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Case Report

Hypocomplementaemic immune complex tubulointerstitial nephritis

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Abstract

We report a rare cause of rapidly progressive renal failure associated with low complement, positive ANA but negative anti DS-DNA. A renal biopsy demonstrated tubulointerstitial nephritis with positive immunoglobulin staining involving the interstitium and tubular basement membrane but glomerular sparing. A review of the literature and differential diagnosis are discussed.

Keywords: hypocomplementaemic; immune complex; tubulointerstitial

Introduction

Rapidly progressive renal failure (RPRF) warrants rapid diagnosis so that treatment options can be readily instituted. Most often, in association with other clinical and laboratory findings, the diagnosis will be a rapidly progressive glomerulonephritis. However tubulointerstitial processes can sometimes present with similar patterns. Below we describe a rare case of immune complex tubulointerstitial renal disease.

Case

A 41-year-old female was referred to our centre for rapidly progressive renal failure in January 2009. Her symptoms began in September 2008 with dysuria, diagnosed as a urinary-tract infection treated with a short course of ciprofloxacin. After 1 month, she had recurrence of her dysuria and further investigations done at that time revealed a creatinine of 205 μmol/l; haemoglobin 90 g/l; urine blood 1+, protein 1+ and a urine culture positive for *Klebsiella pneumonia*. She was treated with cotrimoxazole. Her baseline creatinine was 72 μmol/l in May 2007 which increased to 393 μmol/l by December 2008. There was no history of arthralgias, skin rash, oral ulcers, hypersensitivity, sicca, Raynaud's phenomenon, jaundice, use of herbal medicines or non-steroidal anti-inflammatory medications. Her blood pressure was 140/80 mmHg and the remainder of the physical examination was non-contributory.

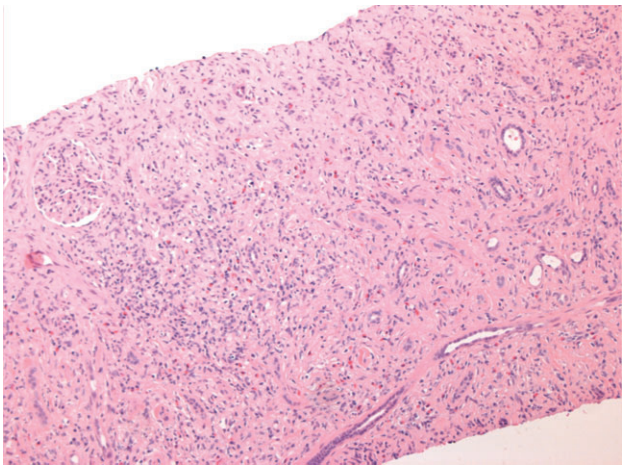

Fig. 1. Histology of the renal cortex. The interstitium contains a large number of inflammatory cells: plasma cells, lymphocytes, macrophages and occasional eosinophils (haematoxylin and eosin stain).

Urine analysis showed 4+ blood; 2+ protein; haem-granular and RBC casts; 24-h urine protein 1 g/day; haemoglobin 88 g/l (normochromic, normocytic); creatinine 448 μmol/l; C3 0.30 g/l (0.79–1.52); C4 0.02 g/l (0.16–0.38); CH50 1.9 (60–145); positive p-ANCA at 1:80; positive RA factor 46 IU/ml (normal 0–19), ANA >1:640. The remainder of the serologic work up including, anti-dsDNA, anti-Smith, LE cells, anti-Sm/RNP, anti-Jo 1, anti-Scl 70, anti-SSB (La), anti-SSA (Ro), HBsAg, anti-HCV, anti-HIV and serum protein electrophoresis, was negative. Chest X-ray, ECG and 2D echo were normal. A renal ultrasound demonstrated normal sized kidneys with increased echogenicity and no hydronephrosis. On renal biopsy, one of six glomeruli was sclerosed and few demonstrated collapsed capillary loops with increased mesangial matrix, but neither necrosis, nor spikes on silver stain were revealed. Within the interstitium, there were a large number of inflammatory cells predominantly composed of plasma cells, lymphocytes, macrophages and occasional eosinophils (Figure 1). There were no granulomas. There was marked diffuse interstitial fibrosis with atrophic tubules in most

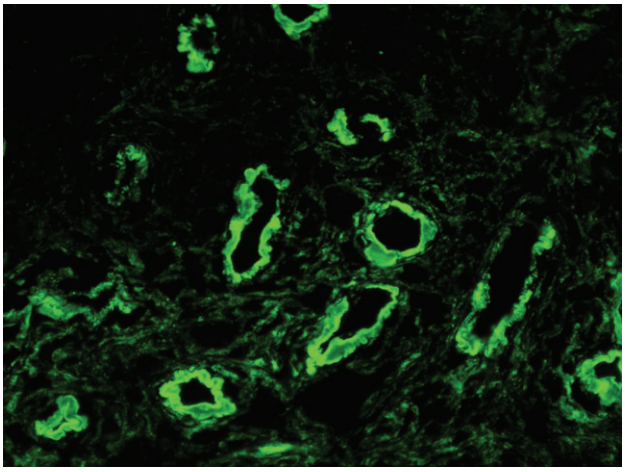

Fig. 2. (Online supplementary material): Immunofluorescence stain. Immunostaining shows a heavy deposition of IgG along the tubular basement membrane (immunofluorescence, FTIC-labelled anti-human IgG).

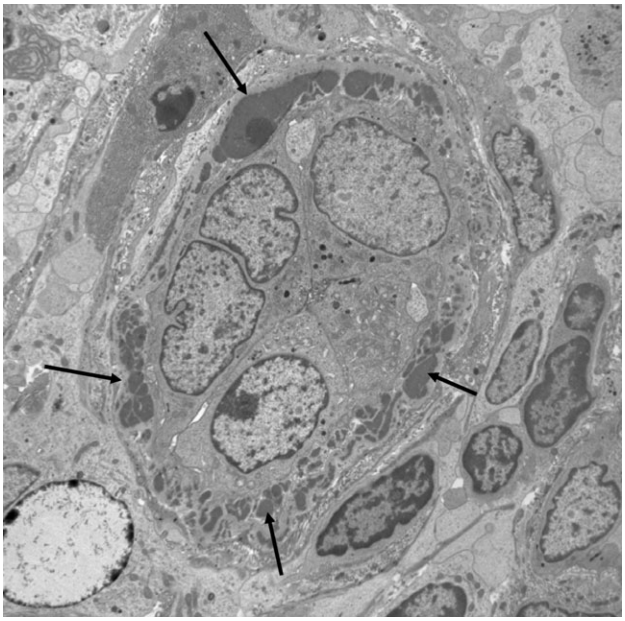

Fig. 3. Electron microscopy. The tubular basement membrane contains abundant electron-dense deposits (arrows), consistent with immune complexes.

areas. There was arterial medial thickening, but no vasculitis. Immunofluorescence (IF) staining showed tubular basement membrane (TBM) deposits of IgG, IgM and C3, with deposition of immunoglobulin around the Bowman's capsule (Figure 2 online supplementary material). Electron microscopy (EM) revealed abundant electron-dense deposits in TBM (Figure 3).

The patient was treated with 1 g IV methylprednisone for three consecutive days followed by oral prednisone 1 mg/kg (60 mg). Her creatinine decreased from 493 to 273 μmol/l over next week. She was discharged and followed up in the ambulatory clinic. At 10 weeks post-therapy, her last creatinine was 156 μmol/l and the prednisone was tapered to 15 mg daily.

Discussion

This patient presented with RPRF with associated features of active urine sediment, strongly positive ANA and low complements. The differential diagnosis in this setting included lupus nephritis, membranoproliferative glomerulonephritis (MPGN), cryoglobulinaemia and post-infectious glomerulonephritis. The positive p-ANCA adds consideration to a diagnosis of vasculitis. All of the above diagnoses have significant glomerular pathology with minimal or no tubulointerstitial nephritis. We diagnosed this case as hypocomplementaemic immune-complex tubulointerstitial nephritis, a very rare cause of tubulointerstitial nephritis. Only 11 such cases have been described in the literature [1–4]. Kambham *et al.* reported the largest series, with eight cases of tubulointerstitial nephritis with tubulointerstitial immune deposits in adults with hypocomplementaemia with no evidence of SLE or Sjogren's disease [3]. Hypocomplementemia, TBM immune complexes and glomerular sparing were consistent findings in all these cases [1–4]. The pathogenesis of the deposits is unknown. TBM immune complexes are either formed *in situ* or deposited preformed. ANA was positive in 4/11 cases [1–4]. The disease appears to be progressive in nature. Experience regarding treatment is limited. Prednisone was used in 10/11 cases either alone (7/11) or in combination with other immunosuppressive agents [2–5]. The duration of treatment and follow-up ranged from 3 to 12 and 3 to 36 months, respectively. Renal function as reflected by serum creatinine improved in 7/11 and deteriorated in 2/11 cases. Potential response to immunosuppression warrants early identification and treatment. Systemic lupus nephritis (SLE) sometimes presents predominantly with tubulointerstitial nephritis [5]. Mori *et al.* reported such a case and reviewed the literature of only 10 reported cases. All of them fulfilled American Rheumatology Association (ARA) criteria for the diagnosis of SLE. The biopsy showed severe tubulointerstitial nephritis without significant glomerular changes. SLE as the underlying disease was excluded in our case presented here, as it did not meet ARA criteria. Sjogren's syndrome (SS) is another important differential in this case scenario. Negative serology for anti-Ro and anti-La, low complements and paucity of clinical symptoms ruled out SS in this case [6]. TINU (tubulointerstitial nephritis and uveitis) was ruled out due to the absence of ocular symptoms, low complements and the presence of immune-complex TBM deposits [7]. ANCA-associated vasculitis presenting as isolated tubulointerstitial nephritis has been reported in the literature [8]. However, the presence of low complements and positive IF excluded this possibility. A similar argument discounted any possibility of drug (ciprofloxacin)-induced acute interstitial nephritis (AIN) [9].

In summary, this appears to be a rare cause of AIN. The weight of evidence suggests that it is immunologically mediated predominant tubulointerstitial nephritis with sparing of glomeruli. It is associated with multiple autoantibodies including ANA, ANCA and RA. However, at present, this appears to be a heterogeneous disorder of unknown specific aetiology.

Supplementary data

Supplementary data is available online at http://ndtplus.oxfordjournals.org.

Conflict of interest statement. None declared.

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