Crescentic glomerulonephritis associated with p-ANCA positivity in fludarabine-treated chronic lymphocytic leukaemia

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Key words: chronic lymphocytic leukaemia; crescentic glomerulonephritis; fludarabine; perinuclear antineutrophil cytoplasmic antibodies

Introduction

Fludarabine, a 2-fluoro-5'-monophosphate derivative of vidarabine has been shown to be highly effective against low-grade malignant B-cell lymphoproliferative diseases, particularly against chronic lymphocytic leukaemia [1]. Chronic lymphocytic leukaemia (CLL) has been associated with renal involvement, caused either by the disease itself or its treatment. Although several types of glomerulonephritis [2, 3], leukaemic infiltration of the kidneys [4] and urate nephropathy [5] have been described in patients with CLL, rapidly progressive glomerulonephritis (RPGN) with crescent formation in CLL, to our knowledge, has been reported in only one case [2]. We present a case of RPGN in a patient with CLL who developed antineutrophil antibody-positive (ANCA) glomerulonephritis after treatment with fludarabine. Administration of certain medications has been associated with development of RPGN accompanied by positive ANCA [6-12], but such an association to fludarabine has not been described before.

Case report

A 76-year-old Caucasian woman was diagnosed with CLL in 1988 but received no treatment for this condition until October 1993. At that time she was staged at Rai 3 and received three courses of treatment as part of a clinical study with chlorambucil and fludarabine, completed in January 1994. Her kidney function was normal until April 1994 but subsequently, a progressive increase in serum creatinine to 518 µmol/l was noted in June 1994, when she was admitted to the hospital. Past history included Hashimoto’s thyroiditis, diagnosed in 1975, treated with L-thyroxine, and systemic lupus erythematosus, diagnosed in 1975. The disease was quiescent throughout and never required any treatment. She had been treated with captopril and hydrochlorothiazide for hypertension since 1986 and had a curative operation for colon cancer (Duke’s B) in 1986.

On admission she complained of shortness of breath, fatigue, and nausea. Her blood pressure was 160/90 mmHg, heart rate 94 beats/min, and temperature 36.8°C. The chest, cardiovascular and abdominal examinations were normal. There was no skin rash or articular involvement.

Laboratory tests on admission showed creatinine of 518 umol/l, urea nitrogen 27.6 mmol/l, phosphate 1.8 mmol/l, total protein 67 g/l; the rest of the biochemical parameters were within normal limits. Haemoglobin was 100 g/l with normal platelet count and the WBC 9.4 G/l with normal differential count. Urine showed a specific gravity of 1.010, pH 5.0, protein 0.3 g/l, blood 3+. Microscopic examination revealed occasional haem-granular casts and epithelial cells. Renal Tc-DTPA scan showed decreased kidney function bilaterally and abdominal ultrasound showed slightly echogenic normal sized kidneys. Chest X-ray was normal.

A kidney biopsy was performed. On light-microscope examination, the glomeruli showed focal segmental necrotizing crescentic glomerulonephritis with 50% of the glomeruli containing crescents. Vascular necrosis was not seen. On immunofluorescence, slight pseudolinear IgG deposition was seen, with focal staining for fibrinogen. No IgM, IgA, C3, C4, kappa or lambda light chains were detected. No dense deposits were seen on electron-microscopy. Immunological tests revealed negative ANA, anti-DNA antibodies (Crithidia), and anti-GBM antibodies; CH50, C3 and C4 were within normal limits.
ANCA was positive at 1:160 dilution with perinuclear pattern (p-ANCA).

During hospitalization the patient's creatinine remained between 518 and 627 μmol/l, but haemodialysis was not necessary. Treatment with methylprednisolone 800 mg i.v.daily for 3 days was initiated, followed by 80 mg prednisone and 100 mg cyclophosphamide orally daily. Cyclophosphamide was discontinued within 4 months, and prednisone was tapered off over 15 months. Her creatinine decreased rapidly and has been stable between 200 and 250 μmol/l for the last year. On her last visit in November 1995 ANCA was negative and CLL remained in complete remission.

Discussion

The development of rapidly progressive glomerulonephritis is associated either with anti-GBM antibodies or immune complex deposition or ANCA (cytoplasmic or perinuclear pattern) positivity [13]. Secondary forms of this disease may be related, among others, to SLE, malignancies (usually carcinoma [14] or non-Hodgkin lymphoma [15, 16]) or to medications. SLE cannot explain the RPGN in our patient, since she was free of clinical symptoms for 20 years and had no immunological evidence of disease activity for the last 15 years. Although she had a history of colonic carcinoma, no recurrence has been noted since then. Thus it is unlikely that the colonic carcinoma was responsible for the development of RPGN. Although CLL may present with several types of glomerular involvement (membranoproliferative glomerulonephritis being the most prevalent, membranous nephropathy, minimal-change disease, fribillary glomerulonephritis, focal segmental glomerular necrosis, amyloidosis, light-chain nephropathy) [2, 3], the association of CLL and glomerulonephritis seems to be extremely rare despite the relatively high prevalence of this type of leukaemia. CLL itself has been related to RPGN in only one reported case [2]. This patient developed the RPGN in the setting of severe infectious complication of CLL. No sample was available for immunofluorescence microscopy. Thus the possibility of immune-mediated disease cannot be excluded. There is no documented case of pauci-immune glomerulonephritis associated with CLL.

RPGN following therapy with rifampin [11], warfarin [12], hydralazine [10], propylthiouracil [9], enalapril [8], and penicillamine [6, 7] have been reported. The characteristic of these reports is that the development of renal damage is usually obvious several months (1-34 months) after the commencement of the therapy and that in the majority of cases the RPGN is associated with perinuclear ANCA positivity, although immune complex mediated [17] and anti-GBM positivity [18] has also been reported. Our patient developed renal failure 6 months after treatment and was found to have perinuclear ANCA positivity.

The adverse events of fludarabine treatment are myelosuppression, infections, pneumonitis, reversible neurological deficit [19, 20] and acute renal failure as a consequence of urinary retention [21].

We believe that in our patient the treatment with fludarabine might have played a role in the development of RPGN. Based on the normal complement levels and the absence of complement and immune complex deposition in the biopsy specimen, immune complex mediated injury can be excluded. Anti-GBM antibody associated mechanism is unlikely, since in such cases, the anti-GBM antibody deposition in the glomeruli is usually accompanied by linear or granular C3 deposition [22]. This feature was not observed in our case. Linear deposition of immunoglobulins alone is not diagnostic for anti-GBM-mediated mechanism; this may be seen in other glomerular diseases [22]. In addition, our patient had no circulating anti-GBM antibodies. The most probable cause for the crescentic glomerulonephritis is the p-ANCA-associated mechanism. Could it be that fludarabine treatment has played a role in triggering RPGN in our patient? The background of CLL with the immunosuppression during treatment may have provided a disruption of the immune regulation which favoured the genesis of anti-neutrophil antibodies and subsequent glomerulonephritis. There is a known tendency in patients with CLL to develop autoantibodies [23]. Fludarabine has been said to decrease the number of CD4 and CD8 lymphocytes, resulting in immunosuppression [24]. The question arises whether fludarabine treatment played a more direct role in the development of RPGN. This question cannot be answered by our case, but it is useful to collect and report such cases in order to see whether such coincidence will occur more often than expected by chance.

References

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Received for publication: 13.4.96
Accepted in revised form: 4.7.96