Successful Treatment of a Patient with Nephrotic Syndrome Associated with Chronic Lymphocytic Leukemia

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Abstract

We report the case of a 62-year-old man with nephrotic syndrome associated with stage B chronic lymphocytic leukemia (CLL). Kappa Bence Jones proteinuria and the glomerular deposition of kappa-light chain were observed. Although treatment with cyclophosphamide and prednisolone tended to reduce the level of proteinuria, the administration of angiotensin-converting enzyme inhibitor, enalapril, resulted in complete remission of nephrotic syndrome. (Internal Medicine 39: 256–259, 2000)

Key words: glomerulonephritis, malignancy, angiotensin-converting enzyme inhibitor

Introduction

The development of a nephrotic syndrome during the course of malignant disease is a well-known phenomenon (1). However, chronic lymphocytic leukemia (CLL) is rarely associated with nephrotic syndrome (2–4). Since the pathogenesis of this association is unclear, an effective treatment for both CLL and nephrotic syndrome has not been established. The proteinuria was successfully reduced when CLL was controlled with immunosuppressive drugs (2, 3, 5). However, such immunosuppressive therapy also failed to treat nephrotic syndrome (4, 6). We report a case of nephrotic syndrome associated with B-cell CLL, which was successfully treated with a combination of cyclophosphamide and prednisolone, and enalapril.

Case Report

A 62-year-old Japanese man was admitted to Asahikawa Medical College Hospital on February 29, 1996, complaining of generalized edema and easy fatigability. He had a history of

a blood transfusion 9 years earlier because of multiple bone fractures of both lower limbs. He had no history of renal disease.

His blood pressure was 110/60 mmHg. He had generalized edema and lymphadenopathy. Urinalysis showed proteinuria in the range of nephrotic syndrome (4.9 g/day) and microscopic hematuria (20/high power field). His serum total protein concentration was 41 g/l and his serum albumin was 21 g/l. Other pertinent findings included serum urea nitrogen concentration of 17 mg/dl (6.1 mmol/l of urea), a serum creatinine concentration of 0.8 mg/dl (70.7 μ mol/l) and a 24-hour creatinine clearance of 76 ml/min/m². His white blood cell count was $10.3 \times 10^9/l$ with 89% small, mature-appearing lymphocytes (Fig. 1). His hemoglobin concentration was 107 g/l and his platelet count was $120 \times 10^9/l$. By flow cytometry using monoclonal antibodies, the lymphocytes were positive for CD5, CD19, CD24, and HLA-DR, and negative for CD3, and CD10. Cell surface membrane immunoglobulins contained IgG, IgA, IgM, kappa, and lambda. His bone marrow contained 70.8% lymphoid cells. These hematologic and immunologic findings were consistent with B-cell chronic lymphocytic leukemia (stage B) (7). No monoclonal proteins were detected in his serum, but free monoclonal kappa-light chains were present in his urine. His quantitative serum immunoglobulins were (g/l): IgG 9.32, IgA 1.11, IgM 0.70. His total hemolytic complement level was under 12 U (normal, 30 to 40 U). An anti-nuclear antigen assay was negative and no cryoglobulin was detected. There was no hepatitis C virus antibody in his serum.

A kidney biopsy was performed on March 26. Light microscopy (Fig. 2) showed capillary wall thickening and duplication, and focal mesangial cell proliferation in the glomeruli, which were the characteristic features of membranoproliferative glomerulonephritis. Staining for amyloid was negative. No significant tubulointerstitial changes were evident. Immunofluorescent microscopy of the glomeruli revealed moderate to intense fringe-pattern staining for IgM, IgG, C₃, C₄, and kappa-light chain (Fig. 3). Electron microscopy demonstrated prolif-

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Figure 1. A photomicrograph of the patient's peripheral blood leukemic cells resembling small, mature lymphocytes (May-Giemsa stain, $\times 1,000$).

Figure 2. Light micrograph of a renal biopsy specimen. Capillary wall thickening and duplication, and focal mesangial cell proliferation in the glomerulus are present (periodic acid-Schiff stain, $\times 400$).

eration of mesangial cells and matrix, glomerular capillary wall thickening and duplication, and subendothelial dense deposits.

He was diagnosed as having nephrotic syndrome due to membranoproliferative glomerulonephritis, which was associated with CLL. To control the nephrotic syndrome, he was treated with a combination of prednisolone (60 mg/day) and cyclophosphamide (100 mg/day) on April 6. The clinical course of the patient is shown in Fig. 4. After 3 weeks of this treatment, the cyclophosphamide was stopped because he developed thrombocytopenia. Although this treatment failed to reduce the number of leukemic cells, the level of proteinuria tended to decrease. Then, enalapril (2.5 mg/day) was started

Figure 3. Immunofluorescent micrograph of a renal biopsy specimen. Diffuse fringe-pattern staining for kappa-light chain is present along the capillary walls ($\times 400$).

on May 23, for the reduction of proteinuria. His prednisolone dose was tapered gradually.

His urinary protein excretion decreased gradually to the level of 1 g/day by the end of June. His serum total protein and albumin levels returned to normal. His leukemic cell count did not change significantly. His renal function remained stable and he was discharged on September 28, with his nephrotic syndrome in complete remission.

Discussion

CLL is rarely complicated by nephrotic syndrome. The frequency of nephrotic syndrome in patients with CLL is estimated to be less than 1 to 2% (4). Moreover, various pathological features of the kidneys have been reported in CLL (2–6), suggesting that the pathogenesis of the nephrotic syndrome may not be unique. The association of glomerular lesions and monoclonal M-protein is well-established in patients with myeloma (8). Glomerular lesions associated with dysproteinemias could occur in other lymphoproliferative disorders (9). Moulin et al (3) have demonstrated that the onset of glomerulonephritis in CLL is mediated by the secretion, deposition, and possibly processing of an M-component. In this case, since kappa Bence Jones proteinuria and the glomerular deposition of kappa-light chains were observed, the kappa-light chain might play an important role in the pathophysiology of the nephrotic syndrome.

There is no standard therapy for the nephrotic syndrome associated with CLL. Some authors have reported that effectively treating the CLL can induce a remission of nephrotic syndrome (2, 3). At present, however, there is no curative therapy for CLL. The indications for therapy in CLL include hemolytic anemia, severe thrombocytopenia, symptomatic lymphadenopathy or organomegaly, or marked disease-related symptoms (10). Moulin et al (3) showed that treatment of the

Figure 4. The patient's clinical course. The patient's daily urine protein excretion is shown against several clinical parameters, including his treatment. CPM: cyclophosphamide, PSL: prednisolone, WBC: white blood cell count ($\circ$), Lymphoid cell count ($\bullet$), and platelet count ($\triangle$).

B-cell proliferation could induce regression of nephrotic syndrome and/or renal insufficiency in patients with CLL. In this patient, the objective for therapy was to control the nephrotic syndrome. Treatment with cyclophosphamide and prednisolone seemed to be effective for the reduction of proteinuria, although the number of leukemic cells was unchanged.

However, it has been reported that the nephrotic syndrome was not controllable by immunosuppressive drugs in some CLL patients (4, 6). In addition, some patients could not tolerate immunosuppressive drugs because of myelosuppression. In the present patient, treatment of enalapril after withdrawal of cyclophosphamide had a beneficial effect on his proteinuria. Angiotensin-converting enzyme inhibitors reduce glomerular capillary pressure by decreasing efferent arteriolar resistance (11, 12). Long-term studies with angiotensin-converting enzyme inhibitors in diabetic nephropathy and various other renal diseases have demonstrated that they exert an antiproteinuric effect and protection against further progression of renal insufficiency (13, 14). Angiotensin-converting enzyme inhibitors may also have a beneficial effect on the nephrotic syndrome associated with CLL. Angiotensin-converting enzyme inhibitors could be second-line drugs for CLL-associated nephrotic syndrome, which is resistant to chemotherapy.

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CLL-associated Nephrotic Syndrome

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