on 15 September 2017

Sir,

Hepatitis C virus (HCV) infection is among the known main causes of glomerulonephritis. Membranoproliferative glomerulonephritis associated with cryoglobulinaemia is the predominant form in HCV-infected patients. Less common glomerular diseases, i.e. membranoproliferative glomerulonephritis without cryoglobulinaemia, membranous glomerulonephritis, focal segmental glomerular sclerosis, proliferative glomerulonephritis, renal thrombotic microangiopathy associated with anti-cardiolipin antibodies and fibrillary and immunotactoid glomerulopathies, have also occurred in these patients. We encountered a patient with chronic HCV infection presenting nephrotic syndrome due to minimal-change nephropathy.

A 49-year-old Japanese man with a 15-year history of chronic hepatitis C was admitted because of sudden onset of systemic oedema. He had no past history of urinary abnormalities, oedema, hypertension, interferon treatment, or non-steroidal anti-inflammatory drug use. On admission, he showed normotension, bilateral leg oedema, massive proteinuria (13.6 g/day) with 4+ haematuria, hypo-albuminaemia (2.1 g/dl) and renal dysfunction (serum creatinine, 2.33 mg/dl; blood urea nitrogen, 31 mg/dl), indicating acute renal failure due to nephrotic syndrome. He showed progressive anaemia (haemoglobin 9.6 g/dl) and thrombocytopenia (6.3 × 10^9/l) with no remarkable findings for blood smear. Coagulation screening and liver biochemistry results were normal, but haptoglobin levels were undetectable, suggesting possible haemolytic anaemia. Serological tests showed normal complement concentrations and negative results for direct Coomb’s test, anti-nuclear antibodies, anti-double-stranded-DNA antibodies and anti-cardiolipin antibodies except for cryoglobulin. Serum HCV RNA quantified by polymerase chain reaction was 3100 kIU/ml (reference range, <0.5). The specimen obtained at percutaneous renal biopsy performed on day 10 showed minor glomerular abnormalities with slight interstitial mononuclear cell infiltration. Glomeruli showed no thrombus, endothelialmesangial cell swelling, or crescent formation. No remarkable vascular lesions were identified. Immunofluorescence study revealed no significant deposits of immunoglobulins or complements, and no staining for IgA, IgG, IgM, complement, or cryoglobulins. Electron-microscopic examination showed effacement of foot process of epithelial cells without electron-dense deposits along capillary walls, compatible with minimal-change nephropathy. During the 3 week hospitalization, his haemolytic anaemia, thrombocytopenia and renal dysfunction spontaneously improved (haemoglobin, 12.3 g/dl; platelets, 170.0 × 10^9/l; haptoglobin, 61 mg/dl; serum creatinine, 1.18 mg/dl). Marked proteinuria (10.1 g/day) and leg oedema, however, remained; thus, oral prednisolone (40 mg/day) was started. One month later, his proteinuria was dramatically decreased and renal function was improved (proteinuria, 0.18 g/day; serum creatinine, 0.92 mg/dl).

Renal pathological findings and his clinical course suggested nephrotic syndrome due to minimal-change nephropathy. As he had thrombocytopenia and haemolytic anaemia, we initially suspected thrombotic microangiopathy as the cause of acute renal failure. However, we found no associated pathological changes of glomeruli, i.e. endothelialmesangial cell swelling and microthombi, suggesting that thrombotic microangiopathy was unlikely as the cause of his

Conflict of interest statement. None declared.

1Laboratory on Pathophysiology of Uremia Istituto G. Gaslini, Genova 2Renal Child Foundation, Genoa 3Nephrology Sections Ospedale Bambin Gesù Roma 4Department of Nephrology Dialysis and Transplantation Ospedale Regina Margherita Torino 5Section of Nephrology Istituto G. Gaslini, Genova, Italy Email: labnefro@ospedale-gaslini.ge.it


doi:10.1093/ndt/gfl833

© The Author [2007]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved. For Permissions, please email: journals.permissions@oxfordjournals.org

Advance Access publication 8 January 2007

Minimal-change nephropathy and chronic hepatitis C infection: coincidental or associated?
renal dysfunction. Urine dipstick test showed marked 4+ haematuria, but urinary sediments showed few red blood cells (1-2-1/high-power fields). His renal function recovered concomitantly with improvement of haemolytic anaemia; thus, haemolysis might also have contributed to the development of his renal dysfunction. Indeed, haemolysis-related renal dysfunction has occurred in patients with HCV infection [1]. Our patient showed cryoglobulinaemia, but cryoglobulin-related glomerulonephritis was unlikely because no immune-complexes were deposited in glomeruli.

There are several reported cases of minimal-change nephropathy occurring in HCV-infected patients, but these patients were treated with interferon; thus, minimal-change nephropathy was thought to be caused by interferon-related immunological abnormalities, rather than directly by HCV infection [2,3]. Our patient had no history of interferon treatment. We could not identify the causes of our patient’s haematological abnormalities, thrombocytopenia and haemolytic anaemia, but these haematological abnormalities have been reported as HCV-related autoimmune disorders [4], indicating that HCV-related immune dysregulation might have caused his haematological abnormalities. Further, thrombocytopenia/haemolytic anaemia and nephrotic syndrome occurred simultaneously in our case; therefore, HCV-related immune dysregulation might also have contributed to the development of minimal-change nephropathy. A similar case, autoimmune haemolytic anaemia occurring prior to evident nephropathy in a chronic HCV-infected patient has been reported, but the nephropathy was an immune-complex type nephropathy: membranous nephropathy [5]. Therefore, the question remains as to whether our patient’s HCV infection was a root cause, a simple coincidence, or a precipitating factor of minimal-change nephropathy.

Conflict of interest statement. None declared.

1Department of Internal Medicine, Shiga University of Medical Science, Otsu, Japan
2Department of Gastroenterology, Hikone municipal hospital, Hikone, Shiga, Japan
Email: toshiro@belle.shiga-med.ac.jp


doi:10.1093/ndt/gfl808

© The Author [2006]. Published by Oxford University Press on behalf of ERA-EDTA. All rights reserved.

For Permissions, please email: journals.permissions@oupjournals.org

New insight on crescentic glomerulonephritis

Sir,

Diseases involving the renal glomeruli are encountered frequently in clinical practice and are the most common cause of end-stage renal disease worldwide. Crescentic glomerulonephritis and its clinical corollary, rapidly progressive glomerulonephritis (RPGN), is a potentially fatal disease and one of the few diagnostic emergencies that occur in nephrology in which affected individuals lose kidney function over a period of days to weeks. Early diagnosis is essential, as intervention can make a significant impact on minimizing irreversible kidney damage and improving patient outcomes.

The histopathological hallmark of RPGN is proliferation of cells in Bowman’s space to form glomerular crescents, which may contain parietal epithelial cells, inflammatory cells and podocytes. Circulating factors [1,2] and chronic hypoxia [3] have been proposed as common pathogenic mechanisms of this disease.

The best classification of RPGN has divided patients into three groups on the basis of the underlying immunopathology: those with antibodies to glomerular basement membrane (GBM, e.g. Goodpasture syndrome), those with immune deposits and cellular proliferation within the glomerular tuft (e.g. infections, cryoglobulinaemic GN, etc.) and those without immune deposits (pauci-immune, e.g. Wegener’s granulomatosis, microscopic polyangiitis, etc.) [4]. The incidence of pauci-immune RPGN is 1 out of 12 patients among those hospitalized for acute renal failure [5]. However, the pathogenesis of pauci-immune RPGN is incompletely understood and currently the role of the anti-neutrophil cytoplasmic antibodies (ANCA) in the pathogenesis and progression of this disease was recognized as a determinant of clinical management [1,2,6].

ANCA are predominantly IgG autoantibodies directed against constituents of primary granules of neutrophils and monocytes’ lysosomes. Although several antigenic targets have been identified, those ANCA directed to proteinase 3 or myeloperoxidase are clinically relevant, whereas the importance of other ANCA remains unknown. Both are strongly associated with small vessel vasculitides, the ANCA-associated vasculitides, which include Wegener’s granulomatosis, microscopic polyangiitis and Churg–Strauss syndrome, and the localized forms of these diseases (e.g. pauci-immune necrotizing and crescentic glomerulonephritis) [7].

However, 20% of individuals with pauci-immune RPGN never have circulating ANCA-specific antibodies and are diagnosed as ‘idiopathic’ pauci-immune GN [5]. Ding et al. [8] hypothesized an alternative pathogenic mechanism for negative-ANCA-pauci-immune RPGN. The authors suggested that podocytes are required for maintenance of glomerular capillary health and that an intrinsic defect within this cell population may trigger glomerular vasculitis and RPGN. They showed that the Von Hippel–Lindau gene (*Vhl*) is required in the podocyte to maintain glomerular integrity. Loss of Vhl leads to stabilization of hypoxia-inducible factor α subunits (HIFs). From intrinsic glomerular cells of mice, loss of Vhl initiates necrotizing crescentic GN and the clinical features that accompany RPGN [8]. It has been identified *de novo* expression of the HIF target gene *Ccxr4* [9] in glomeruli from both mice and humans with RPGN. The course of RPGN is markedly improved in mice treated with a blocking antibody to Ccxr4, whereas overexpression of Ccxr4 alone in