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 in 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 coincidence, or a precipitating factor of minimal-change pathy [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.

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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 very 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 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 (Vhlh) is required in the podocyte to maintain glomerular integrity. Loss of Vhlh leads to stabilization of hypoxia-inducible factor α subunits (HIFs). From intrinsic glomerular cells of mice, loss of Vhlh initiates necrotizing crescentic GN and the clinical features that accompany RPGN [8]. It has been identified de novo expression of the HIF target gene Cxcr4 [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 Cxcr4, whereas overexpression of Cxcr4 alone in
podocytes of transgenic mice is sufficient to cause glomerular disease [8].

The pathogenic mechanism identified by Ding et al. [8] may underlie 20% of pauci-immune RPGN that is ANCA-negative and provide a new clinical paradigm for the diagnosis of crescentic GN (Figure 1).

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Thrombotic microangiopathy and anti-VEGF agents

Sir,

We report the occurrence of thrombotic microangiopathy (TMA) that may be directly related to vascular endothelial growth factor (VEGF) Trap treatment, a fully humanized recombinant fusion protein containing extracellular portions of the extracellular domains of two different VEGF receptors, VEGFR-1 and VEGFR-2. VEGF Trap is currently under evaluation in combination with LV5FU2-CPT11 in a dose-escalation, sequential-cohort, Phase I clinical trial that has enrolled and treated 18 heavily...