Case Report

Fibrillary glomerulonephritis occurring in association with hereditary angioneurotic oedema, pernicious anaemia and hypothyroidism

Graham Whitaker, Edwina A. Brown, Jill Moss, David Woodrow and Andrew Frankel

Division of Nephrology, Department of Medicine, Charing Cross Hospital, London, UK

Key words: fibrillary glomerulonephritis; hereditary angioneurotic oedema; proteinuria

Introduction

Glomerular disease characterized by Congo red-negative extracellular fibrillary deposits has been increasingly described in reviews of renal biopsies [1,2]. Duffy et al. [1] used the term ‘fibrillary nephritis’ in 1983 to characterize fibrillary glomerular deposits that resembled amyloid, but which differed in that they were larger and did not react to conventional reagents used to identify amyloid histochemically, such as Congo red. Ultrastructural examination of these Congo red-negative deposits reveals predominantly mesangial randomly arranged non-tubular fibrils of 10–18 nm diameter characteristic of fibrillary glomerulonephritis [2].

Hereditary angioneurotic oedema is a relatively rare disorder, transmitted in an autosomal dominant manner characterized by a deficiency in C1 esterase inhibitor.

Hereditary angioneurotic oedema has been described in association with other immunoregulatory disorders including systemic lupus erythematositis, Sjogren’s syndrome, inflammatory bowel disease and pernicious anaemia [3]. Hereditary angioneurotic oedema has also been linked with membranoproliferative glomerulonephritis [3], IgA nephropathy [4], and diffuse proliferative glomerulonephritis [5].

We present the case of a 43-year-old man with a history of hereditary angioneurotic oedema, who presented with proteinuria and who, on renal biopsy, had fibrillary glomerulonephritis.

Case

The patient was first diagnosed with hereditary angioneurotic oedema aged 25, having a low C1 esterase inhibitor level. Six years later, he was found to have a macrocytic anaemia and to be hypothyroid. B12 levels were reduced, parietal cell and microsomal antibodies were positive and a Schilling test confirmed pernicious anaemia. He had first been noted to have one plus proteinuria on urinary dipstick measurement 6 years previously, and at 43 he was referred with proteinuria.

On presentation, he was relatively asymptomatic complaining only of tiring easily. In particular, he had no joint pains or rashes, and described no ankle swelling or shortness of breath. There is a family history for angioedema on the father’s side.

At presentation, the patient was taking thyroxine 175 µg/day, aspirin 75 mg/day, danazol 200 mg/day, eight weekly vitamin B12 and monthly testosterone injections.

On examination, he was overweight, had a blood pressure of 150/100 mmHg and had no oedema. The rest of the examination was unremarkable.

His biochemistry disclosed a serum sodium of 138 mmol/l, potassium 4.7 mmol/l urea 5.7 mmol/l (34.2 mg/dl), creatinine 145 µmol/l (1.64 mg/100 ml) and glucose 5 mmol/l. Total protein was 67 g/l, albumin 30 g/l and protein electrophoresis revealed a high α2-globulin level. Measurements of plasma calcium, phosphorus, C-reactive protein, thyroid function and liver function were all within normal limits.

In a 24-hour venous blood, Haemoglobin was 14.8 g/dl with a white cell count of 9.8 x 10⁹/l and a platelet count of 401 x 10⁹/l.

Complement levels were normal, anti-nuclear antibodies were negative, and the midstream urine sample revealed 3–5 white blood cells/hpf, 3–5 red blood cells/hpf and no casts. Twenty four hour urinary protein excretion was 7.9 g and an ultrasound showed two normal sized kidneys 11.5 cm in size.

Renal biopsy subsequently was performed.

Microscopy

The renal biopsy specimen contained eight glomeruli; one glomerulus was sclerosed while the remainder showed a diffuse increase in mesangial matrix. The matrix increase within the glomeruli was Congo red negative. Small foci of tubule atrophy and tubular...
basement membrane thickening were seen throughout the biopsy, and in these regions lymphocytic infiltrates were present.

Immune studies
There was strongly positive diffuse staining for C3 in the capillary loops and mesangial regions. IgM stains revealed wispy outlining of capillary loops, and fibrin stains revealed wispy staining within the glomerulus. There was no staining for IgA or IgG.

Electron microscopy
Electron microscopy (see Figure 1) revealed glomerular basement membranes to be within normal limits, with segmental foot process effacement of epithelial cells. There was an increase in mesangial matrix, and electron-dense fibrillar material was seen. The fibrils were arranged randomly and were ~20 nm in diameter. These fibrils were about twice the thickness of amyloid fibrils. These findings are consistent with fibrillary glomerulonephritis.

Discussion
Cases of fibrillary glomerulonephritis show a heterogeneous pattern on light microscopy, with mesangiocapillary glomerulonephritis, mesangial glomerulonephritis, crescentic glomerulonephritis and membranous glomerulonephritis all described [6,7]. It is possible that the fibrils represent a form of immune deposits, as immunofluorescent studies have localized IgG, κ and λ light chains and C3 specifically along the fibrils [7].

The term ‘immunotactoid glomerulopathy’ was introduced in 1980 [9] to describe an unusual renal biopsy case demonstrating organized glomerular deposits of IgG. There is some controversy as to whether immunotactoid glomerulopathy can be used as a term to include all Congo red-negative fibrillary/microtubular deposition seen on renal biopsies, or whether the terms fibrillary and immunotactoid glomerulonephritis should be used to describe two separate disorders. We have used the term fibrillary glomerulonephritis to describe random fibrillary deposits of 10–18 nm in size compared with immunotactoid glomerulopathy which is characterized on electron microscopy by larger microtubular fibrils of 16–90 nm in diameter which frequently are more organized. Morphological separation into immunotactoid and fibrillar glomerulonephritis may be relevant clinically as immunotactoid glomerulopathy may have a better prognosis [8].

A study by Fogo et al. [2] found 26 patients with fibrillary glomerulonephritis, all of whom on presentation had marked proteinuria and 16 of whom had microscopic haematuria. At an average of 23 months follow-up, 11 patients had end-stage renal disease and one death due to renal failure had occurred. Fibrillary glomerulonephritis is usually of unknown cause although an association with chronic lymphoctic leukaemia or related B-cell lymphomas has been suggested [8].

This man with hereditary angioneurotic oedema autoimmune hypothyroidism and pernicious anaemia developed nephrotic range proteinuria and microscopic haematuria, and renal biopsy disclosed features of fibrillary glomerulonephritis. The mechanism linking these disorders is unclear. The fact that hereditary angioneurotic oedema, a deficiency in complement,
and two other autoimmune disorders have occurred in association with fibrillary glomerulonephritis suggests that an alteration of immune regulation may act as a common pathogenic mechanism. However, this association remains speculative at this stage.

References


Received for publication: 13.11.97
Accepted: 25.2.98