Renal failure caused by leukaemic infiltration in chronic lymphocytic leukaemia

J K Phillips, P S Bass, G Majumdar, D R Davies, N F Jones, T C Pearson

Abstract
A case of B-CLL which was complicated by chronic renal failure due to leukaemic infiltration of the kidney is reported. Treatment with chlorambucil, prednisolone, and renal bed irradiation resulted in a substantial improvement in renal function which persisted until the death of the patient from marrow failure some eight years later. The temporal association between treatments and response suggested that renal bed radiotherapy had contributed to the improvement in renal function. This case is one of only two reported cases in which chronic renal failure due to CLL has been treated with radiotherapy. It is unique in that the renal response was shown histologically.

Leukaemic infiltration of the kidney is common in CLL but, characteristically, is not associated with renal impairment. An improvement in renal function has been described in two patients with acute renal failure after chemotherapy.

the preceding three weeks. Examination showed generalised lymphadenopathy without splenomegaly, mild hypertension (blood pressure 150/100 mm Hg) and grade II hypertensive retinopathy. Investigation showed: haemoglobin 106 g/l; white cell count 90.5 x 10⁹/l (lymphocytes 81.5 x 10⁹/l); a platelet count of 153 x 10⁹/l; urea of 27-8 mmol/l; creatinine of 563 µmol; creatinine clearance 15 ml/minute; and a urinary protein excretion of 0.7 g/day. Serum calcium and uric acid values remained normal. Moderate glycosuria was noted on urinalysis in the presence of a plasma glucose concentration of 4.8 mmol/l. A renal ultrasound scan showed normal sized kidneys with no evidence of obstructive nephropathy; the only abnormality on plain tomography was the presence of slightly irregular renal outlines. A needle renal biopsy specimen showed severe tubular atrophy with wide separation of tubules by interstitial connective tissue heavily infiltrated by small lymphocytes exhibiting the same surface marker pattern as the peripheral blood lymphocytes. The infiltrate was more pronounced in the cortex than in the medulla. Twenty nine of 33 glomeruli showed ischaemic collapse with periglomerular fibrosis, the remainder showing global sclerosis. The arteries showed moderate fibroelastic intimal proliferation and mild hyaline arteriolar sclerosis was present (fig 1). These appearances were interpreted as showing severe ischaemic nephrosclerosis with infiltration of the cortical interstitium by CLL.

The patient received oral chlorambucil 20 mg daily for two days with oral Allopurinol 200 mg daily. Treatment for renal failure consisted of a low protein diet and oral bicarbonate. Atenolol 50 mg daily was given for the hypertension. Three weeks later the lymphocyte count had fallen to 61 x 10⁹/l but there had been a substantial decline in renal function with urea reaching 31.9 mmol/l and creatinine 1124 µmol/l. Further oral treatment with chlorambucil 20 mg once a day for three days and prednisolone 20 mg three times a day for 10 days was given in addition to low dose renal bed irradiation (400 cGy in two fractions given on successive days). Over the next two weeks the serum creatinine concentration fell to 496 µmol/l and the urea to 17.9 mmol/l. This was followed by a fall in the lymphocyte count to 14 x 10⁹/l at about five weeks after the second course of chemotherapy. Figure 2 shows the changes in serum creatinine and lymphocyte count in relation to treatment during this period.

Treatment for CLL was continued with monthly courses of chlorambucil for a total of nine courses. One month after completing chemotherapy the patient was asymptomatic, with lymphadenopathy confined to two small cervical nodes. The lymphocyte count was normal at 2.6 x 10⁹/l and renal function had shown further slight improvement with a serum creatinine of 362 µmol/l and urea of 16.1 mmol/l. Renal biopsy was repeated five months after radiotherapy and this showed a pronounced reduction in the extent of

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**Figure 1** Renal biopsy specimen taken before radiotherapy showing a heavy lymphoid infiltrate in the interstitium, pronounced tubular atrophy, and a relatively normal glomerulus.

**Figure 2** Temporal relations of changes in peripheral lymphocyte count and serum creatinine to radiotherapy and chemotherapy. --- urea; .......... creatinine; --- --- --- lymphocyte count.
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Cortical lymphocytic infiltration, although ischaemic nephrosclerotic changes remained unchanged (fig 3).

Subsequently the patient received intermittent treatment with oral chlorambucil with or without prednisolone whenever there was evidence of disease progression. Renal function remained stable until he died, eight years later, of septicaemia secondary to bone marrow failure associated with extensive marrow infiltration by CLL.

Discussion

Necropsy studies report a prevalence of renal infiltration in CLL of between 63% and 90%.1-5 The histological appearance of infiltration of the kidney by CLL has been described in two previous publications. A case report describes foci of lymphocytes scattered irregularly throughout the kidney, more common in the cortex than the medulla.4 In a study of 42 cases Schwartz et al observed discrete lymphocytic foci in the cortical interstitium, particularly the subcapsular cortex, and along the vasa recta at the corticomedullary junction.1 In this study leukaemic foci were associated with fibrosis, tubular atrophy, and glomerulosclerosis.

In our patient initial treatment with chlorambucil resulted in an improvement in the peripheral lymphocyte count but was accompanied by a deterioration in renal function without evidence of renal cause for this. It was unlikely to have been due to uric acid nephropathy as the serum uric acid was never significantly raised and chemotherapy was accompanied by prophylaxis with Allopurinol. Light chain nephropathy is also unlikely as a paraprotein was not demonstrated in either plasma or urine. No evidence of amyloid was seen on the renal biopsy specimen and the serum calcium concentration remained normal. It has been suggested that the kidney may act as a sanctuary site for leukaemic cells in response to treatment with chemotherapy which may explain our finding of worsening renal failure in the face of otherwise responsive disease.3 This is consistent with the subsequent improvement in renal function accompanied by documented reduction in lymphocytic infiltration of the kidney.

The improvement in renal function followed treatment with a combination of chlorambucil, prednisolone, and renal bed irradiation. This response is not likely to be related to chlorambucil as previous exposure to this agent had been ineffective. Either prednisolone or radiotherapy might have been responsible, but it is clear from fig 2 that the renal function improved before there was any evidence of an effect on peripheral lymphocytes. A possible synergistic effect of local radiotherapy with chemotherapy cannot, however, be excluded.

Although renal infiltration by CLL is common, reports of impairment of renal function associated with such infiltration are rare.1,6-8 Acute renal failure responded to oral chlorambucil in one case1 and chronic renal failure seemed to respond to combination chemotherapy (cyclophosphamide, vincristine, and prednisolone) in another.8 Merrill and Jackson reported that renal bed irradiation (of unspecified dose) was effective in one patient,4 but Saggi et al found renal radiotherapy (850 rads to one and 700 rads to the other kidney over three weeks), together with oral prednisolone and chlorambucil, to be ineffective in their patient.8 In each of these four cases response was assessed on the basis of changes in renal function alone. Our patient is at present unique in that prolonged improvement in chronic renal failure followed treatment and was accompanied by a demonstrable reduction in lymphocytic infiltration of the kidneys.

Our case shows that when chronic renal failure occurs in CLL, leukaemic infiltration of the kidney should be considered as a possible cause. Renal bed irradiation may then be effective treatment, leading to improvement in renal function.

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J Clin Pathol 1993 46: 1131-1133
doi: 10.1136/jcp.46.12.1131