Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3902-24
Intern Med 64: 1388-1392, 2025
http://internmed.jp

【 CASE REPORT 】

Successful Treatment of Monoclonal Immunotactoid Glomerulopathy Associated with Chronic Lymphocytic Leukemia Using Ibrutinib

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Abstract:
A 71-year-old woman developed nephrotic syndrome during 10-year follow-up for chronic lymphocytic leukemia. A renal biopsy sample analysis revealed IgG1-lambda-positive monoclonal immunotactoid glomerulopathy (mITG). The patient was treated with ibrutinib, a Bruton tyrosine kinase inhibitor, and complete renal remission was achieved after 24 months. ITG is a rare disease that is characterized by glomerular deposition. In particular, mITG, which presents immune deposits that exhibit light-chain restriction, is often associated with hematologic disorders. Most patients with mITG receive immunosuppressive therapy and/or chemotherapy; however, to our knowledge, there have been no reports of treatment with ibrutinib.

Key words: immunotactoid glomerulopathy, chronic lymphocytic leukemia, nephrotic syndrome, ibrutinib, Bruton's tyrosine kinase inhibitor, IgG1-lambda monoclonal gammopathy

(Intern Med 64: 1388-1392, 2025)
(DOI: 10.2169/internalmedicine.3902-24)

Introduction

Immunotactoid glomerulopathy (ITG) is a rare glomerular disease originally described by Schwartz and Lewis (1). Congo red-negative Ig deposits show typical ultrastructural organization into parallel microtubules 10-60 nm in external diameter with distinct hollow cores (2, 3). Light microscopy commonly reveals membranoproliferative and membranous patterns of glomerular injury (2-5). In an immunofluorescence (IF) study, glomerular deposits were typically positive for IgG and C3, showing the usual light chain restriction (3-5). Notably, 67% of ITG cases show monoclonal ITG (mITGs), and 62% of mITG cases exhibit kappa light-chain restriction (5). Most patients present with nephrotic-range proteinuria, hematuria, renal dysfunction, and hypertension. ITG has mostly been reported in patients with monoclonal gammopathy and/or hematologic malignancies, particularly chronic lymphocytic leukemia (CLL) (3, 5).

CLL is an indolent lymphoproliferative malignancy characterized by clonal expansion of small mature CD5+ CD23+ B cells. CLL is considered incurable, and clinical observation is the standard of care for asymptomatic patients. Purine analogs or alkylating agents with anti-CD20 monoclonal antibodies have been used to treat CLL. Recently, the prognosis of CLL has improved with the development of Bruton's tyrosine kinase (BTK) and B-cell lymphoma 2 inhibitors (6). Strati and Shanafelt reported a 7.5% incidence of kidney disease in patients with CLL at the diagnosis (7). Frequently reported findings in several cases of glomerular diseases with CLL include membranoproliferative glomerulonephritis (MPGN), membranous nephropathy (MN), and minimal change disease (8).

This report is the first to present a case of mITG associ-

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Received: March 27, 2024; Accepted: August 16, 2024; Advance Publication by J-STAGE: October 4, 2024
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ated with CLL that was successfully treated with ibrutinib, a BTK inhibitor.

Case Report

A 71-year-old Japanese woman with a 10-year history of CLL presented with proteinuria and leg edema. The vital status on admission was as follows: height, 144.5 cm; weight, 51.9 kg; body temperature, 36.5°C; and blood pressure, 138/64 mmHg. A physical examination revealed lower leg edema. The liver, spleen, and superficial lymph nodes were not palpable. Laboratory investigations revealed the following: white blood cells (WBCs), 31,200/μL with 90% lymphocytes; hemoglobin (Hb), 8.7 g/dL; platelets, 114,000/μL; total protein, 4.7 g/dL; albumin, 3.0 g/dL; blood urea nitrogen, 18.9 mg/dL; and creatinine, 1.08 mg/dL. Furthermore, the serum C-reactive protein was 0.03 mg/dL; IgG, 300 mg/dL; IgA, 26 mg/dL; IgM, 22 mg/dL; C3, 37 mg/dL; C4, 8 mg/dL; and CH50, 20 U/mL. The serum-free light chains of kappa and lambda were 14.4 mg/L and 13.5 mg/L, respectively. The kappa/lambda ratio was 1.07. A urinalysis revealed a urinary protein level of 8.42 g/gCr and urine occult blood of 10-19 red blood cells/high-power field. Tests for antinuclear antibodies, cryoglobulin, hepatitis B virus antigen, and anti-hepatitis C antibodies were negative. Monoclonal proteins were not detected in serum or urine.

Peripheral blood flow cytometry revealed a clonal population of mature B cells with a CD19+, CD20+, CD5+, CD10-, CD23+, kappa-, and lambda+ phenotype. Fluorescent in situ hybridization of tumor cells did not show deletion of chromosome 17p. A bone marrow aspiration analysis revealed hypercellular marrow with a marked increase in mature B lymphocytes (90.8%). A diagnosis of Rai Stage III and Binet Stage C of CLL was made.

IF findings of the renal biopsy sample revealed global granular mesangial and glomerular basement membrane staining for IgG, lambda light-chain, C3, and C1q. The results were negative for IgA, IgM, and kappa light chain. The IgG subclass only showed IgG1 positivity (Fig. 1A-L). Light microscopy revealed a mild mesangial expansion, focal mesangiolysis, endocapillary hypercellularity, endothelial cell swelling, and mild interstitial inflammation. Interstitial fibrosis and tubular atrophy were observed in 20% of the cortical parenchyma. Global sclerosis was observed in 1/21 glomeruli showing mesangial expansion, endocapillary proliferation, and glomerular epithelial cell swelling (Fig. 1M). Amyloid and DNAJB9 staining results were negative. Electron microscopy revealed that parallel microtubules (25-30 nm) were predominantly located in the subepithelial and subendothelial spaces (Fig. 2). Based on these findings, mITG associated with CLL was diagnosed.

Treatment with ibrutinib 420 mg/day was initiated. A skin rash was observed 2 weeks after initiation, which improved with the administration of prednisolone (5 mg). Eight months after treatment initiation, the elevated WBC count improved by half, and anemia and thrombocytopenia also improved. Urinary protein improved with hematologic response, and 24 months after initiation, the WBC count improved to 8000-9000/μL and urinary protein to 0.2 g/gCr; serum creatinine was 1.2 mg/dL, showing no deterioration (Fig. 3).

Discussion

This is a rare case of CLL presenting nephrotic syndrome diagnosed with mITG. Although 7.5% of CLL patients present with kidney disease at the diagnosis, and MPGN, MN, and amyloid light-chain amyloidosis are frequent glomerular diseases (8), only a few reports of ITG exist.

ITG is a rare glomerular disease detected in only 0.06% of native kidney biopsy specimens (5, 9). Patients with ITG usually present with proteinuria, hematuria, renal dysfunction, and hypertension (3, 5). Light microscopy revealed atypical MN in 59% and MPGN in 41% of patients with ITG (3). ITG is defined by glomerular Congo red-negative Ig deposits that exhibit typical ultrastructural organization into parallel microtubules of external diameter 10-60 nm with distinct hollow cores (3). Electron microscopy findings are essential for the diagnosis of ITG. Our patient presented with renal dysfunction and nephrotic levels of urinary protein, showing an MPGN pattern of injury due to monoclonal gammopathy and tumor cell infiltration in the kidney.

The diagnosis of mITG was made based on the presence of IgG subclass, light chain restriction, and typical ultrastructural organization of the microtubules on electron microscopy. Monoclonal ITG accounts for 67% of ITG cases, and hematologic disorders are present in 82% of patients with mITG, including malignant lymphoma in 51% and CLL in 45% of patients (5). IgG-kappa and IgG-lambda are reported in 62% and 37% of patients with mITG, respectively; the predominant IgG subclass was IgG1 (61%), and our case was IgG1-lambda. Abnormal serum-free kappa/lambda ratios have been reported in 19-28% of patients with mITG, but our patient had a normal kappa/lambda ratio (3, 5). Bridoux et al. reported microtubular organization deposits within lymphocytes; however, why B cells produce tactoidogenic Igs or why the deposits are renal-specific is unclear (2). Our case showed hypocomplementemia. Twenty-five percent of patients with mITG have decreased complement levels (5). Immunoglobulins may activate the classical complement pathway, leading to glomerular inflammation and endocapillary proliferation (10).

Approximately 80% of patients with mITG were treated with immunosuppressive therapy or chemotherapy with or without steroids. Chemotherapeutic regimens usually include rituximab and/or alkylators (5, 11, 12). Renal manifestations and the prognosis in ITG are closely dependent on hematologic status (3, 5, 13). Javaugue et al. reported that among 78% of patients with mITG undergoing chemotherapy, 85% had sustained a complete or partial renal response, whereas 26% had end-stage renal disease (ESRD) at a median of 24 months after the diagnosis (3). The median baseline esti-

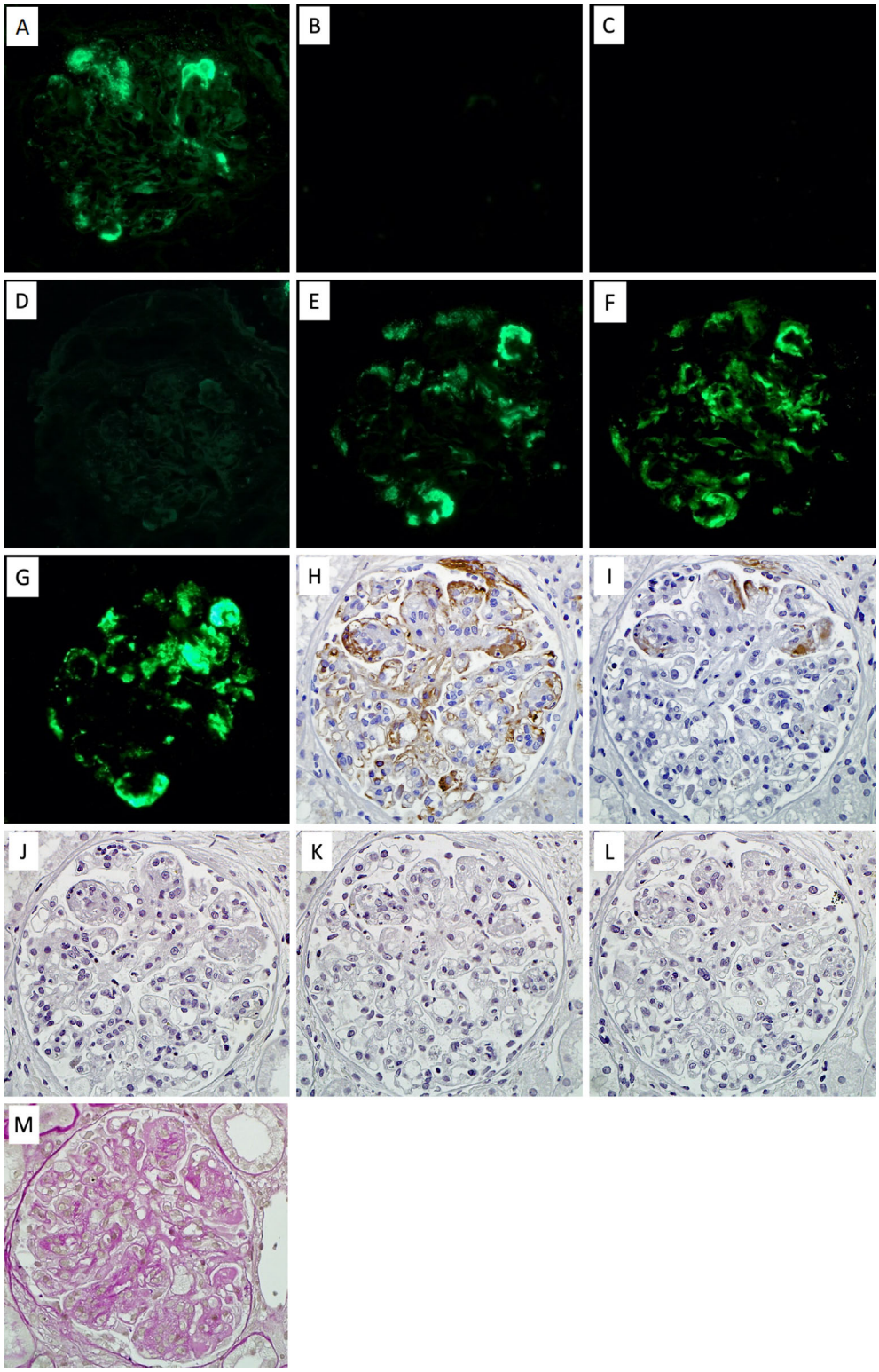

Figure 1. **Immunofluorescence and light micrographs of a kidney biopsy specimen. Granular mesangial and glomerular basement membrane staining was positive for IgG (A), lambda light chain (E), C3 (F), and C1q (G), and negative for IgA (B), IgM (C), and kappa light chain (D) (original magnification, ×200). Immunohistochemistry showed positive staining for IgG (H) and IgG1 (I), and negative staining for IgG2 (J), IgG3 (K), and IgG4 (L). PAS staining showed mild mesangial expansion, focal mesangiolysis, endocapillary hypercellularity, and endothelial cell swelling (M) (original magnification, ×400). Ig: immunoglobulin, PAS: Periodic acid-Schiff**

mated glomerular filtration rate was significantly lower in patients who progressed to ESRD than in those who did not progress to ESRD (3). Nasr et al. reported that after a median follow-up duration of 43 months, among 80% of pa-

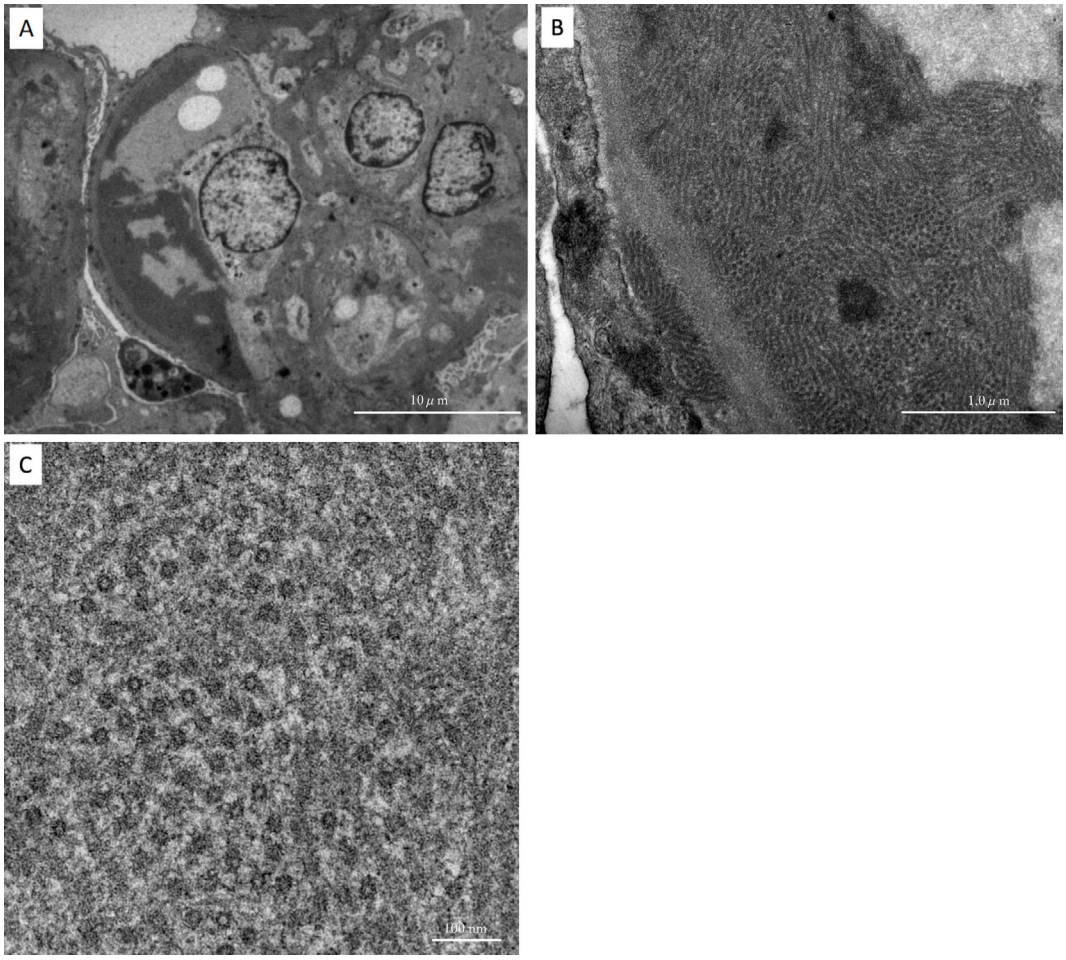

Figure 2. **Electron microscopy findings of a kidney biopsy specimen. Microtubular glomerular deposits were predominantly located in the endothelial space. Some microtubules are arranged in parallel (A and B). Microtubules are 25-30 nm in diameter and have distinct hollow cores (C).**

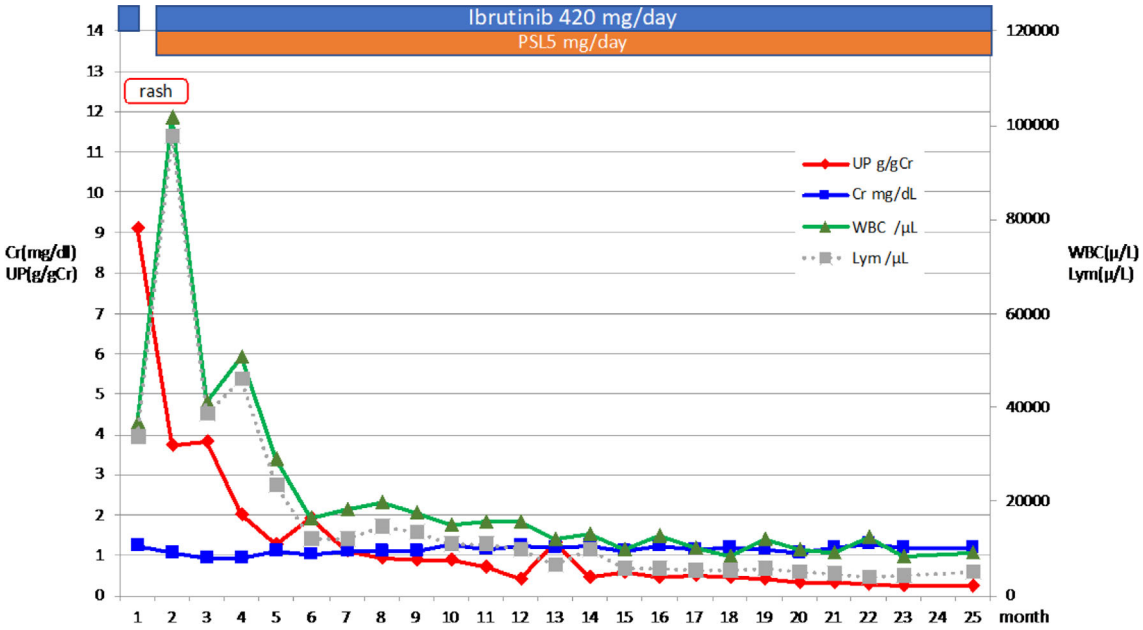

Figure 3. **Clinical course of the laboratory parameters after ibrutinib treatment. WBC: white blood cell, Cr: creatinine, PSL: prednisolone, UP: urinary protein, Lym: lymphocyte**

tients with mITG receiving chemotherapy, urinary protein levels had improved and the renal function had been maintained in 50%, 11% had progressed to ESRD, and 8% had died (5). Serum creatinine levels at the time of the biopsy and the presence of diabetes were associated with ESRD or death, whereas the presence of moderate or severe tubulointerstitial scarring was associated with worse outcomes. Chemotherapy was the sole covariate independently associated with a reduced risk of combined outcome (5). Multidisciplinary collaboration between hematologists and nephrologists is important for identifying mITG associated with hematologic disorders. Furthermore, it is important to define proteinuria in CLL patients. When proteinuria is present, defining the type of kidney disease by performing a kidney biopsy is crucial (14).

Ibrutinib is an irreversible inhibitor of BTK, a B-cell signaling protein involved in the B-cell development, differentiation, proliferation, and survival. The progression-free survival and overall survival rates of the ibrutinib-rituximab regimen were superior to those of the standard chemotherapy regimen in patients ≤70 years old with previously untreated CLL (15).

Although ibrutinib has been approved for CLL treatment in Japan since 2016, there are no reports on the treatment of mITG complicated by CLL with ibrutinib. Our patient achieved a partial hematologic response and a complete renal response after 24 months of treatment with ibrutinib. Nephrotic syndrome caused by mITG tends to be successfully controlled with specific treatments for CLL. Chemotherapy without steroid treatment may improve mITG (16). Ibrutinib is expected to be effective in treating mITG complicated by CLL; however, further investigation is required to confirm this.

Author's disclosure of potential Conflicts of Interest (COI).
Naoto Takahashi: Honoraria, Novartis, Otsuka Pharmaceutical and Pfizer.

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