

[CASE REPORT]

Proliferative Glomerulonephritis with Monoclonal IgG Deposits and Refractory Ascites: Successful Treatment with Rituximab and Cell-free and Concentrated Ascites Reinfusion Therapy

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Abstract:

A 49-year-old woman presented with nephrotic-range proteinuria, microhematuria, and moderate renal dysfunction. Diuretic-resistant refractory ascites associated with nephrotic syndrome were observed. Based on the histopathological findings, the patient was diagnosed with proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGNMID). Rituximab was administered due to steroid and immunosuppressive drug resistance, and partial remission was achieved after six months. Cell-free and concentrated ascites reinfusion therapy (CART) performed to treat the refractory ascites improved the ascites and anasarca. Rituximab successfully treated the PGNMID, while CART effectively treated the refractory ascites associated with nephrotic syndrome.

Key words: proliferative glomerulonephritis with monoclonal immunoglobulin G deposits, membranoproliferative glomerulonephritis, rituximab, cell-free concentrated ascites reinfusion therapy

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Introduction

In 2004, Nasr et al. reported proliferative glomerulonephritis with monoclonal immunoglobulin G deposits (PGNMID), a monoclonal gammopathy characterized by the glomerular deposition of immunoglobulin G (IgG) (1). PGNMID presents as membranoproliferative or endocapillary proliferative glomerulonephritis on light microscopy, monoclonal IgG deposits on immunofluorescence, and granular electron-dense deposits on electron microscopy (1). Its clinical presentations include proteinuria in 100% (about half with nephrotic syndrome), microhematuria in 77%, and renal insufficiency in 68% of patients. In contrast, monoclonal proteins are identified on serum or urine electrophoresis, immunofixation, or bone marrow examinations in only about 20-30% of cases (2-5). The lack of an established treatment for PGNMID often results in a course of steroid and immunosuppressive drug resistance. Clinical outcomes can be

poor, especially in cases associated with the membranoproliferative glomerulonephritis (MPGN) pattern (3).

Cell-free and concentrated ascites reinfusion therapy (CART), a treatment system for ascites developed in 1977, removes unnecessary components, such as cells and bacteria, in the ascites using a filtration membrane and intravenously reinfuses the collected proteins. CART is expected to improve the quality of life and increase urine output by maintaining hemodynamics through increasing the serum albumin level. Although there have been few reports on the use of CART for refractory ascites due to nephrotic syndrome, it is often used in patients with liver cirrhosis or cancer (6, 7).

We herein report our experience treating proliferative glomerulonephritis showing an MPGN pattern and diagnosing PGNMID based on light-chain staining, IgG subclass staining, and characteristic electron microscopy. The patient's clinical course was complicated by steroid- and immunosuppressive drug-resistant nephrotic syndrome and refractory ascites associated with fluid retention; however, ri-

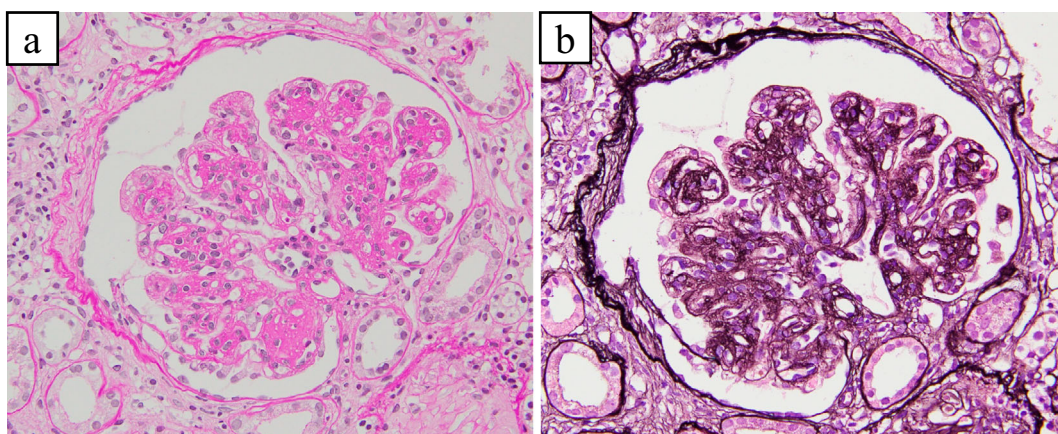


Figure 1. Renal biopsy specimen on light microscopy. Diffuse lobular membranoproliferative glomerulonephritis with severe endocapillary and mesangial hypercellularity as well as duplication of the glomerular basement membranes. (a) Periodic acid-Schiff (magnification $\times 400$); (b) periodic acid methenamine silver (magnification $\times 400$).

tuximab and CART achieved a good therapeutic response.

Case Report

A 49-year-old woman with no significant medical history sought treatment for acute and progressive leg edema and weight gain. She had no recent history of infectious disease. Her blood pressure was 122/74 mmHg, pulse was 70/min, respiratory rate was 16 breaths/min, and O_2 saturation was 99% on room air. There were no abnormal physical findings other than edema of the lower limbs.

A urinalysis showed nephrotic-range proteinuria (protein excretion, 9.9 g/d) and microscopic hematuria (50-99 red blood cells/high-power field). Laboratory investigations revealed hypoalbuminemia and hypocomplementemia, a serum total protein level of 4.5 g/dL, a serum albumin level of 1.9 g/dL, a blood urea nitrogen level of 19.5 mg/dL, a serum creatinine level of 0.79 mg/dL, an estimated glomerular filtration rate of 60.7 mL/min/1.73 m², a serum complement C3 level of 64 mg/dL, a serum complement C4 level of 17 mg/dL, and serum complement activity (CH50) of 29 U/mL. Other laboratory values were as follows: leukocyte count, $9.90 \times 10^3/\mu\text{L}$; hemoglobin, 12.7 g/dL; platelet count, $330 \times 10^3/\mu\text{L}$; serum IgG, 359 mg/dL; serum IgA, 121 mg/dL; serum IgM, 69 mg/dL; total serum cholesterol, 397 mg/dL; and blood glucose, 95 mg/dL. Antinuclear antibody (ANA), cryoglobulin, anti-neutrophil cytoplasmic antibody, and hepatitis B and C antibody tests were negative. No monoclonal proteins were detected in the serum or urine inspections of immunofixation, and the free κ/λ ratio was 1.57 (reference range, 0.26-1.65).

A renal biopsy was performed to rule out nephrotic syndrome with hematuria. A bone marrow examination performed based on the renal biopsy findings demonstrated no abnormalities.

The renal biopsy specimen contained 13 glomeruli, with 1 showing global sclerosis and no crescent formation. Periodic

acid-Schiff and periodic acid methenamine silver staining of a renal biopsy specimen (Fig. 1) revealed diffuse lobular MPGN with severe endocapillary and mesangial hypercellularity as well as duplication of the glomerular basement membranes. The extent of tubular atrophy and interstitial fibrosis was estimated to be 20% each. Immunofluorescent staining (Fig. 2) showed granular deposits of IgG, C3, C1q, and κ light-chain localized to the glomerular capillary wall and mesangial region as well as strong staining for the κ versus λ isotype. Additional IgG subclass staining was positive only for the IgG3 subclass. The electron micrograph (Fig. 3) showed granular electron-dense deposits mainly in the subendothelial and mesangial areas. No fibrillar or annular-tubular structures of electron-dense deposits were observed on electron microscopy. Based on the above pathological findings and laboratory findings, PGNMID was diagnosed.

Treatment consisted of prednisolone (0.6 mg/kg/day) and intravenous cyclophosphamide (500 mg/m²) for PGNMID. Partial remission (PR) was achieved soon thereafter, but relapse occurred a month later. Subsequently, intravenous methylprednisolone (500 mg for 3 days) and cyclosporine were administered, but the proteinuria worsened, and the renal function declined without any response. The fluid retention was mainly subcutaneous, but it progressed to the abdominal and thoracic cavities, resulting in considerable ascites retention. Despite the combined use of diuretics (furosemide, tolvaptan, spironolactone, and thiazide) and replacement of albumin, sufficient diuresis could not be achieved, and the patient gained more than 30 kg.

Since her condition was considered to be steroid- and immunosuppressant-resistant, rituximab infusions were administered at a standard dose of 500 mg infused once a week for two consecutive weeks. The number of CD19-positive B cells was 0/mm³ after using rituximab. No infusion reaction was observed after the rituximab administration. CART was performed for the refractory ascites at the

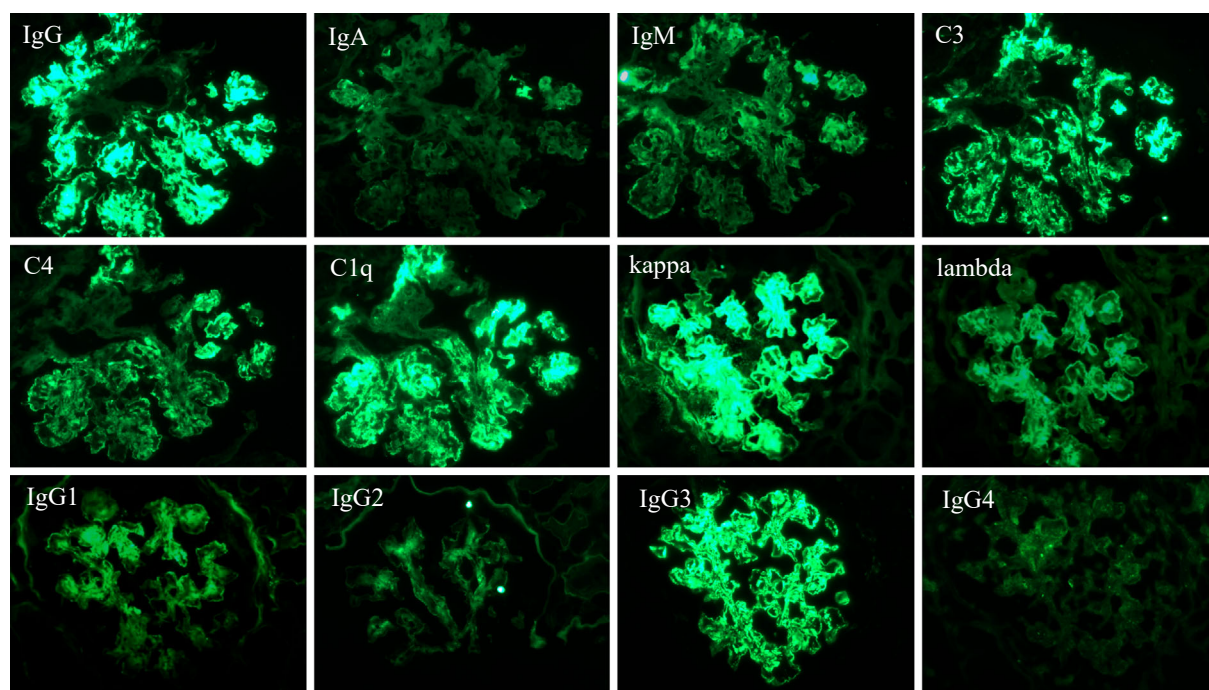


Figure 2. Immunofluorescence staining showed granular deposits dominantly of IgG, C3, C1q, κ light-chain, and IgG3 heavy-chain in the glomerular capillary wall and mesangial region. Granular deposits of κ light-chain and IgG3 heavy-chain were clearly stronger than those of λ light-chain and other IgG subclasses (IgG1, IgG2, IgG4) respectively.

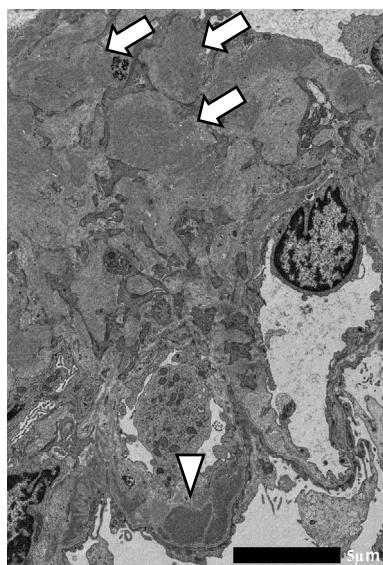


Figure 3. The electron micrograph showed granular electron-dense deposits in the subendothelial (arrowhead) and mesangial areas (arrows).

same time. The AHF-MO and AHF-UP ascitic and ascitic concentration filters (Asahi Kasei Medical, Tokyo, Japan) were used for CART, respectively. The ascites was processed at 2 L/h to prevent a fever developing. A total of 8 L of ascites fluid was collected in the first CART, while 6 L was collected in the second CART 3 weeks later. No adverse events were observed during the collection or reinfusion. The ascites fluid was a transudative effusion. The urine

volume increased, the anasarca gradually disappeared, and the body weight improved to baseline a month after CART was performed (Fig. 4). The degree of proteinuria gradually decreased from 15 g/day to 2.5 g/day, and a PR was achieved 6 months after the administration of rituximab. Serum albumin and creatinine levels also improved; thus, the prednisolone was tapered to 10 mg/day (Fig. 5). Rituximab was administered every six months depending on the patient's condition.

Discussion

In 2009, Nasr et al. reported a clinicopathological study of 37 cases of PGNMID (2). In this study, the most common histologic pattern was MPGN in 57%, followed by endocapillary proliferative glomerulonephritis in 35%. Immunofluorescence staining showed a single light-chain isotype and a single heavy-chain subtype, most commonly IgG3- κ (53%) and IgG1- κ (22%). The glomerular deposition of C3 was detected in 97% of cases, while C1q was detected in 64%. For the mean duration of the 30.3-month follow-up, 38% of patients experienced complete or partial recovery, 38% had persistent renal dysfunction, and 22% experienced progression to end-stage renal disease. We suspected PGNMID on light microscopy after observing MPGN and light-chain staining dominantly for κ and added IgG subclass staining to confirm monoclonal IgG deposits restricted to the IgG3 subclass. The diagnosis was finally made based on the presence of glomerular deposits similar to immune complexes in mesangial and subendothelial loca-

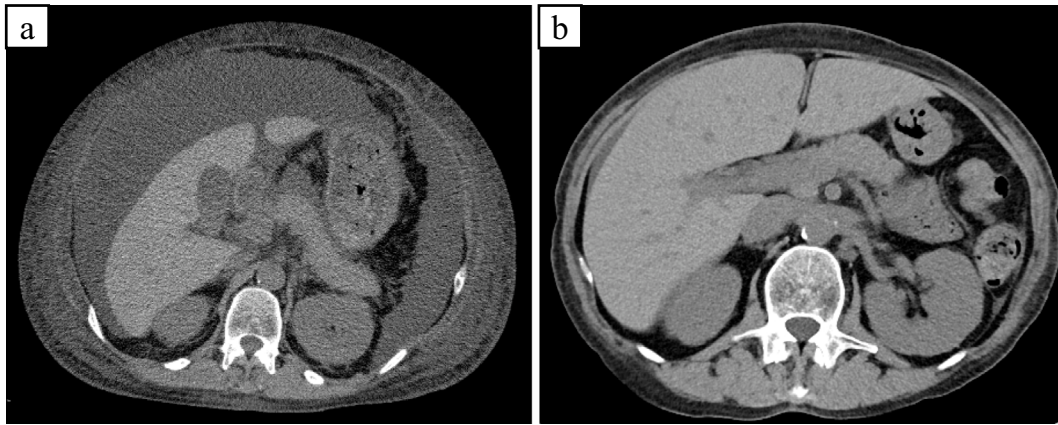


Figure 4. Computed tomography of the abdomen showed massive ascites before CART (a), whereas little ascites was noted a month after CART (b).

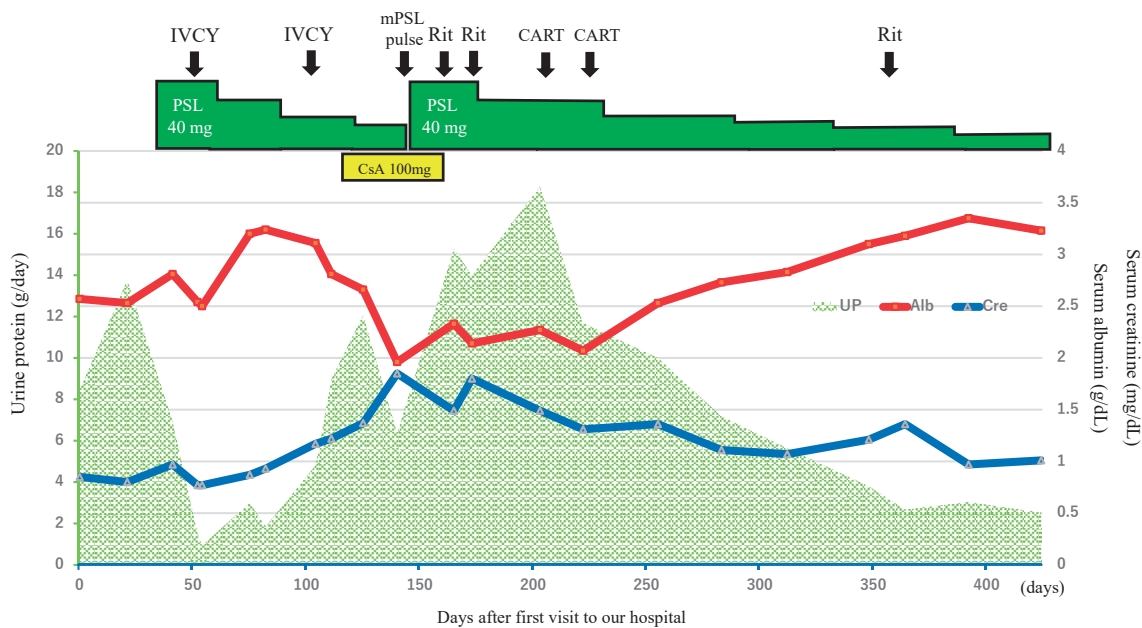


Figure 5. Clinical course of the patient. Partial remission was achieved after treatment with prednisolone and intravenous cyclophosphamide, but relapse occurred a month later. Subsequently, intravenous methylprednisolone and cyclosporin were administered, but the proteinuria worsened, and the renal function declined. Rituximab infusions were then administered once a week for two consecutive weeks, and partial remission was achieved after six months. Rituximab was administered every six months subsequently depending on the patient's condition. CART performed to treat the refractory ascites improved the ascites and anasarca. CART: cell-free and concentrated ascites reinfusion therapy, CsA: cyclosporine, IVCY: intravenous cyclophosphamide, mPSL: methylprednisolone, PSL: prednisolone, Rit: rituximab, sCr: serum creatinine, UP: urine protein, Cre: creatinine, Alb: albumin

tions on electron microscopy. Typical histological findings of PGNMID were noted in the present case, as the histological pattern was MPGN, and the deposition of monoclonal protein was IgG3- κ . Some case studies reported that cases with predominant IgG3 glomerular deposits tended to have MPGN histologic patterns, and the renal outcomes were poor in cases with these patterns (3, 4). This case initially showed steroid and immunosuppressive drug resistance, which may have been associated with the histological pat-

tern of MPGN.

The pathogenesis of PGNMID remains unknown. Most patients have no background of autoimmune disease or infection, and there is no polyclonal nature of the immune deposits, suggesting immune complex-mediated glomerulonephritis. Furthermore, similar to our case, since a monoclonal protein is not detected even after long-term follow-up in many cases, Nasr et al. proposed that B cell clones may proliferate in the course of normal immune responses and

produce a slight degree in monoclonal IgG with self-aggregation and rapid deposition in glomeruli with high affinity (2). In addition, a pathologic clone may exist but simply be unable to be detected by our current methodology (5, 8).

There is no established view concerning the treatment of PGNMID, but when a clone is detected, targeting the underlying clone with chemotherapy is the consensus of experts (9-11). The majority of patients with PGNMID do not have an identifiable clone, and no consensus has been reached regarding treatment when a clone is not detected. In contrast, some reports have found that rituximab, a monoclonal antibody against CD20 and a clone-directed approach, was effective in cases of PGNMID without a detectable clone (4, 9, 12). Zand et al. recently reported the efficacy and safety of daratumumab, a monoclonal antibody against CD38 (8). In our case, the patient showed steroid and immunosuppressive drug resistance, but the proteinuria gradually decreased, and the renal function improved after rituximab administration. Thereafter, steroid tapering became possible, and a PR was achieved six months later. Rituximab may thus be effective in patients with PGNMID whose disease is refractory to empirical treatment with steroids and immunosuppressants.

However, transudative ascites became complicated as the fluid retention progressed, although the patient had no history of heart disease, liver disease, endocrine disease, or neoplasia, suggesting that the ascites was associated with nephrotic syndrome. Despite the combined use of diuretics for body fluid management, the refractory ascites persisted and worsened. Ascite puncture drainage may be performed in such cases, but it is likely that many proteins will be lost, and the patient's nutritional status will deteriorate. The intravenous injection of albumin also has problems related to medical costs and the risk of infectious diseases. In 2001, a multicenter observational study investigated the safety and efficacy of CART in patients with ascites mainly caused by liver cirrhosis or cancer (6). As a result, the albumin concentration was maintained, and no serious side effects were observed. As the most common complication, some patients had an increased body temperature during CART, but this was able to be prevented by reducing the ascites processing rate to <3 L/h. In 2017, post-marketing surveillance evaluated CART safety and efficacy (7). In that report, the total protein and albumin levels were significantly higher after CART than before CART, indicating the effect of the reinfusion of autologous proteins. In addition, it was suggested that the reinfusion of autologous proteins might increase the urine volume by increasing the circulating plasma volume through increasing the plasma colloid osmotic pressure. While an increased body temperature was observed, it was a slight and transient change. In our case, no adverse events, including a fever or decreased blood pressure, were observed at an ascites processing rate of 2 L/h. There are few CART reports on patients with nephrotic syndrome compared to those of liver cirrhosis or cancer. Therefore, the ac-

tual efficacy and side effects of CART may differ from those reported to date. The improvement in fluid retention in ascites and anasarca may be due to the fact that CART replenished albumin and contributed to the stabilization of a patient's hemodynamics. Guiard et al. reported that rituximab therapy for PGNMID with nephrotic syndrome took 9 months (range, 4-24 months) to achieve the desired result (4); therefore, achieving remission immediately is impossible. We thus suggest that CART may be an option for fluid management, including refractory ascites associated with nephrotic syndrome, until the effect of rituximab appears.

In conclusion, the clinical course of PGNMID may improve with rituximab administration in addition to steroids and immunosuppressants. We propose that rituximab and CART may be effective and safe treatment options for patients with PGNMID and refractory ascites. The further accumulation and analyses of cases are needed to confirm the appropriate treatment of PGNMID without a detectable clone and CART for refractory ascites due to nephrotic syndrome.

The authors state that they have no Conflict of Interest (COI).

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