# Membranoproliferative Glomerulonephritis, Chronic Lymphocytic Leukemia, and Cryoglobulinemia

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The coexistence of chronic lymphocytic leukemia (CLL) and nephrotic syndrome was described first by Scott[1] in 1957. The incidence of nephrotic syndrome in patients with CLL is approximately 1% to 2%.[2] Although membranous glomerulonephritis, minimal change, crescentic glomerulonephritis, light-chain deposition disease, amyloidosis, and focal segmental glomerulosclerosis may account for nephrotic syndrome in some instances, the most common lesion is membranoproliferative glomerulonephritis (MPGN).[2-8] MPGN in the setting of CLL may be caused by cryoglobulinemia, predominantly type II,[9] or be associated with organized immunotactoid deposits made of a monoclonal immunoglobulin G (IgG), classically without cryoglobulinemia and complement activation.[4,10] The link between CLL and glomerular disease is the monoclonal immunoglobulin produced by the B-cell clone. Furthermore, similar organized deposits with microtubule formation may be found in leukemic lymphocytes and glomeruli of patients with immunotactoid glomerulopathy.[10,11] The causal relationship between CLL and the glomerulopathy is supported further by parallel improvement of the 2 diseases with chemotherapy.

Here, we report the case of a patient with CLL, type I MPGN, and type III cryoglobulinemia without detectable circulating or deposited monoclonal immunoglobulin. We discuss the potential connection between hematologic and glomerular diseases that both resolved with chemotherapy.

## CASE REPORT

### Clinical History and Initial Laboratory Data

A 53-year-old white man without a medical history was referred with fatigue and acute glomerular syndrome. Physical examination showed hypertension (blood pressure, 210/120 mm Hg), hepatomegaly with peripheral bulky lymph nodes, and pitting edema. Computed tomographic scan showed mediastinal and abdominal lymphadenopathy. Serum creatinine level was 2.0 mg/dL (178 $\mu$mol/L; estimated glomerular filtration rate, 37 mL/min/1.73 m$^2$ [0.62 mL/s/1.73 m$^2$] according to the Modification of Diet in Renal Disease Study equation), and urinalysis showed nephrotic-range proteinuria (protein, 4.3 g/d; 4.4 g/g creatinine) with hematuria ($10^5$ red blood cells/mL). Serum albumin level was 3.4 g/dL (34 g/L). Total hemolytic complement activity was markedly decreased (<10%; normal value, >50%), as well as C4 (<0.01 g/L; reference range, 0.10 to 0.34 g/L) and C3 levels (0.47 g/L; reference range, 0.75 to 1.40 g/L). Type III cryoglobulinemia made of polyclonal IgG was identified by means of immunofixation and immunoelectrophoresis (Fig 1), and rheumatoid factor was detected. Serological test results for hepatitis C virus, hepatitis B virus, and human immunodeficiency virus (HIV) infection were negative. Antinuclear antibody test result was negative, and serum and urine immunofixation showed no monoclonal immunoglobulin. White blood cell count was $10.2 \times 10^3/\mu$L ($10.2 \times 10^9$/L), with $4.9 \times 10^9$/L polymorphonuclear neutrophils and $3.85 \times 10^9$/L lymphocytes; platelet count was $218 \times 10^3/\mu$L ($218 \times 10^9$/L); and hemoglobin level was 11.4 g/dL (114 g/L). A kidney biopsy was performed.

### Kidney Biopsy

Light microscopy sections showed 16 glomeruli. Severe diffuse endocapillary proliferation was present, with abundant mononuclear cells and rare polymorphonuclear cells (Fig 2A). Mesangial proliferation was associated with double contours of the glomerular basement membrane. Large subendothelial deposits were seen in rare capillary loops. Two glomeruli showed hyaline eosinophilic thrombi. There were no crescents.

A mild diffuse interstitial fibrosis was present, with focal flattening of the epithelium. Blood vessels were unremarkable.

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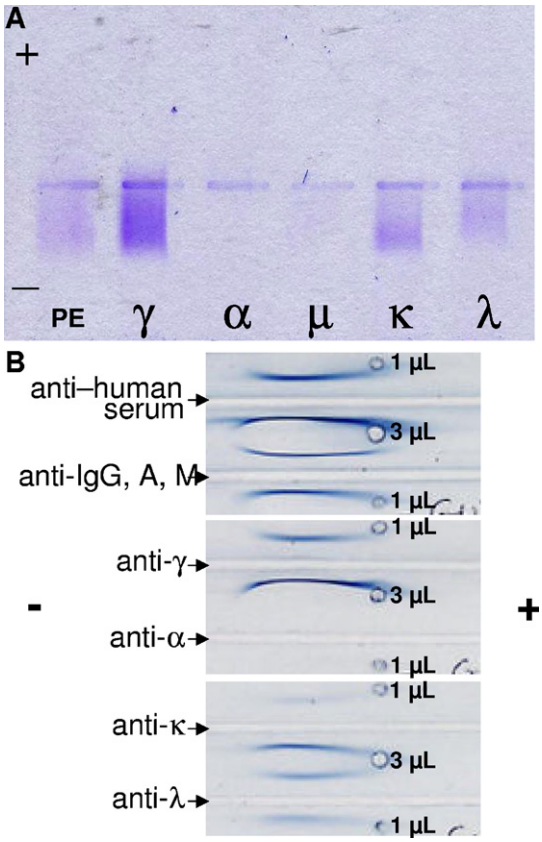


**Figure 1.** (A) Immunofixation electrophoresis of serum cryoglobulin. After electrophoresis, immunoglobulins are precipitated in situ with antibodies to immunoglobulin G (IgG) ($\gamma$), IgA ($\alpha$), and IgM ($\mu$) heavy chains and $\kappa$ and $\lambda$ light chains. After washing to remove unfixed proteins, the gel is stained. Results show predominant polyclonal IgG and no detectable monoclonal component. The reference lane, which shows protein electrophoresis (PE) without antibody application or washing, assesses purity. (B) Immunoelectrophoresis of dissolved purified cryoglobulin. Each sample well was loaded with 1 or 3 $\mu$L of cryoglobulin, as indicated, and electrophoresed toward the anode (right side of the gel). Each trough then was loaded with the indicated antibody solution, and the antibody and samples were left to diffuse. Staining shows arcs indicating precipitation of antigen-antibody complexes and confirms the exclusive presence of polyclonal IgG.

Twenty glomeruli were available for immunofluorescent examination. Subendothelial deposits of IgG, IgA, C3, C1q, and $\kappa$ and $\lambda$ light chains were seen (Fig 2B). Segmental reinforcement of staining was observed in several glomeruli.

Electron microscopy showed abundant subendothelial electron-dense deposits without an organized structure (Fig 2C).

### Diagnosis

Blood immunophenotyping showed a monoclonal B-lymphocyte population that stained for $\kappa$ light chain, CD5, CD19, CD20, and CD23. Histological examination of a supraclavicular lymph node, bone marrow biopsy specimen, and accessory salivary glands showed diffuse infiltration by small mature B lymphocytes. A diagnosis of CLL was made.

### Clinical Follow-up

The patient was scored stage B of Binet's classification,[12] which led to the initiation of chemotherapy.[13] Chlorambucil treatment failed to improve hematologic and kidney diseases. After 2 months, the therapeutic regimen was changed to rituximab (375 mg/m$^2$ on day 1), fludarabine (25 mg/m$^2$ on days 2 to 4), and cyclophosphamide (250 mg/m$^2$ on days 2 to 4). After 6 courses of this regimen (18 weeks), serum creatinine level was 1.6 mg/dL (143 $\mu$mol/L); urinalysis results were normal; total hemolytic complement activity, C3, and C4 had returned to the normal range; and cryoglobulin was undetectable.

## DISCUSSION

We report on the association of type I MPGN and type III cryoglobulinemia in a patient with CLL. Although we could not detect monoclonal immunoglobulin in serum or urine or among renal deposits, the parallel improvement of the hemopathy, kidney disease, and immunologic parameters favors a causal relationship between CLL and MPGN.

In the largest study including 81 patients with cryoglobulinemia and a lymphoproliferative disorder at diagnosis, types I and II cryoglobulinemias (ie, including a monoclonal immunoglobulin) accounted for 95% of cases.[9] Those cryoglobulins may precipitate in the glomerular capillary loop, usually leading to the development of MPGN with significant macrophage infiltration and organized electron-dense deposits by means of electron microscopy. In 4 patients with CLL, MPGN related to type I monoclonal IgG cryoglobulin.[4,10,14] However, in our patient, we unexpectedly found type III cryoglobulinemia, which is a cryoglobulin containing only polyclonal immunoglobulin according to Brouet's classification.[9] In the seminal study of Brouet et al,[9] only 4 of 81 patients had a lymphoproliferative disorder with type III cryoglobulinemia, and this low incidence was confirmed in later studies.[15] In contrast, the most prevalent cryoglobulinemia in patients with hepatitis C virus infection is type III cryoglobulinemia,[16-18] which may precede the emergence of an IgM-secreting clone responsible for type II cryoglobulinemia and the onset of MPGN. Type II cryoglobulins are immune complexes in which a monoclonal rheumatoid IgM is bound to polyclonal immunoglobulins, which may be en-