteinuria have underlying renal amyloidosis. Review of literature revealed one report of membranous nephropathy associated with B-cell lymphoma [1] and one with polycythaemia [2].

In most cases of secondary membranous glomerulonephritis, the relationship to the associated disease is tentative and etiologic implication unproven. However, in this case the deposits were clearly monoclonal and are thus related to the underlying monoclonal gammopathy. Furthermore, the deposits show a fine tubular substructure that is often seen in paraproteins.

This case was also complicated by cellular crescents. Typically, membranous nephropathy with crescents occurs in one of two settings: (i) underlying autoimmune disease [3], or (ii) associated ANCA positive vasculitis [4]. In our case, ANA and ANCA titers were negative.

As a speculation to the underlying etiology, it is possible that the circulating monoclonal immunoglobulin recognizes an epitope on the visceral epithelial cells, and forms immune complexes in the subepithelial location leading to membranous glomerulonephritis.

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Actions on erythropoiesis is ongoing. Of direct relevance to haemodialysis patients [3] provide additional support for their findings.

It is well recognized that a reduction in erythropoiesis due to a decrease in renal erythropoietin (EPO) production, shortened erythrocyte (RBC) lifespan, and induction of oxidative stress and apoptosis are important causes of renal anaemia in patients with HD or end-stage renal disease (ESRD) [4]. L-carnitine has been shown to prolong RBC lifespan and to be beneficial in the treatment of anaemia in animal and human studies including haemodialysis patients. Antioxidant and antiapoptotic effects of L-carnitine have also been described and the elucidation of carnitine-mediated actions on erythropoiesis is ongoing. Of direct relevance to the report of Kitamura et al. [1] is our recent demonstration that the incubation of human endothelial cells in culture with L-carnitine and its acyl derivatives increased both haeme oxygenase-1 (HO-1) mRNA and protein expression [2]. HO-1 is a phase II enzyme induced by oxidative stress [4] and has been shown to possess potent antioxidant and antiapoptotic activity [5]. HO-1 expression in response to oxidative stress is regulated at transcriptional level by phosphatidylinositol 3-kinase (PI3K)/Akt pathway [6]. Interestingly, the antiapoptotic action of EPO, which occurs via EPO-mediated inhibition of proapoptotic caspase activation and attenuation of cell death in response to oxidative stress, has been shown to be dependent on JAK2 signalling and PI3K-mediated phosphorylation of Akt which, once triggered, activates multiple targets with antiapoptotic effects. Therefore, given that both EPO and HO-1 antiapoptotic effects occur via activation of the PI3K/Akt pathway and that carnitines induce HO-1, it appears reasonable to suggest that HO-1 plays an important role in the antiapoptotic effect of both EPO and carnitines. The results of our recent human study further support the existence and in vivo relevance of the importance of HO-1 for the effects of EPO, showing that EPO treatment of chronic haemodialysis patients increased mononuclear cell HO-1 gene expression and improved plasma antioxidant levels [3]. This is in favour of a potentially important increase in antioxidant status. Moreover, the high degree of correlation between haemoglobin and HO-1 expression in our study suggests a possible direct EPO effect [3]. Finally, reports that addition of carnitine improved the response to EPO and the anaemia [7] of chronic haemodialysis patients who failed to respond to EPO and HO-1 related antiapoptotic effects suggest an association between carnitine, EPO and HO-1 pathways. Thus variety of studies, including personal work, show HO-1’s interrelated roles as both an antioxidant and antiapoptotic enzyme and provide a plausible mechanism for the L-carnitine induced increment in mouse bone marrow CFU-E colonies reported by Kitamura et al. [1] as well as the effects of EPO and carnitine on haemopoietic cells in ESRD and patients.

Conflict of interest statement. None declared.

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Fig. 1. The glomeruli show (A) thickened glomerular basement membranes and a cellular crescent, granular capillary wall staining for (B) IgA and (C) k light chains, and (D) subepithelial electron dense deposits.