A male nephrotic patient with rapid decline of renal function

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Case

A 56-year-old African American male presented to the emergency room after 2 weeks of gradually worsening dyspnoea, cough, periorbital and lower extremity oedema, a 20 lb weight gain and dark coloured urine. The patient had a history of hypertension and hypercholesterolaemia, and had been treated with hydrochlorothiazide, lisinopril and atorvastatin.

Three months previously, his blood urea nitrogen (BUN) was 22 mg/dl (7.8 mmol/l), serum creatinine was 1.3 mg/dl (115 μmol/l) and urinalysis showed 3+ proteinuria by dipstick.

Currently, his physical examination revealed a blood pressure of 177/125 mmHg and periorbital and 3+ lower extremity oedema. Initial abnormal laboratory data included BUN of 47 mg/dl, serum creatinine of 3.5 mg/dl, albumin of 1.2 gm/dl, cholesterol of 348 mg/dl, triglycerides of 252 mg/dl and serum creatine kinase of 783 U/l. Blood cell counts and coagulation parameters were within normal limits. Urinalysis showed a pH of 5.5, specific gravity of 1.025, 3+ protein and 2+ blood by dipstick, with a urine sediment notable for 0–4 white blood cells (WBCs) per high power field, 10–15 red blood cells (RBCs) per high power field, some dysmorphic, one RBC cast, few granular casts, occasional epithelial cells and no crystals. No urine eosinophils were identified. Chest radiograph was normal. A 24 h urine collection revealed 11.5 g of protein. Nephrosonogram showed a right kidney 12.5 cm in length, left kidney 12.6 cm in length, no hydronephrosis, but bilaterally increased echogenicity. Additional laboratory work-up revealed normal complement fraction (C3 and C4) levels and negative anti-nuclear antibody, anti-streptolysin-O antibody, anti-neutrophil cytoplasmic antibodies (ANCAs), anti-glomerular basement membrane (GBM) antibody, human immunodeficiency virus-1 antibodies, serum hepatitis B surface antigen, hepatitis C antibodies and cryoglobulins. Serum and urine protein immunofixation electrophoreses revealed no monoclonal gammopathy.

Table 1 summarizes the pertinent clinical course, therapy and renal function parameters, both before and after percutaneous renal biopsy was performed on day 3. Treatment with steroids, followed by mycophenolate mofetil (MMF), resulted in normal renal function and trace proteinuria within 1 year (see Table 1).

Renal biopsy revealed focal (present in 20% of glomeruli) extracapillary cellular crescents, each surrounding a conglomerate of fibrin within Bowman’s space (Fig. 1). No intracapillary fibrinoid necrotizing lesions were identified. Moderate interstitial fibrosis and tubular atrophy were present.

Immunofluorescence microscopy showed diffuse, global finely granular glomerular capillary loop staining for IgG (3+) (Fig. 2), C3 (2–3+), κ (3+), λ (2–3+) and IgA (1+), with no mesangial staining. The extracapillary epithelial cell proliferation showed bright streaks when stained for fibrinogen (3+).

Electron microscopy showed numerous small epi-membranous and partially intramembranous electron-dense immune-type deposits with no mesangial deposits. No endothelial cell tubuloreticular inclusions were identified (Fig. 3).

A diagnosis of membranous nephropathy with epithelial crescents was rendered.

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**Discussion**

Idiopathic membranous nephropathy, although histologically characterized by diffusely thickened glomerular capillary loops, is seldom if ever accompanied by extracapillary epithelial cell proliferation, i.e. crescents. Certain secondary forms, such as those associated with systemic lupus erythematosus, may show intracapillary proliferative features. However, unless accompanied by an active glomerulonephritis, such as class III or IV lupus nephritis, anti-GBM disease or ANCA-associated pauci-immune glomerulonephritis, glomerular crescents are rare.

There have been fairly numerous reports of membranous nephropathy with epithelial crescents, the earliest of which appeared in the literature in the 1970s [1–4], and which included cases of membranous nephropathy both with [2,3] and without [1] superimposed anti-GBM disease. These early reports were followed by additional such cases throughout the 1980s [5–11], which also included cases both with [9] and without [5–8,10] superimposed anti-GBM disease. In some case reports, testing for anti-GBM was either not mentioned [4] or not done [11].

However, with the discovery of ANCA in 1982 [12] and subsequent routine testing for ANCA beginning in the 1990s, all cases of membranous nephropathy with crescents demanded ANCA testing in order to rule out concurrent pauci-immune vasculitic glomerulonephritis. Thus, reports of primary or secondary membranous nephropathy with crescents in the 1990s and beyond stressed the negativity of their cases for ANCA [13–16] unless superimposed ANCA-associated glomerulonephritis was the main focus of their studies [17,18].

Biopsy-proven pauci-immune crescentic glomerulonephritis is not necessarily accompanied by a positive serological test for either c- or p-ANCA. In fact, up to 35% of Wegener’s granulomatous patients and 42% of microscopic polyangiitis patients test negative for ANCA [12].

Thus, the true incidence of membranous nephropathy with crescents, but without associated vasculitic glomerulonephritis or anti-GBM disease, remains nebulous. Experimental animal models and clinical experience, however, do support its existence.

Okuda et al. studied experimentally induced membranous nephropathy (i.e. ‘Heymann nephritis’) in partially nephrectomized rats. They noted that rats with Heymann nephritis and 5/6 nephrectomy experienced global or segmental glomerulosclerosis in ∼70% of glomeruli, and some glomeruli displayed cellular crescents or extracapillary fibrinous exudates. These rats also suffered rapidly progressive renal functional deterioration and increase in proteinuria. They attribute these dire consequences to enhanced glomerular damage by circulating immune complexes and mechanical stress to the few remaining nephrons [19]. Van Damme et al. described 63 clinical cases of membranous nephropathy with ‘capsular lesions’. These lesions consisted of adhesions, focal sclerosis and/or ‘protein crescents’, all of which most probably arose from segmental podocyte detachment. Such detachment may result in injection of ‘plasma-like’ material between the epithelium of Bowman’s capsule and its basement membrane. All cases of membranous nephropathy with such capsular lesions experienced a lower incidence of remission and higher levels of proteinuria and serum creatinine at their last follow-up [20]. Injection of serum into Bowman’s space may cause significant injury, as fibrin deposition

**Table 1.** Renal function parameters, clinical course and therapy

<table>
<thead>
<tr>
<th>Days after presentation</th>
<th>Scr (md/dl)</th>
<th>BUN (mg/dl)</th>
<th>24 h urinary protein (g)</th>
<th>Urine dipstick protein</th>
<th>Course and therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>3.5</td>
<td>47</td>
<td>11.5</td>
<td>3+</td>
<td>Diuretics, antihypertensives given</td>
</tr>
<tr>
<td>1</td>
<td>5.3</td>
<td>66</td>
<td></td>
<td></td>
<td>Oliguric; i.v. pulse methylprednisolone begun (1 pulse/day × 3 days)</td>
</tr>
<tr>
<td>3</td>
<td>7.3</td>
<td>75</td>
<td></td>
<td></td>
<td>Percutaneous kidney biopsy</td>
</tr>
<tr>
<td>5</td>
<td>10.1</td>
<td>128</td>
<td></td>
<td></td>
<td>I.v. steroids switched to oral</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>66</td>
<td></td>
<td></td>
<td>Non-oliguric; 4.54 kg weight loss; decreased lower extremity oedema</td>
</tr>
<tr>
<td>43</td>
<td>1.6</td>
<td>38</td>
<td>2.2</td>
<td>3+</td>
<td>Urine sediment still containing 6–8 RBCs and 8–10 WBCs; persistently low serum albumin and high cholesterol</td>
</tr>
<tr>
<td>60</td>
<td>1.5</td>
<td>0.906</td>
<td></td>
<td></td>
<td>Steroid taper and MMF begun (maximum dose 1 g bid); oedema subsides on diuretics</td>
</tr>
<tr>
<td>150</td>
<td>1.4</td>
<td>19</td>
<td></td>
<td>0</td>
<td>Cr cl 70 cc/min; urine sediment bland; serum albumin 3.6 g/dl; lipid levels normalized on atorvastatin</td>
</tr>
<tr>
<td>450</td>
<td>1.6</td>
<td>19</td>
<td>0.129</td>
<td></td>
<td>Normal urine sediment and U/A on MMF, metoprolol, nifedipine, furosemide, atorvastatin; random urinary protein/creatinine ratio 101 mg/g (normal). Off steroids × 3 months</td>
</tr>
<tr>
<td>483</td>
<td>1.6</td>
<td>19</td>
<td></td>
<td></td>
<td>Cr cl 61 ml/min; normal serum albumin and lipid profile</td>
</tr>
</tbody>
</table>

Normal ranges: BUN, 8–21 mg/dl; Scr, 0.7–1.3 mg/dl; urine dipstick protein, negative. Scr = serum creatinine; BUN = blood urea nitrogen; RBCs = red blood cells; WBCs = white blood cells; MMF = mycophenolate mofetil; Cr cl = creatinine clearance; U/A, urinalysis.
within Bowman’s space has been shown to be the essential step in cellular crescent formation [21,22].

Our patient had nephrotic syndrome with nephritic sediment and rapidly progressive renal insufficiency, but negative serological work-up for autoimmune conditions, including ANCA-associated glomerulonephritis, lupus or other connective tissue disease, and anti-GBM disease. Considering the absence of a ‘full house’ immunofluorescence pattern, mesangial deposits, tubuloreticular inclusions and intracapillary necrotizing lesions, this case convincingly appears to be one of membranous nephropathy with crescents and without a separate superimposed glomerulonephritis.

The persistence of nephrotic range proteinuria with rapid renal functional deterioration, in the presence of crescents on renal biopsy, places this patient in the category of high-risk membranous nephropathy. Potent immunosuppressive regimens, such as cyclophosphamide, in addition to steroids, are usually used in such cases in an attempt to halt progression to end-stage renal failure [23]. Recently, however, MMF has emerged as an efficient immunosuppressive drug with a lower risk profile compared with other steroid-sparing agents, such as cyclophosphamide [24,25]. Thus, MMF was utilized with success in this patient, while prednisone was gradually tapered and, ultimately, discontinued.

Teaching points

1. When a nephrotic syndrome of unclear origin displays accelerated decline of renal function, with nephritic sediment, a full serological work-up, followed by kidney biopsy, should be performed.
2. In such a case, membranous nephropathy with crescents, unassociated with a separate superimposed glomerulonephritis, is rare but can occur.
3. Prompt identification of this entity followed by aggressive immunosuppressive treatment may rescue renal function.

Conflict of interest statement. None declared.

References