

Case Report

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Chronic urticaria and mesangial proliferative glomerulonephritis: a case report

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Case presentation

A 34-year-old white female first presented with fatigue, oedema and a Raynaud's phenomenon. She was found to be hypertensive and had a nephrotic syndrome with elevated serum creatinine. The medical history was unremarkable except for chronic urticaria and hypothyroidism of unknown origin. She denied any arthralgias, myalgias, dysphagia, dyspnoea or abortions. Immunoserology showed an elevated ANA, positive SS-A antibodies and a profound hypocomplementemia. Kidney biopsy was performed, which showed some intracapillary glomerular precipitations, an irregular contour of glomerular capillaries and a moderate mesangial cell proliferation as well as a mild, focal interstitial nephritis. Immunofluorescence staining showed mesangial deposits of IgM with some IgG as well as C3 and C1q in the glomerular capillary loops. EM revealed immunoprecipitations in the mesangial cells including scarce deposits in the subepithelial space.

Lupus nephritis was considered to be the most likely differential diagnosis, because patient did not fulfil the diagnostic criteria for SLE. Oral prednisone, cyclophosphamide and an ACE inhibitor were started because of the impaired kidney function and the nephrotic range proteinuria. After 6 weeks of therapy, serum creatinine and complement C3 levels were within normal limits, and proteinuria regressed below 1 g/gCrea after only 3 months. C4 remained suppressed. Cyclophosphamide was given over a total of 6 months and prednisone over 9 months. At 3 months following discontinuation of the oral steroid the patient was referred back because of an increase in proteinuria. Concomitantly, a microhematuria was found in the otherwise asymptomatic patient. Serum creatinine was normal. Although the response to oral steroid therapy was prompt, any prednisone dose reduction <7.5 mg/day was followed by the development of urticarial skin lesions and a relapse of

Background

In glomerulonephritis (GN), glomerular deposition of immune complexes produces complement activation which usually results in hypocomplementemia. Decreased complement levels are most commonly found in patients with membranoproliferative GN and membranous nephropathy due to lupus or to hepatitis B virus infection, while IgA nephropathy and other forms of membranous nephropathy lead to less complement activation [1]. Furthermore, both hereditary complement deficiency and the presence of circulating factors that promote complement activation can cause or contribute to hypocomplementemia in GN. All forms of hereditary hypocomplementemia are associated with a predisposition to immune complex diseases because of an impaired clearance of immune complexes. The most common deficiency is of C1q, and >90% of C1q deficient individuals develop systemic lupus erythematosus (SLE) [2]. Moreover, systemic diseases with renal involvement, such as acute atheroembolic disease, haemolytic-uraemic syndrome or thrombotic thrombocytopenic purpura and sepsis are necessarily excluded when hypocomplementemia is found in the setting of renal insufficiency.

We hereby report on a patient with chronic urticaria who presented with an acute nephrotic syndrome caused by a mesangial proliferative GN and that had the particular feature of persistently depressed serum complement C4 levels.

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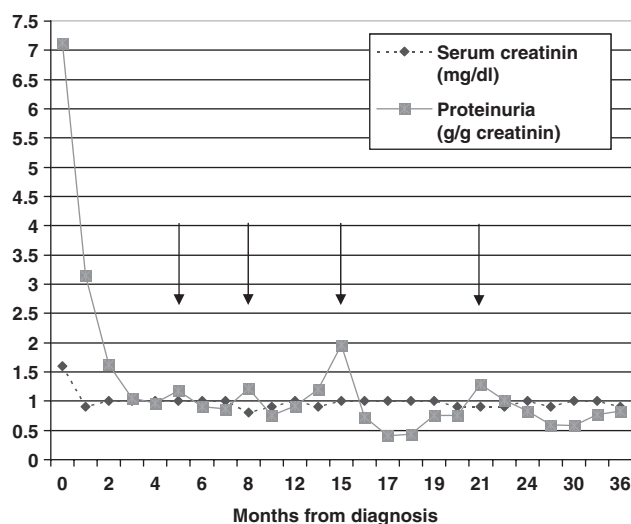


Fig. 1. Time course of urticarial skin lesions (arrows) and proteinuria.

proteinuria (Figure 1). Because the patient preferred not to switch to an alternative immunosuppressive regimen, she was kept on low-dose steroid treatment.

Since our patient showed a complete absence of C4 over the entire disease course, whereas both C3 and C4 were lowered while disease activity was high, an inherited C4 deficiency provided a probable explanation. Measurements of the total haemolytic complement (THC or CH50), used to screen for classical pathway deficiencies and complement levels of both parents were normal. C1q levels were normal and no C1 inhibitor deficiency could be found. Despite a persistently elevated ANA, no dsDNA antibodies or ENA could be detected. A slightly elevated anti-cardiolipin IgG was found on one occasion with anti- β_2 -glycoprotein antibodies being persistently negative. Cryoglobulins were repeatedly negative. No viral hepatitis was detected. Schirmer and Saxon tests were negative and no signs of sialadenitis were found. The common causes of chronic urticaria including *Helicobacter pylori* infection were excluded. In spite of a suspected food allergy, no allergens were identified using either skin and RAST testing or food challenges.

Discussion

Up to now, there have been no published associations between chronic urticaria and kidney disease, although up to 50% of cases of chronic urticaria appear to be autoimmune in origin and urticaria may be the presenting feature of other systemic diseases such as SLE, cryoglobulinemia and urticarial vasculitis. In all these diseases, the pathophysiological role of B cells is well established and all are known to be associated with different forms of GN caused by immune deposits.

To treat the kidney disease of our patient, a variety of differential diagnoses were necessarily considered. Mesangial cell proliferation is a relatively non-specific

response to glomerular injury and is found in a variety of diseases including IgA and lupus nephropathy. In addition, there are apparently idiopathic forms of mesangial proliferative GN which either lack immune deposits or are characterized by focal or diffuse deposits of IgM and complement C3 in the mesangium. The latter disease is called IgM nephropathy and has clinical features similar to minimal change disease except for the lower response rate to steroid therapy [3]. However, serum complement levels are usually normal in mesangial proliferative GN.

To explain the C4 deficiency observed in our patient, it should be realized that non-functional alleles of the two tandemly arranged genes encoding C4, C4A and C4B are common in the general population. Levels of C4 may be 0–75% of normal depending upon the number of null alleles the patient inherits. Deficiencies of C4A or C4B have been associated with the development of membranous nephropathy, IgA nephropathy, Henoch-Schönlein purpura, and scleroderma. Total and partial deficiencies of C4 are also associated with SLE. Indeed, the incidence of homozygous deficiency of C4A is elevated to about 15% in SLE patients compared to <5% in the normal population [4,5].

In SLE, mesangial proliferative lupus nephritis is caused by immune deposits in the mesangium and in the subendothelial space. Mesangial abnormalities can also be found in class V membranous lupus nephritis associated with subepithelial immune deposits; this latter form of lupus nephritis is known to occasionally present with no other clinical or serologic manifestations of SLE.

In patients with primary Sjögren's syndrome, glomerular involvement that usually consists of membranous nephropathy or membranoproliferative GN is much less common than interstitial nephritis. However, in one clinical study following 471 Sjögren patients, 4 of the 20 patients presenting with renal involvement had predominant features of a mesangial proliferative GN. One of these had low C4 levels and two were found to have mixed IgM cryoglobulinemia, but none had a Raynaud's phenomenon or thyroiditis [6].

As a final note, both mesangial and membranoproliferative GN as well as membranous nephropathy have been reported in the context of the hypocomplementemic urticarial vasculitis syndrome (HUVS) [7,8]. The diagnosis can be confirmed by the finding of leukocytoclastic vasculitis, decreased C1q levels, and detection of a C1q antibody in patients with recurrent urticaria-like lesions. The classification of HUV as an overlap syndrome with SLE has been suggested.

In summary, the overall clinical picture of our patient, which includes long-standing chronic urticaria, the clinical presentation of a nephrotic syndrome, hypertension and hypocomplementemia as well as the histopathological findings of a mesangial proliferative GN with some characteristics of membranous nephropathy, strongly suggests an underlying autoimmune disorder, and more specifically an immune complex-related disease. However, diagnostic criteria for SLE,

Sjögren's disease or HUVS were not fulfilled, and sufficient support for a C4 deficiency was not found. Alternatively, an allergen induced B-cell activation could conceivably cause the disease, particularly with regard to the repeated proteinuria accompanied by bouts of urticarial skin lesions.

It is intriguing to speculate that a common mechanism of B-cell activation was responsible for both the skin and glomerular diseases. Assuming that the allergen was a cross-reactive antigen which shared B-cell epitopes with self molecules, GN may have been caused by the activation of autoreactive B-cells. An additional genetic predisposition caused by B cells having an immunoglobulin repertoire biased towards autoantigens or an impaired clearance of immune complexes may be required for disease progression. It is also possible that the increase in vascular permeability caused by allergen-induced mast cell activation and mediator release could promote the deposition of immune complexes in glomerular capillaries with subsequent development of GN.

Conflict of interest statement. None declared.

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