CASE REPORT: EARLY AND PERSISTENT POST-TRANSPLANT PROTEINURIA DUE TO MULTIPLE CONCOMITANT ETIOLOGIES

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ABSTRACT

Post-transplant proteinuria is an early warning sign of allograft injury and is often caused by multiple concurrent mechanisms, originating either from the transplanted kidney or from the native kidneys. We report the case of a 26-year-old male who developed low-grade proteinuria immediately after kidney transplantation, which rapidly progressed to overt nephrotic syndrome within the first three months. The initial allograft biopsy revealed features of membranoproliferative glomerulonephritis (MPGN) with diffuse C4d deposition in the glomerular capillaries, suggesting chronic active antibody-mediated rejection. The patient was treated with high-dose corticosteroids and rituximab, resulting in partial improvement of proteinuria; however, recurrence occurred, accompanied by deterioration of graft function. A second allograft biopsy demonstrated combined lesions of chronic antibody-mediated rejection, acute calcineurin inhibitor (CNI) nephrotoxicity, and chronic glomerular injury, which guided treatment modification, leading to better control of proteinuria and improvement of graft function. This case highlights the importance of early recognition of post-transplant proteinuria and emphasizes a multifactorial diagnostic and therapeutic approach to optimize management and preserve long-term graft function.

Keywords: *post-transplant proteinuria; renal allograft biopsy; antibody-mediated rejection; calcineurin inhibitor toxicity.*

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I. INTRODUCTION

Proteinuria is a common complication after kidney transplantation, with a reported prevalence ranging from 7.5% to 45%, depending on the definition and timing of assessment [1]. In approximately 70% of cases, early post-transplant proteinuria is transient, typically resolving within 8–9 weeks, and does not significantly impact graft prognosis [2]. However, persistent proteinuria lasting more than three months, even at low levels (>0.15 g/day), has been demonstrated to be an independent predictor of graft loss, cardiovascular events, and patient mortality [3].

A major clinical challenge lies in differentiating between transient and persistent proteinuria, and more importantly, in determining whether the origin of proteinuria arises from the transplanted kidney or from the recipient's native kidneys. The etiologies of post-transplant proteinuria are diverse and can be broadly categorized as follows: glomerular diseases (including recurrent primary glomerulopathies such as focal segmental glomerulosclerosis or IgA nephropathy, or de novo glomerular diseases in the allograft); antibody-mediated rejection; hemodynamic and vascular factors (e.g., uncontrolled hypertension, transplant renal artery stenosis); and adverse effects of immunosuppressive agents (calcineurin inhibitors, mTOR inhibitors, etc.).

When proteinuria persists or shows a progressive increase, particularly in association with elevated serum creatinine, allograft biopsy is essential to identify the underlying cause and to guide appropriate therapeutic strategies [4].

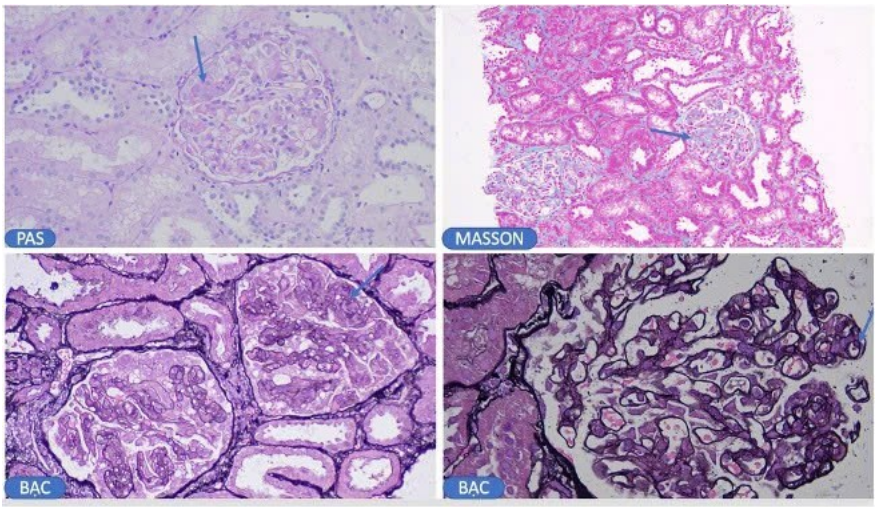
We herein report a representative case of a 26-year-old male who developed low-grade proteinuria immediately after kidney transplantation, which rapidly progressed to nephrotic syndrome with declining graft function and recurrent episodes. Histological evaluations revealed a combination of chronic active antibody-mediated rejection, acute calcineurin inhibitor (CNI) nephrotoxicity, and chronic glomerular injury. This case emphasizes the importance of early detection of post-transplant proteinuria, timely allograft biopsy, and a multifactorial diagnostic approach as critical determinants in guiding treatment decisions and optimizing long-term graft outcomes.

II. CASE PRESENTATION

A 26-year-old male patient with end-stage kidney disease underwent a living-related kidney transplantation from an unrelated donor in May 2022. Pre-transplant immunological evaluation showed an HLA mismatch of 3/6, negative panel-reactive antibody (PRA), and negative crossmatch results. The immunosuppressive regimen consisted of basiliximab induction, followed by maintenance therapy with tacrolimus (Prograf), mycophenolate mofetil (Cellcept), and corticosteroids. Post-transplant allograft function was initially stable, with serum creatinine levels ranging between 85–95 µmol/L.

During the three months after transplantation, the patient exhibited persistent low-grade proteinuria (0.3 g/L) accompanied by microscopic hematuria (50 RBC/µL). The condition progressed rapidly, and by the third month post-transplant the patient developed overt nephrotic syndrome, characterized by massive proteinuria (8.25 g/24h), generalized edema, hypoalbuminemia (29.8 g/L), and a mild increase in serum creatinine (113.6 µmol/L).

A first allograft biopsy (October 2022) revealed histopathological findings consistent with membranoproliferative glomerulonephritis (MPGN), mild interstitial inflammation, and diffuse C4d positivity along the glomerular capillaries.



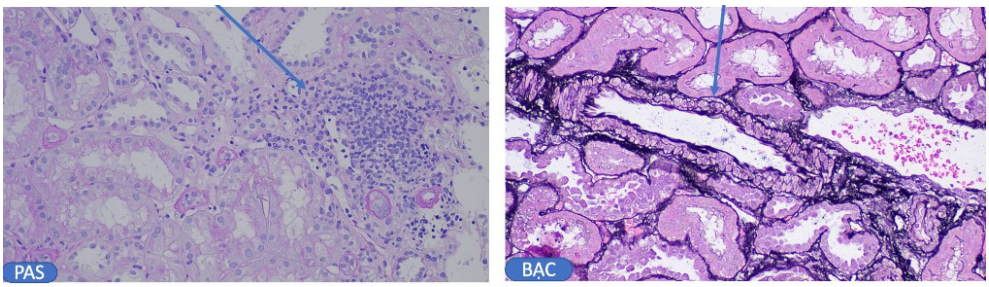


Figure 1. Glomerular lesion: Mesangial cell and matrix proliferation with mild glomerular basement membrane thickening and hyaline nodule formation. **Tubulointerstitial lesion:** Mild interstitial inflammation.

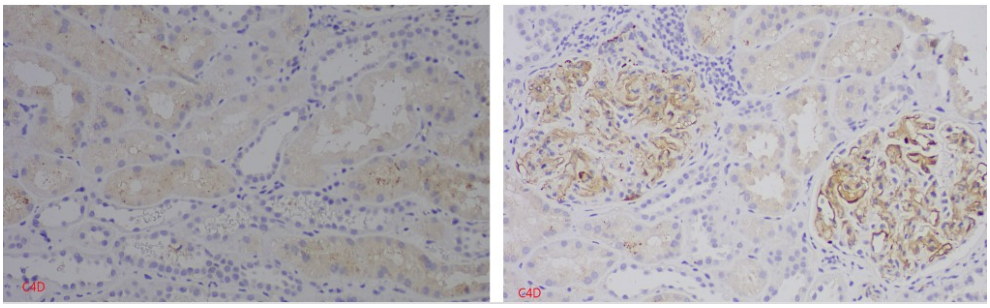
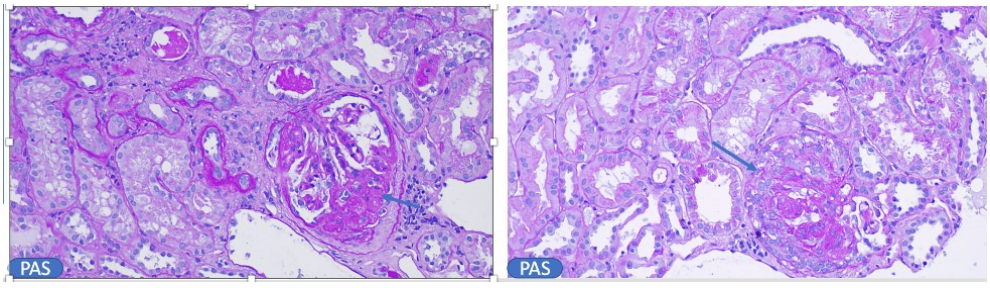


Figure 2. Immunofluorescence staining: Diffuse C4d positivity along glomerular capillaries; negative C4d staining around renal tubules.

The patient was treated with pulse methylprednisolone (250 mg/day for 3 consecutive days) and rituximab, resulting in clinical improvement with reduction of proteinuria and normalization of serum creatinine levels (89–95 µmol/L).

Recurrence (July 2023): Approximately 14 months after transplantation, the patient developed recurrent nephrotic-range proteinuria (3.6 g/24h), accompanied by hematuria, generalized edema, and a rise in serum creatinine to 110 µmol/L.

Second allograft biopsy (July 2023): Histopathological findings were more complex, demonstrating chronic active antibody-mediated rejection (C4d-positive staining without evidence of ongoing microvascular inflammation), acute calcineurin inhibitor (CNI) nephrotoxicity with tubular and arteriolar lesions, and chronic glomerular injury characterized by mesangial cell proliferation, hyaline nodules, cellular crescents, and focal segmental glomerulosclerosis.



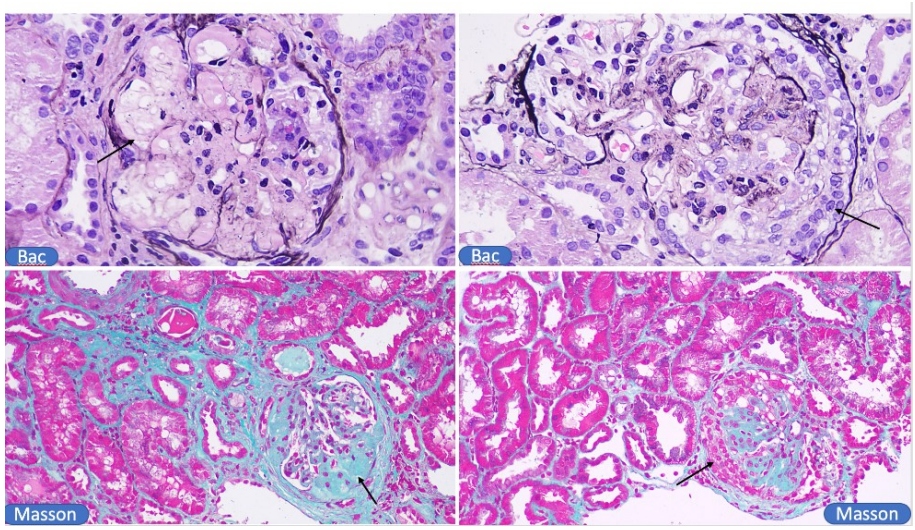


Figure 3. Glomerular lesions (involving >50% of glomeruli): Mesangial cell proliferation, hyaline nodule formation, cellular crescents, and segmental glomerulosclerosis.

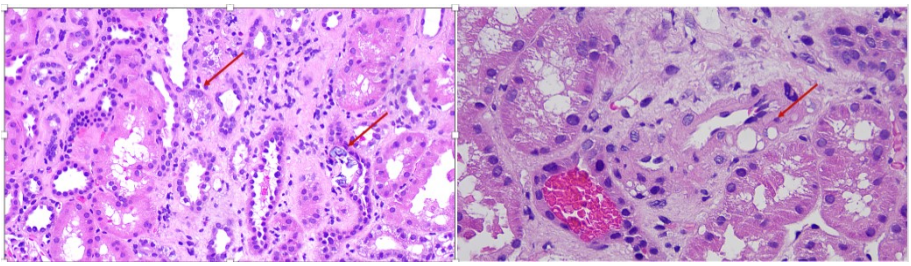


Figure 4. Tubulointerstitial and vascular lesions: Tubular epithelial vacuolar degeneration and arteriolar smooth muscle cell injury.

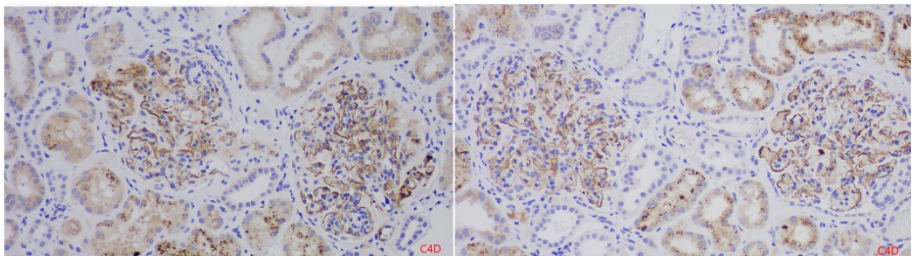


Figure 5. Immunofluorescence staining: Diffuse C4d positivity along glomerular capillaries; no IgG/IgM deposition; C3d deposition in areas of hyaline sclerosis.

The patient's immunosuppressive regimen was adjusted: tacrolimus dose was reduced (target trough level 4.5–5.5 ng/mL) to minimize tubular and vascular toxicity, while low-dose mycophenolate mofetil (Cellcept) and corticosteroids were continued. An angiotensin-converting enzyme (ACE) inhibitor was added to reduce proteinuria. Supportive measures included diuretic therapy, strict blood pressure control, and close monitoring of graft function.

Follow-up:

At 3 months post-adjustment (October 2023): proteinuria decreased to 1.95 g/24h; serum creatinine remained stable at 100–105 µmol/L; edema markedly improved.

At 6 months post-adjustment (January 2024): proteinuria stabilized between 1.2–1.6 g/24h; serum albumin slightly improved (34.5 g/L); edema resolved; serum creatinine remained stable at 100–110 µmol/L.

No recurrence of nephrotic syndrome was observed. The patient was closely monitored on the adjusted immunosuppressive regimen, with relatively stable response and preservation of long-term graft function.

III. DISCUSSION

Proteinuria is an important clinical marker that serves as an early indicator of allograft injury. Although proteinuria may occur transiently in the early post-transplant period due to hyperfiltration or persistent proteinuria from native kidneys, progressive or persistent proteinuria lasting more than three months, or reaching the nephrotic range, warrants particular attention to possible graft pathology. Allograft biopsy is mandatory in cases of progressive or persistent proteinuria, especially when accompanied by an increase in serum creatinine, in order to determine the underlying etiology and guide appropriate treatment [4].

In the present case, the first allograft biopsy revealed histopathological features of membranoproliferative glomerulonephritis (MPGN) with diffuse C4d deposition along the glomerular capillaries. Post-transplant MPGN, particularly when associated with immune complex and complement deposition, often indicates an immune-mediated mechanism, especially related to donor-specific antibodies (DSA) produced by the recipient [6]. The presence of C4d, a degradation product of complement component C4 deposited on glomerular endothelial cells, is considered a specific biomarker for antibody-mediated rejection (ABMR), confirming activation of the classical complement pathway triggered by DSAs directed against the donor endothelium [5]. Although DSA testing was not available in this case, the combination of MPGN and diffuse C4d deposition strongly supported the diagnosis of chronic active ABMR as the primary underlying mechanism of graft injury.

Based on the diagnosis of antibody-mediated rejection (ABMR), the initial treatment strategy with high-dose corticosteroid pulses (methylprednisolone 250 mg/day for 3 consecutive days) combined with rituximab was selected, aiming to suppress B-cell activity—the primary source of donor-specific antibody (DSA) production. Several studies have demonstrated the efficacy of rituximab in cases of mild to moderate ABMR [8]. Clinically, the patient showed a partial response, with reduced proteinuria, stable serum creatinine, and improvement of edema. However, the subsequent recurrence of proteinuria indicated incomplete immunologic control and suggested the coexistence of additional pathogenic mechanisms.

A second allograft biopsy was performed after recurrence of nephrotic syndrome and a mild increase in serum creatinine. Histopathological examination revealed a more complex pattern of lesions, including chronic active ABMR (diffuse C4d positivity without evidence of ongoing microvascular inflammation), tubular and arteriolar changes suggestive of acute calcineurin inhibitor

(CNI) nephrotoxicity, and chronic glomerular injury.

Chronic active ABMR (inactive phase): Diffuse C4d positivity in peritubular capillaries in the absence of active inflammation, indicating a late stage of chronic alloimmune injury in which microvascular fibrosis becomes the predominant lesion [6].

Acute CNI nephrotoxicity: Characterized by typical tubular and arteriolar lesions, including tubular epithelial vacuolization and arteriolar smooth muscle cell injury. Importantly, CNI toxicity may occur even when tacrolimus trough levels remain within the therapeutic range, through mechanisms involving afferent arteriolar vasoconstriction, ischemia, endothelial injury, and tubular cell necrosis [7]. This could explain the recurrence of proteinuria and the rise in serum creatinine, especially in the presence of prominent microvascular and tubular lesions on histology. ABMR may enhance graft susceptibility to CNI toxicity, while CNI toxicity itself can exacerbate allograft injury caused by rejection. This interplay poses a major therapeutic challenge, as reducing CNI dosage or switching to alternative agents (such as mTOR inhibitors or belatacept) may mitigate toxicity but increase the risk of rejection; conversely, maintaining CNI therapy may worsen vascular and glomerular damage.

Chronic glomerular injury: Evidenced by mesangial hypercellularity, hyaline nodule formation, cellular crescents, and segmental glomerulosclerosis involving more than 50% of glomeruli. These findings reflect advanced and irreversible lesions, likely resulting from progression of initial MPGN, persistent chronic ABMR (leading to diffuse fibrosis), and chronic CNI-induced interstitial and mesangial scarring.

The coexistence of chronic ABMR and CNI nephrotoxicity represents a significant therapeutic dilemma. Without the second biopsy, the patient might have continued receiving intensified immunosuppressive therapy targeting ABMR alone, while the critical contribution of CNI toxicity would have been overlooked.

Post-transplant proteinuria remains an important clinical marker requiring comprehensive monitoring and evaluation. This case highlights the necessity of routine surveillance of proteinuria and timely, repeated allograft biopsies in patients with persistent (>3 months) or rapidly progressive proteinuria, even when serum creatinine levels are within the normal range or only partially improved after treatment [8]. Allograft injury is often multifactorial; the coexistence and interplay of mechanisms such as rejection, immunosuppressive drug toxicity, recurrent primary glomerulopathy, and infections are common. Etiology-oriented treatment (e.g., rituximab/IVIG/plasmapheresis for ABMR; CNI dose reduction or conversion to mTOR inhibitors or belatacept in cases of CNI toxicity), combined with optimized supportive care, plays a crucial role in preserving graft function and improving long-term patient outcomes [9].

IV. CONCLUSION

Early post-transplant proteinuria is an important warning sign of allograft injury. Differentiating transient from persistent proteinuria, timely indication for allograft biopsy, and a multifactorial diagnostic approach are essential for optimizing treatment and preserving long-term graft function.

ETHICAL STATEMENT

This study was conducted in accordance with the regulations of Military Hospital 103 and the Vietnam Military Medical University. Data were used and published with permission from Military Hospital 103 and the Vietnam Military Medical University.

CONFLICT OF INTEREST:

The authors declare no conflict of interest related to this study.

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