Immune complex membranoproliferative glomerulonephritis in a kidney transplant recipient: diagnostic and therapeutic challenge

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In the context of a renal allograft, the occurrence of membranoproliferative glomerulonephritis (MPGN) represents a significant clinical challenge, signifying a substantial risk of allograft dysfunction and loss. We aimed to present a case of MPGN in a kidney transplant recipient with its diagnostic and therapeutic challenge. We report a case of a 62-year-old woman with recurrent glomerular disease following renal transplantation, initially diagnosed – before transplant – as C3 glomerulopathy (C3G) secondary to a paraprotein. Her clinical course illustrates the diagnostic and pathophysiologic overlap between C3G and immune complex (IC)-mediated MPGN, highlighting the evolving nature of complement-mediated kidney injury in the setting of monoclonal gammopathy. This case highlights the diagnostic complexity of complement-mediated glomerulonephritis in the setting of monoclonal gammopathy. The transformation from C3G (before transplantation) to C1q-positive IC-MPGN posttransplant highlights the continuum of complement and IC activation pathways. Long-term follow-up with serial histopathologic evaluation and hematologic correlation is crucial to guide prognosis and management.

Keywords:
C3 glomerulopathy, complement, membranoproliferative glomerulonephritis, monoclonal gammopathy, recurrent glomerulonephritis, renal transplantation

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Introduction

Renal transplantation remains the definitive treatment for end-stage kidney disease; however, the long-term success of allografts is continually challenged by disease recurrence and the development of *de novo* glomerular diseases [1]. Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury historically classified into types based on ultrastructural findings, but it is now broadly classified by etiology into: immune complex-mediated MPGN (IC-MPGN) and C3 glomerulopathy (C3G) [2].

MPGN is a histopathological pattern of injury characterized by mesangial hypercellularity, endocapillary proliferation, and thickening of the glomerular basement membrane, often with a "double contour" or "tram-track" appearance on light microscopy. In the context of a renal allograft, the occurrence of MPGN represents a significant clinical challenge, signifying a substantial risk of allograft dysfunction and loss. The pathogenesis of MPGN in transplant recipients is complex, but it can be broadly categorized into two main pathways: complement-mediated (often C3G) and IC-mediated. IC-mediated MPGN in a renal allograft can arise via recurrent disease (the most common scenario). The recurrence rate varies significantly by the original disease, with some studies reporting recurrence rates of MPGN (historically defined) as high as 30–70% [3]. The continuation of the underlying immune system dysregulation in the recipient, despite immunosuppression, allows the pathogenic ICs to be deposited in the graft's glomeruli. *De novo* disease (less common) can be triggered by chronic viral infections (e.g. hepatitis B or C), which act as a persistent source of antigen, leading to the formation of circulating ICs [4]. Rarely can develop in chronic rejection or other alloimmune responses, where donor-specific antibodies may contribute to IC formation.

The diagnosis of MPGN is confirmed by renal allograft biopsy, which shows the classic triad: light microscopy: glomerular hypercellularity due to proliferation of mesangial and endothelial cells and infiltration by monocytes/macrophages, leading to lobular accentuation. Interposition of mesangial cells and newly formed basement membrane material

between the endothelial cells and the original GBM induces capillary wall thickening with double contours. Immunofluorescence: this is critical for recognizing IC-mediated MPGN from complement-mediated MPGN (C3G). It typically shows granular deposits of immunoglobulins (e.g. IgG, IgM, and sometimes IgA) and complement components (C3 and often C1q and C4) along the capillary walls and in the mesangium. This "full house" pattern (if IgG, IgA, IgM, C3, and C1q are all positive) is highly suggestive of lupus nephritis but can be seen in other conditions. Electron microscopy reveals electron-dense deposits. In IC-mediated MPGN, subendothelial deposits are the most characteristic and prominent finding, corresponding to the double contours seen on light microscopy. Mesangial and, less commonly, subepithelial deposits may also be present [5,6].

IC-MPGN in the allograft is a particularly aggressive and challenging entity, frequently leading to graft loss and recurrence rates that can exceed 50% [7]. While specific etiologies such as hepatitis C virus, systemic lupus erythematosus, and monoclonal gammopathy have been clearly associated with IC-MPGN, a substantial proportion remains idiopathic or cryptogenic, making targeted therapy difficult [8].

Familial IC-MPGN is a rare kidney disease characterized by a pattern of glomerular injury seen on kidney biopsy, primarily resulting from the deposition of ICs (antibodies and antigens) and complement proteins in the glomeruli. It appears to have a familial or hereditary predisposition [9].

We present the case of a patient who developed (recurrent/de novo) IC-mediated MPGN in their renal allograft. This report aims to highlight the diagnostic complexities of distinguishing IC-MPGN from other transplant glomerulopathies and discuss the therapeutic challenges and potential management strategies in the context of persistent immune activation.

Case presentation

A 62-year-old lady was first diagnosed with kidney disease in 2013 after a brief history of hypertension. Her family history was notable for kidney disease: her mother, aged 87, was approaching dialysis dependence, and her brother had received a renal transplant in his 50s. Moreover, the patient's son reported that several relatives with renal dysfunction.

Initially, she presented with acute kidney injury and pulmonary edema and underwent a kidney biopsy in the UK in 2017. Her virology and autoimmune screen were negative. Histopathology revealed features consistent with monoclonal gammopathy-associated membranoproliferative glomerular pattern of injury with excess lambda light-chain deposition. She later returned to Kuwait, where she experienced recurrent episodes of acute kidney injury requiring intermittent dialysis and diuretics.

A repeat kidney biopsy in early 2019 revealed marked chronic scarring and C3 deposition within the glomeruli, accompanied by minimal immunoglobulin staining. Light-chain analysis confirmed persistent lambda restriction. However, her serum C3 was slightly below the normal limit (0.38 g/l). The working diagnosis was supporting C3G secondary to a paraprotein, rather than a monogenic complement defect. Her clinicians noted a risk of posttransplant recurrence but anticipated slow progression. They advised ongoing surveillance for an occult plasma-cell clone that might warrant future therapy if detected.

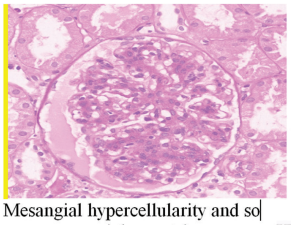
Her comorbidities included hypothyroidism managed with levothyroxine and moderate-to-severe cardiac impairment with grade 1 diastolic dysfunction, attributed to uremic cardiomyopathy. After cardiology clearance, she underwent live-unrelated renal transplantation by the end of 2019, in Pakistan, and then landed in Kuwait shortly after transplantation to start follow-up in our center.

A few months later, because of resistant hypertension during February 2020, her computed tomography angiography revealed severe renal allograft artery stenosis, which was successfully treated with balloon dilatation. Her graft function subsequently stabilized (serum creatinine ≈ 70 μmol/L), but by mid-2020, she developed nonnephrotic proteinuria (1.5 g/day). Renal allograft biopsy revealed IC-MPGN with focal basement membrane duplication and early segmental sclerosis (Fig. 1). There was no histological evidence of rejection. Immunohistochemistry demonstrated: negative C4d in peritubular capillaries, but 3+ granular deposits in the mesangium and capillary loops, 2+ IgG smudgy, mesangial deposition, but negative IgM, and noncontributory C3. Kappa and lambda light chains showed kappa-restricted patterns.

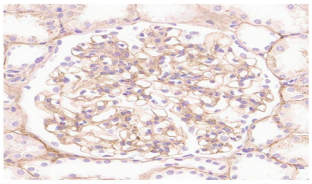
Laboratory features of secondary MPGN were negative for autoimmune disease and virology.

Serum protein electrophoresis showed no paraproteinemia and only hypogammaglobulinemia, and urine protein electrophoresis did not detect any Bence Jones protein.

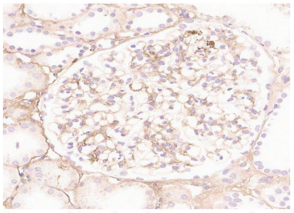
Figure 1



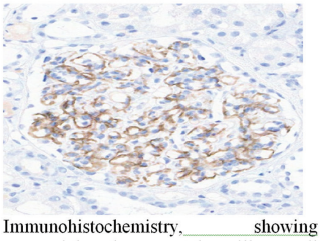
Mesangial hypercellularity and some mesangial matrix excess. HE, original magnification x200



Immunohistochemistry, showing mesangial IgA deposition. Fine granular 1+ intensity. Immunoperoxidase, original magnification x200.



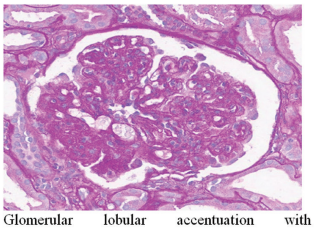
Immunohistochemistry, showing mesangial IgG deposition. Fine granular 2+ intensity. Immunoperoxidase, original magnification x200.



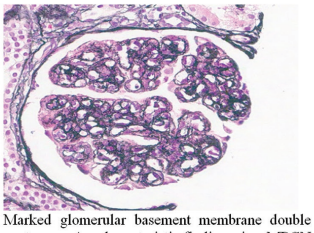
Immunohistochemistry, showing mesangial and segmental capillary wall C4d deposition. Granular 3+ intensity. Immunoperoxidase, original magnification x200.

Biopsy findings done in 2020.

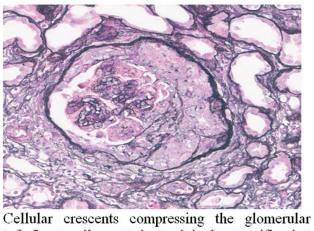
Figure 2



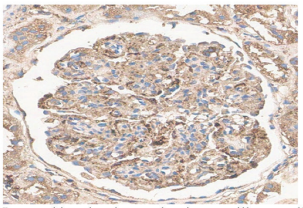
Glomerular lobular accentuation with endocapillary and mesangial hypercellularity. Segmental scarring is also seen on the right side of the image. PAS, original magnification x400.



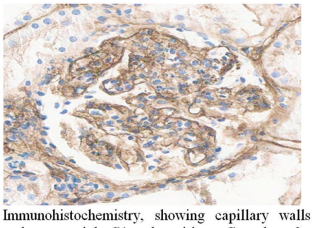
Marked glomerular basement membrane double contours. A characteristic finding in MPGN pattern of glomerular injury.
Jones Silver stain, original magnification x400



Cellular crescents compressing the glomerular tuft. Jones silver stain, original magnification x200.



Immunohistochemistry, showing capillary walls and mesangial IgG deposition. Granular, 3+ intensity. Immunoperoxidase, original magnification x200.



Immunohistochemistry, showing capillary walls and mesangial C1q deposition. Granular, 3+ intensity. Immunoperoxidase, original magnification x200.

The biopsy findings done in 2025.

In October 2025, she presented again with graft dysfunction and worsening proteinuria (3.9 g/day). Her PRA, autoimmune screen [ANA, anti-ds DNA, ANCA (P and C)] were negative. Her virology profile (HBV, HCV, EBV, CMV, HIV) were all negative. Her repeated serum protein electrophoresis was negative for paraproteinemia. The Kappa/lambda ratio was normal. Bence John's protein in urine was negative. Her ultrasound ruled out postrenal causes of acute kidney injury.

Repeat graft biopsy (Fig. 2) revealed a membranoproliferative glomerular pattern of injury with 20% crescents. Immunofluorescence proved IgG 2+ granular deposits along capillary loops and mesangium, negative IgA and IgM, positive C3 (2+) and C1q (3+) granular, mainly in capillary loops, but negative C4d in peritubular capillaries. No monoclonal immunoglobulin deposition or morphologic evidence of antibody-mediated rejection was observed. Therefore, the overall pattern was inconsistent with recurrent C3G, instead suggesting IC-mediated MPGN.

The patient was managed with pulse steroids and diuretics, initially experiencing diuretic resistance. She had fluid overload that necessitated ultrafiltration five times. Later, her urine output increased, alongside improvements in graft function. However, her proteinuria continued to rise. The plan was to administer Pegcetacoplan, which has been recently approved for IC-MPGN (Figs. 3–5 and Table 1).

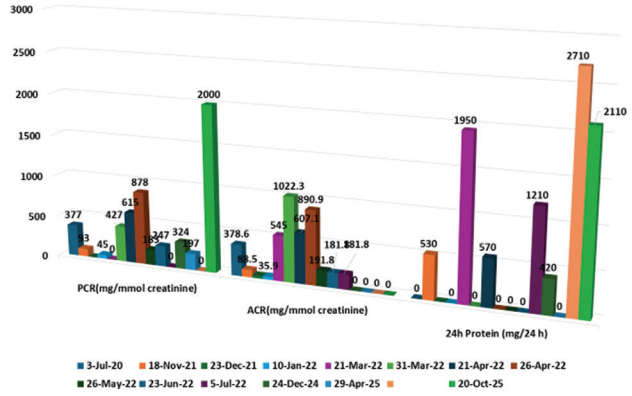
Discussion

The development of IC-MPGN in a renal allograft is a serious complication. It typically presents with proteinuria (often in the nephrotic range), hematuria, and a declining glomerular filtration rate. The prognosis is variable but usually guarded with 5-year graft survival rates reported to be as low as 50–60% in some historical cohorts [10]. The bad omens of graft loss are higher with severe proteinuria at presentation, advanced chronicity changes (tubular atrophy, interstitial fibrosis) on biopsy, and a rapid course of recurrence.

De novo glomerulonephritis occurs in up to 10–20% of renal allografts and may be underrecognized, particularly when overlapping immunopathologic features obscure the underlying mechanism. The detection of light-chain restriction in the early biopsies supports a monoclonal process; however, subsequent kappa restriction and absence of Bence Jones protein indicated possible clonal evolution or immune rebalancing posttransplant. The absence of antibody-mediated rejection features reinforced the diagnosis of a primary glomerular process.

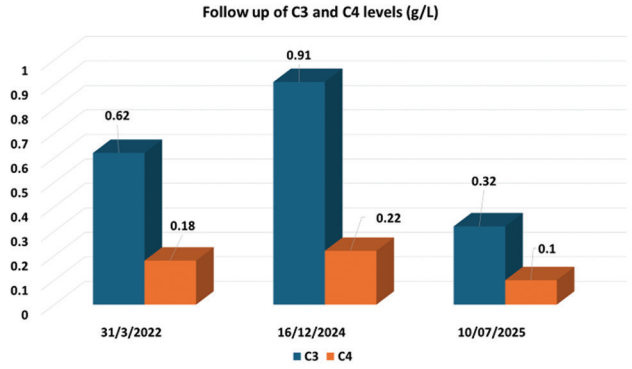
Our case highlights the dynamic interplay between paraprotein-driven complement dysregulation and

Figure 3



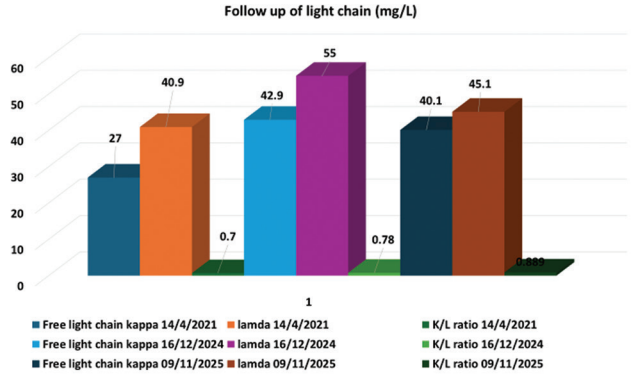
Follow-up of proteinuria (ACR, PCR, and 24 urinary protein).

Figure 4



The follow-up of her complement components.

Figure 5



Follow up of light chain levels.

glomerular IC injury. The differential diagnosis included either transformation of prior C3G toward an IC-dominant pattern or misclassification of the original native disease. The initial diagnosis (2017 biopsy) showed MPGN with monoclonal immunoglobulin deposits, specifically with excess lambda light-chain deposition. Lambda light-chain restriction is associated with a single clone of plasma cells producing a pathogenic immunoglobulin. The strong family history of kidney disease and a "blood problem" is highly suggestive of an inherited predisposition to plasma-cell dyscrasias or a specific complement defect, though the latter was initially ruled out. Leung *et al.* [11] emphasized the need to track and treat the underlying clone even in the absence of myeloma.

Second diagnosis (2019 biopsy) showed marked chronic scarring and C3 deposition within the glomeruli, with minimal immunoglobulin staining. This is a critical transition. The monoclonal lambda light chain is now acting as an "autoantibody" that dysregulates the complement alternative pathway [7].

First posttransplant biopsy (mid-2020) showed IC GN, kappa-restricted pattern denoting shift from lambda to kappa restriction, which signifies the emergence of a new clone and suppresses the original lambda clone by the immunosuppressive regimen. The absence of Bence Jones protein and hypogammaglobulinemia suggests the clone was still very subtle (MGRS) and not a full-blown myeloma. The second posttransplant biopsy (2025) revealed an IC-MPGN pattern, which is inconsistent with recurrent C3G. The source of this IgG could be a class-switched clone, a de novo autoimmune process (with negative autoimmune markers excluding this possibility), or chronic, smoldering C4d-negative antibody-mediated rejection (ABMR was ruled out by negative histological features of rejection, negative anti-HLA antibodies, and C4d).

Monoclonal gammopathy can serve as a trigger for both C3G and IC-MPGN, reflecting a continuum rather than discrete disease entities. The temporal progression from C3G in the native kidney to IC-dominant MPGN in the allograft suggested possible reconstitution of humoral immunity or

Table 1 Summary of the biopsies performed for the case

Biopsy, year, country	Histopathology findings	Immunohistochemistry/IF	Proteinuria	Serum creatinine	Remarks
Renal allograft (Kuwait) 2020 (Fig. 1)	Mesangioproliferative GN with focal basement membrane duplication	IgG 2+ smudgy, IgM neg, C4d 3+ granular (mesangium), kappa restriction	1.5 g/day	70 µmol/l	Stable graft; no rejection
Renal allograft (Kuwait) 2020 (Fig. 2)	Membranoproliferative GN	IgG 2+ granular, IgA/M neg, C3c 2+ granular, C1q 3+granular, C4d neg	3.9 g/day	250 µmol/l	Immune complex-mediated MPGN; no monoclonal deposition

MPGN, membranoproliferative glomerulonephritis.

re-emergence of a subclinical paraprotein with altered complement activation pathways.

Management remains a formidable challenge due to the lack of large, randomized controlled trials. The therapeutic approach is often extrapolated from the treatment of native kidney MPGN and involves optimizing baseline immunosuppression (e.g. calcineurin inhibitors) and considering adjunctive therapies. These may include corticosteroids, mycophenolate mofetil, rituximab (for B-cell driven diseases), or plasma exchange, depending on the suspected or proven underlying etiology (e.g. for lupus or cryoglobulinemia) [12]. The balance between augmenting immunosuppression to control the GN and the associated risks of infection and malignancy is a constant clinical dilemma.

The clinical course varies according to the histological damage, including nephritic and nephrotic phenotypes, as well as rapidly progressive glomerulonephritis [12]. The posttransplant MPGN recurrence rates range from 11.8 to 18.9% after 5 and 15 years, respectively, with a negative impact on graft survival [13–15], especially in cases of MPGN I recurrence associated with crescents [12]. The late recurrence rate of DDD (or MPGN II) approaches 100%, whereas C3GN recurrence tends to occur early after transplant [16]. For IC-MPGN, the glomerular monoclonal immunoglobulin deposition with glomerular C4d deposition is associated with early disease recurrence and poor outcomes [16]. However, in our case the MPGN lesion with crescent developed after 1 year of transplant without significant impact of graft function possibly due to meticulous care and optimal use of immunosuppressive regimen.

Clinically, complement-modulating therapies such as eculizumab have limited evidence in paraprotein-associated C3G, and management remains directed toward the underlying hematologic clone. However, Pegcetacoplan has been recently approved for IC-MPGN [17]. Regular monitoring for paraproteinemia, renal function, and proteinuria is essential, as disease recurrence may occur insidiously.

Conclusion

This case underscores the diagnostic complexity of complement-mediated glomerulonephritis in the setting of monoclonal gammopathy. The transformation from C3G to C1q-positive IC-MPGN posttransplant highlights the continuum of complement and IC activation pathways. Long-term follow-up with serial histopathologic evaluation and hematologic correlation is crucial to guide prognosis and management.

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Conflicts of interest

There are no conflicts of interest.

References

1 Koirala A, Singh A, Geetha D. Recurrence of glomerular diseases (GN) after kidney transplantation: a narrative review. J Clin Med 2025; 14:6686.

2 Kovala M, Seppälä M, Räisänen-Sokolowski A, Meri S, Honkanen E, Kaartinen K. Diagnostic and prognostic comparison of immune-complex-mediated membranoproliferative glomerulonephritis and C3 glomerulopathy. Cells 2023; 12:712.

3 Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med 2002; 347:103–109.

4 Cruzado JM, Carrera M, Torras J, Grinyó JM. Hepatitis C virus infection and de novo glomerular lesions in renal allografts. Am J Transplant 2001; 1:171–178.

5 Zhang H. MPGN pattern of injury. PathologyOutlines.com website. Available at: *https://www.pathologyoutlines.com/topic/kidneymembranoprolif.html*. [Accessed November 4, 2025].

6 Li AH, Li Y, Li MS, Song ZR, Lv JC, Zhang H, *et al.* Repeated kidney biopsy in membranoproliferative glomerulonephritis. Kidney Dis (Basel) 2025; 11:258–269.

7 Bomback AS, Charu V, Fakhouri F. Challenges in the diagnosis and management of immune complex-mediated membranoproliferative glomerulonephritis and complement 3 glomerulopathy. Kid Int Rep 2025; 10:17–28.

8 de Paula LC, Mazzali M, de Sousa MV. Recurrent membranoproliferative glomerulonephritis after kidney transplantation: risk factors and impact on graft survival. Ann Transplant 2023; 28:e940502.

9 Wong EKS, Marchbank KJ, Lomax-Browne H, Pappworth IY, Denton H, Cooke K, *et al.* C3 glomerulopathy and related disorders in children: etiology-phenotype correlation and outcomes. Clin J Am Soc Nephrol 2021; 16:1639–1651.

10 Lorenz EC, Sethi S, Leung N, Dispenzieri A, Fervenza FC, Cosio FG. Recurrent membranoproliferative glomerulonephritis after kidney transplantation. Kidney Int 2010; 77:721–728.

11 Leung N, Bridoux F, Hutchison CA, Nasr SH, Cockwell P, Fermand JP, *et al.* International Kidney and Monoclonal Gammopathy Research Group. Monoclonal gammopathy of renal significance: when MGUS is no longer

undetermined or insignificant. Blood 2012; 120:4292–4295.

12 Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis – a new look at an old entity. N Engl J Med 2012; 366:1119–1131.

13 Aziz F, Singh T, Garg N, Kwon H, Jorgenson M, Patel S, *et al*. Post-transplant idiopathic immune complex membrano-proliferative glomerulonephritis: characteristics and outcomes. Clin Nephrol 2022; 99:69–77.

14 Sprangers B, Kuypers DR. Recurrence of glomerulonephritis after renal transplantation. Transplant Rev (Orlando) 2013; 27(4):126-34. doi: 10.1016/j.trre.2013.07.004.

15 Allen PJ, Chadban SJ, Craig JC, Lim WH, Allen RDM, Clayton PA, *et al*. Recurrent glomerulonephritis after kidney transplantation: risk factors and allograft outcomes. Kidney Int 2017; 92:461–469. doi: 10.1016/j.kint.2017.03.015. PMID: 28601198.

16 De Souza L, Prunster J, Chan D, *et al*. Recurrent glomerulonephritis after kidney transplantation. Curr Opin Organ Transplant 2021; 26:360–380.

17 Nester CM, Bomback AS, Ariceta G, Delmas Y, Dixon BP, Gale DP, *et al*. VALIANT: Randomized, multicenter, double-blind, placebo-controlled, phase 3 trial of pegcetacoplan for patients with native or post-transplant recurrent C3G or primary (idiopathic) IC-MPGN. Immunobiology 2025; 230:153039.