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Case Report

Prolonged Immunosuppressive Therapy in Immune Complex-Membranoproliferative Glomerulonephritis: A Case Report of Sustained Partial Remission Over Three Years

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ABSTRACT

The prevalence of membranoproliferative glomerulonephritis (MPGN) is very low among primary glomerulonephritis. Once MPGN is diagnosed, it is essential to classify the type of MPGN [immune complex (IC), complement-mediated, and without complement or IC deposition]. In cases of IC-MPGN, secondary causes should be thoroughly investigated. However, there are no randomised controlled prospective trials for the optimal treatment regime for primary IC-MPGN. Here, we present a report of primary IC-MPGN that achieved partial remission after 3 years of mycophenolate mofetil treatment, even though significant fibrosis was present in the kidney biopsy. This report may support consideration of prolonged immunosuppression in selected cases with primary IC-MPGN.

1. Introduction

The prevalence of histopathological patterns of glomerulonephritis (GN) varies across countries and time periods. A retrospective study analyzing 356 patients reported that membranoproliferative glomerulonephritis (MPGN) accounted for 3.1% of primary GN cases [1]. In another study from Malaysia (n: 611), MPGN was found in fewer than 1.8% of primary GN cases [2]. A Brazilian study reported that 67.9% of MPGN cases (n:36 out of 53 patients) were classified as primary (idiopathic) MPGN, with a mean age of 38.1 ±16.3 years and a male predominance of 41.7% [3]. Additionally, 60.8% of primary MPGN patients showed no response to therapy, while the rest of them (39.2%) had partial or complete remission [3].

The MPGN cases were classified into three types based on the immunofluorescence microscopy (IFM) findings: immune complex-mediated MPGN (IC-MPGN), complement-mediated MPGN, and MPGN without complement or immune complex deposition [3]. Most IC-MPGN cases have an underlying secondary cause, such as hepatitis C and B virus infections, other chronic infections, monoclonal gammopathies, and autoimmune diseases like lupus nephritis [3].

Here, we present a case of primary IC-MPGN that achieved partial remission three years after the initiation of treatment.

2. Case Presentation

A 54-year-old male patient with a body surface area of 2.0 m2, who had previously been prescribed perindopril (10 mg) + amlodipine (5 mg) at another center, was admitted to our department with uncontrolled hypertension (150/70 mmHg). Nephrotic syndrome associated with a decreased glomerular filtration rate (GFR) was identified through laboratory findings **(Figure 1)**. Urinalysis revealed no specific features with respect to hematuria or leukocyturia. A renal biopsy, which comprised seven glomeruli, was inadequate for complete analysis by light microscopy (LM) only. Eight to ten glomeruli are usually required in order to adequately assess the severity and distribution of lesions in a kidney biopsy by LM, and at least one glomerulus (preferably two to three) is required for immunofluorescence microscopy [4, 5]. Two out of the seven glomeruli were globally sclerotic. Additional findings included glomerular lobulation, mesangial hypercellularity, mesangial matrix expansion, and interstitial fibrosis (50%) **(Figure 2)**. Immunofluorescence microscopy, which was adequate and represented by four glomeruli, revealed diffuse peripheral expression of complement 4d (C4d), with no deposition of C3 or C1q, and immunoglobulin G (IgG) and M deposits at +2 severity **(Figure 3)**. These findings support the diagnosis of IC-MPGN [6].

Further investigations for secondary causes were negative. Viral infections (hepatitis B, C, and Human Immunodeficiency Virus), autoantibodies (such as antinuclear, anti-dsDNA, anti-Ro-52, anti-Ro/SSA, anti-centromere, anti-La/SSB, anti-Scl 70, anti-Smith, anti-glomerular basement membrane, anti-cardiolipin, and anti-neutrophil cytoplasmic antibodies), hypocomplementemia (complement 3: 1.13g/L, complement 4: 0.31g/L, CH50 activity: 127%),

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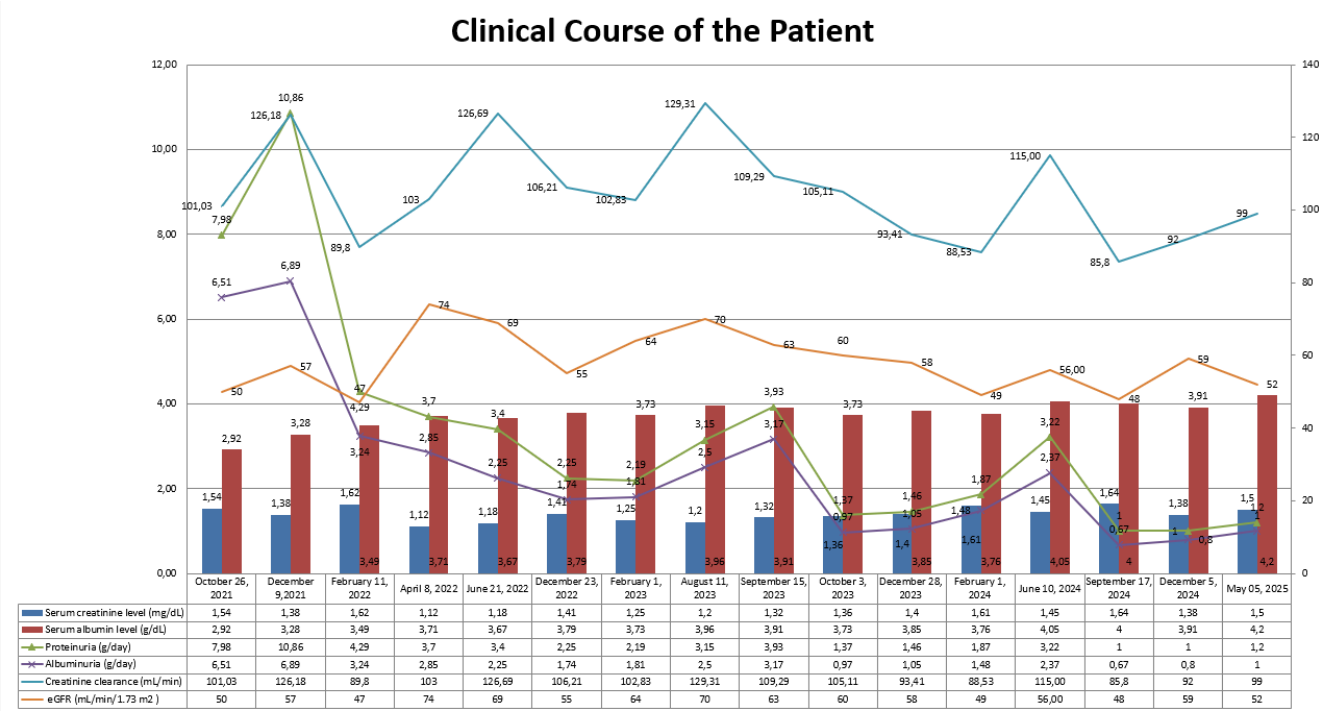

Figure 1: Clinical course of the patient.

Table 1: Timeline showing the therapy changes with respect to laboratory values.

Date	Serum creatinine level (mg/dL)	Proteinuria (g/d)	Albuminuria (g/d)	Received therapy	Prescribed therapy
October 23, 2021	1,56	13,02	9,41	Perindopril, amlodipin	prednisone 1 mg/kg/d, calcium +vitamin D, proton pump inhibitor, amlodipine, and valsartan
April 8, 2022	1,12	3,7	2,85	prednisone 5mg/d, calcium +vitamin D, proton pump inhibitor, amlodipine, and valsartan	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol.
May 05, 2025	1,5	1,2	1	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol.	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol+ dapagliflozin 10 mg
July 23, 2025	1,64	0,8	0,5	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol+ dapagliflozin 10 mg	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol+ dapagliflozin 10 mg

MMF, Mycophenolate mofetil; PPI, Proton pump inhibitor

and monoclonal gammopathies by serum immunofixation electrophoresis were not detected. Screening tests for malignancy also yielded no positive results. Given these findings, the patient was diagnosed with idiopathic IC-MPGN. The patient exhibited decreased eGFR (estimated GFR using Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI equation) of 50 mL/min/1.73 m2 (24-h urine creatinine clearance was 101 mL/min, the muscle mass related difference between the creatinine clearance and eGFR was noticed) and nephrotic syndrome without hematuria and rapidly progressive crescentic disease (**Figure 1**).

The treatment regimen included pneumococcal and influenza vaccinations, prednisone 1 mg/kg/d, calcium +vitamin D, proton pump inhibitor, amlodipine, and valsartan. After three months, prednisone was gradually tapered to 20 mg/day. Proteinuria decreased from 7.98 g/d to 3.7 g/d, and serum albumin levels increased from 2.9 g/dL to 3.7 g/dL in six months of therapy. Given the unsatisfactory response, mycophenolate mofetil (MMF) 500 mg twice daily was added to the treatment regimen. The dose of MMF was prescribed at 2 g/day in the following visit. Throughout follow-up, fluctuations in proteinuria and blood pressure levels were noted. Consequently, the patient continued with a regimen of prednisolone

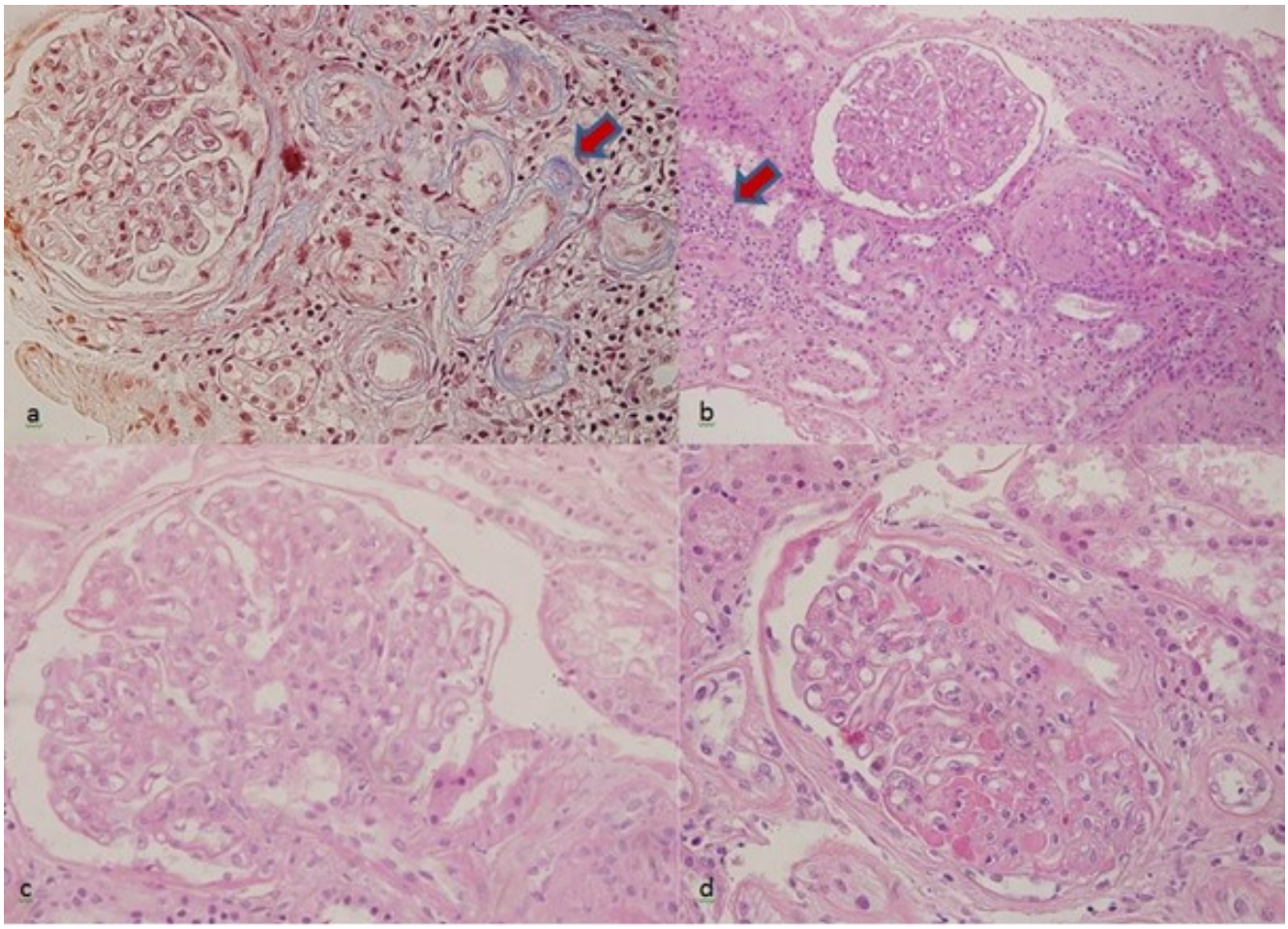

Figure 2: Light microscopy findings showing (a) tubular atrophy and peritubular fibrosis, Masson Trichrome stain × 200; (b) interstitial inflammation H&E × 200; (c) glomerular lobulation and mesangial proliferation, H&E × 400; (d) glomerular fibrin microthrombi H&E × 400.

5 mg/day, MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol. After three years, kidney function was better, proteinuria decreased to ≥ 1 g/day and eGFR increased to 59 mL/min/1.73 m2. In addition, sodium-glucose co-transporter 2 inhibitors have recently been added to the treatment list as recommended to all patients [6]. The benefit of this addition was a greater reduction in albuminuria (500 mg/d), which was observed three months later.

3. Discussion

Complement-mediated MPGN is diagnosed when IFM detects dominant C3 or C4 depositions. IC-MPGN is diagnosed when IFM shows subendothelial and mesangial depositions of Ig ± C3. MPGN without Ig or complement deposition is diagnosed when IFM reveals no staining for Ig, C3, or C4 in patients with characteristic MPGN histology [3, 6, 7]. After a definitive diagnosis of IC-MPGN, it is essential to perform a thorough evaluation to rule out secondary causes. In this case, no secondary causes, including malignancy and hepatitis B infection, which are more common in IC-MPGN cases, were identified, leading to the diagnosis of idiopathic IC-MPGN [8]. The kidney biopsy of our patient was adequate with respect to the number of glomeruli by immunofluorescence microscopy, but had inadequate glomeruli to evaluate by LM.

The initial clinical manifestations of patients with IC-MPGN can vary widely among patients and across different geographical regions [9, 10]. Our patient presented with decreased eGFR and nephrotic syndrome without hematuria, which is consistent with other studies. Nakagawa et al. reported that 20.9% of the 67 IC-MPGN patients in Japan presented without hematuria in their study [10]. On the other hand, most of those patients (56.7%) presented with nephrotic syndrome. Unfortunately, 38.8% of patients, like our case, had the first presentation of IC-MPGN as chronic glomerulonephritis (GN). The study by Nakagawa et al. outlined several treatment regimens for IC-MPGN, including intravenous methylprednisolone (43.3%), cyclosporine (25.4%), cyclophosphamide (10.4%), mizoribine (6%), azathioprine (3%), and mycophenolate mofetil (4.5%). Despite these interventions, the long-term outcomes included: complete remission in 25.4% of patients, end-stage kidney disease in 26.9%, and all-cause death in 17.9 % after a median follow-up of 4.6 years [10]. On the other hand, Elahi T et al. found that most of the IC-MPGN patients (65%) from Pakistan presented with acute kidney injury [9]. In their cohort of 163 patients, 4.9% of IC-MPGN patients did not present with hematuria. The patients were treated with steroids alone or cyclophosphamide, resulting in 34.3% achieving complete remission, 41.71% partial remission, and 19.63% progressing to end-stage kidney disease after a follow-up period of 29.45 ± 21.28 months [9].

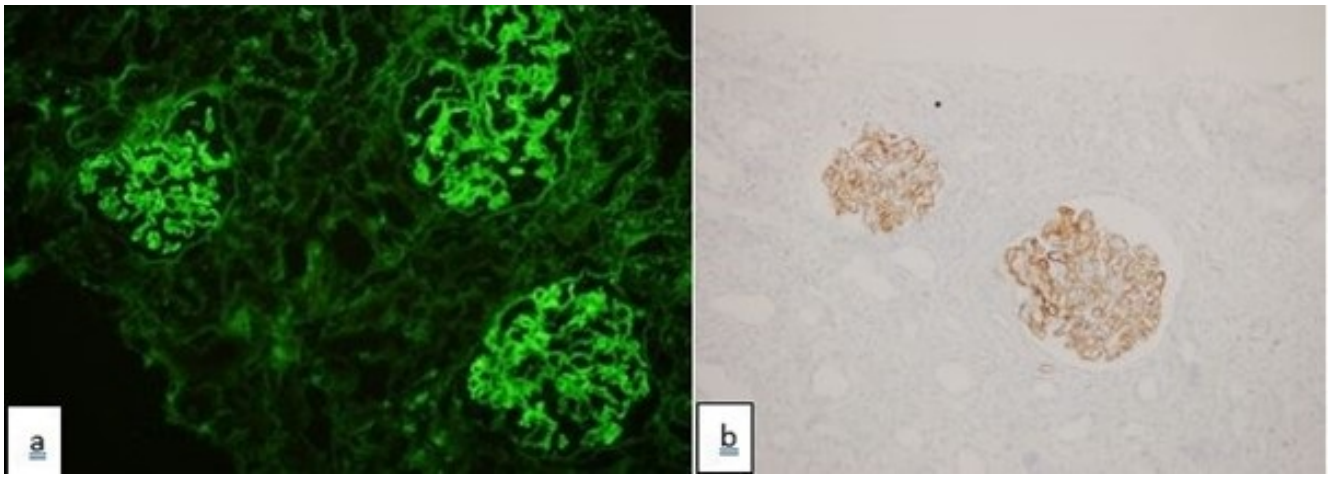

Figure 3: Light microscopy findings showing (a) tubular atrophy and peritubular fibrosis, Masson Trichrome stain × 200; (b) interstitial inflammation H&E × 200; (c) glomerular lobulation and mesangial proliferation, H&E × 400; (d) glomerular fibrin microthrombi H&E × 400.

The treatment options of idiopathic IC-MPGN are not based on randomized controlled intervention trials [11]. Nevertheless, the choice and duration of immunosuppressive drugs depend on the clinical parameters of patients with IC-MPGN. For patients with normal kidney function and nephrotic-range proteinuria, a regimen of prednisone and calcineurin inhibitors (CNI) is typically recommended. In contrast, patients with abnormal kidney function (arbitrarily defined as an estimated GFR [eGFR] <60 mL/min/1.73 m2) without rapidly progressive crescentic disease with varying degrees of proteinuria and hematuria are generally treated with prednisone and MMF [6]. Our patient was in the latter group. Prednisone for 3-6 months and MMF for 6-12 months are typical immunosuppressive treatments for these patients, as in our case [6]. However, even complete remission was achieved after cessation of MMF, and half of these patients were reported to have relapses [11]. So, we had to continue with MMF due to the persistence of proteinuria. However, the long-term benefits of these treatments are not certain [12, 13]. So, this was a limitation for this extended usage of MMF treatment.

For assessment of proteinuria, 24-hour urine protein excretion is considered a gold standard diagnostic tool despite its handicaps [14]. Serum creatinine, 24-hour urine protein excretion, and a urinalysis at least every two to three months are required to assess the response to treatment for all GN [6]. Aiming for a mycophenolic acid trough level of 1 to 3 ng/mL is suggested for cases like ours. However, it is not easily accessible to explore mycophenolic acid trough levels everywhere. It is also wise to prevent and monitor infectious complications of the kidney diseases and the immunosuppressive drugs [15].

Hypertension is also closely related to kidney health, both directly by podocyte injury and indirectly by leading to cardiovascular disease [16]. Drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which target the renin-angiotensin-aldosterone system (RAAS), slow the progression of chronic kidney disease (CKD) by reducing intraglomerular pressure, proteinuria, and inflammation [17]. Many guidelines recommend these RAAS blockers as the first-line treatments in hypertensive patients with CKD and proteinuria [6, 18].

4. Conclusions

Interstitial fibrosis and tubular atrophy have been reported to be key predictors of long-term kidney survival. Our patient had severe glomerulosclerosis and interstitial fibrosis at the initial presentation. However, the chosen treatment regimen has been effective in preserving kidney function. At the third-year follow-up, his kidney function improved compared to the eGFR and proteinuria levels at the time of initial diagnosis, despite severe renal fibrosis. Finally, the early detection of GN is critical in determining patient and kidney survival. Therefore, routine urinalysis to assess proteinuria and hematuria should be a standard procedure for all patients to ensure early diagnosis and intervention.

Conflicts of Interest

All of the authors declare no conflict of interest.

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Large Language Model

No support from artificial intelligence was taken.

Authors Contribution

KK contributed to conception, design, analysis, and interpretation of data, drafting the article, and revising it. YD contributed to literature research and interpretation of data. MK contributed to

literature research and interpretation of data. SM contributed to interpretation of pathological findings.

Data Availability

All data supporting the findings of this single-patient case report are contained within the article.

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