Case Report

Crescentic glomerulonephritis with antineutrophil cytoplasmic antibodies associated with chronic lymphocytic leukaemia

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Key words: antineutrophil cytoplasmic antibody; chronic lymphocytic leukaemia; crescentic glomerulonephritis; T-cell defect

Introduction

Chronic lymphocytic leukaemia (CLL) is a haematological disorder characterized by proliferation of monoclonal B lymphocytes blocked at an intermediate level of differentiation. It may be responsible for renal manifestations common to any haematological malignancy: acute neoplastic interstitial nephritis, uric acid precipitation, secondary amyloidosis. About sixty cases of glomerular lesions have been published [1–5]. The most frequent are type I and II membranoproliferative glomerulonephritis (GN); less frequent are membranous GN, focal or diffuse proliferative GN, and fibrillary GN. Minimal-change disease (MCD) and focal or diffuse glomerulosclerosis have also been described. The pathophysiology of these GN may be related to the glomerular deposition of the monoclonal component (M-component) secreted by the B-cell clone.

We report a case of crescentic GN with antineutrophil cytoplasmic antibody (ANCA) during the evolution of a CLL. The pathophysiology of this form of GN is different from those already described since it may involve a disturbance in cellular immunity.

Case report

A 68-year-old woman was referred in May 1996 for acute renal failure discovered during the systematic survey of a CLL. This patient was diagnosed as stage A (Binet classification) CLL in 1991. At this time, medullar lymphocytosis was 47% with 80% of B lymphocytic monoclonal cells expressing kappa, mu, delta, and CD5+ antigens. Her renal function was normal in March 1996. She received no medication. Upon admission her general condition was good: no fever, normal blood pressure, no lymphadenopathy or hepatosplenomegaly.

Laboratory findings were: serum creatinine 314 µmol/l, BUN 15 mmol/l, total proteins 65 g/l, albumin 35 g/l, serum protein electrophoresis without abnormality. Haemoglobin was 96 g/l, WBC count 33 000/mm³ with 80% of mature looking lymphocytes, platelets 293 000/mm³. Blood glucose, hepatic tests and lipids were normal. Urinary protein excretion was 2.6 g/day; the urine sediment revealed microscopic haematuria.

IgG was 13 g/l (N 6–12), IgM 2.8 g/l (N 0.5–1.5), IgA 1.13 g/l (N 0.8–2.5); serum and urine immunofixations revealed no M-component. Cryoglobulins and rheumatoid factor were negative on three occasions. Antinuclear antibodies and the other autoantibodies were not present. A direct Coombs test was negative. Total complement was 65 U/l (N 60 ± 15 U/l), C3 1.23 g/l (N 0.8–1.5), C4 0.4 g/l (N 0.17–0.38), C1q 0.28 g/l (N 0.1–0.27), activated C3 0.2 g/l (N 0.08–0.24). Circulating immune complexes were negative. No antibasement membrane antibodies were evidenced by ELISA. Perinuclear ANCA were shown to be present by indirect immunofluorescence at a 1/200 dilution; ELISA was positive for antimiteloperoxidase at 50 U/ml (N < 7 U/ml) and negative for antiproteinase 3. Renal ultrasound revealed two normal kidneys. Percutaneous renal biopsy (16 glomeruli) by light-microscopy showed severe extracapillary proliferation affecting 15 glomeruli with cellular or fibrocellular crescents. There was no endocapillary proliferation and no deposits. The interstitium was not infiltrated by lymphocytes. Blood vessels were normal. The immunofluorescence revealed no fixation of any antiserum tested.

Treatment was initiated and repeated every 3 weeks with prednisone 60 mg/m² for 5 days, oncovin 2 mg at D1, adriamycin 30 mg/m² at D1 and cyclophosphamide 750 mg/m² at D1. Between the first three cures prednisone 1 mg/kg/day was given. At the time of the first cure renal function had worsened; creatinine...
377 μmol/l. Renal function improved dramatically after three cures: creatinine was 203 μmol/l.

**Discussion**

We report the first case of crescentic GN with ANCA during CLL. This case raises two questions: is it a fortuitous association of the two diseases? If not, what is the pathophysiologic link between the two diseases relative to ANCA positivity?

A fortuitous association of the two diseases is very unlikely for several reasons: first, the occurrence of glomerular involvement was concomitant with a flare of the haematological disorder as reflected by anaemia. Second, we could not find another aetiology for this pauci-immune crescentic GN. The only differential diagnosis could have been an idiopathic pauci-immune crescentic GN, now referred to as renal vasculitis, but the above considerations argue against this possibility. Even if a coincidence of the two diseases cannot be fully excluded, the rarity of pauci-immune crescentic GN and the 60 cases of CLL-associated GN published to date are two more arguments for a non-fortuitous association between CLL and the crescentic GN we observed.

Glomerulonephritis associated with CLL can be classified into two types: those with immunoglobulin deposits as membranoproliferative GN and those without immunoglobulin deposit. Only one case of crescentic GN has been reported in a large series of CLL-induced GN, but this lesion was diagnosed at the time of a severe lethal infection and no sample was available for immunofluorescence study [1]. Most patients with CLL and GN have an M-component that induced the glomerular lesions by deposition and local processing. Complement consumption usually reflects the activity of the M-component.

The pathophysiology of the CLL-associated crescentic GN in our patient is probably different. In fact no M-component was found in our patient’s serum or kidney, and her complement was normal. Glomerular lesions were therefore not induced by deposition of a M-component. Several immune defects during CLL that affect both humoral and cellular immunity have been described [6]. Defects in T-cell colony-forming capacity and T-cell regulatory functions are usual. An antigen specific T-suppressor-cell defect has been described and may constitute the pathophysiologic link between CLL and crescentic GN because such a defect can induce crescentic GN [7]. Cell-mediated immune reactions are involved in many experimental models of pauci-immune crescentic GN [8]. Thus it is not surprising to find ANCA in our patient since these antibodies are usually detected in diseases with cell-mediated immune crescentic GN such as Wegener’s granulomatosis [9]. In other words ANCA positivity may be a reflection of the T-cell defect that induces cell-mediated immune crescentic GN. Recently a renal antigen has been identified that is related to a lysosomal glycoprotein of neutrophil granulocytes and that reacts with ANCA from patients with crescentic GN [10]. CLL-induced T-suppressor-cell defect for this antigen could have induced the glomerular lesions. This case demonstrates that, besides glomerular lesions induced by the M-component, CLL can be complicated by cell-mediated immune GN.

Note added in proof: In the November issue of *NDT*, Tisler et al. reported a case of pauci-immune crescentic GN associated with p-ANCA positivity in a fludarabine-treated CLL. This case is not quite different from ours even though, in Tisler’s report, a clear-cut relationship exists between the occurrence of the crescentic GN and the treatment with fludarabine. In fact fludarabine may have accentuated the T-cell defect that induces immune crescentic GN.

**References**