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Literature Review

Looking Beyond Common Causes of Renal Dysfunction: Renal GVHD and Thrombotic Microangiopathy after Allogeneic Transplant

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Abstract

Renal dysfunction after allogeneic hematopoietic stem cell transplantation (allo-HSCT) often results from common causes like drug toxicity, infection, or transplant-associated thrombotic microangiopathy (TA-TMA). However, renal graft-versus-host disease (GVHD) may be ignored. We discuss a 49-year-old man who experienced worsening kidney function despite being in hematologic remission and having negative results for infections and autoimmune diseases. A renal biopsy showed chronic tubulointerstitial injury consistent with renal GVHD, along with existing TMA. Treatment with eculizumab did not lead to improvement, likely indicating significant chronic damage. This case highlights the need to maintain clinical suspicion and to perform timely renal biopsies in cases of unexplained kidney dysfunction after transplant.

More Information

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Introduction

Kidney involvement related to graft-versus-host disease (GVHD) remains an uncommon and frequently underrecognized complication after allogeneic hematopoietic stem cell transplantation (allo-HSCT). When post-transplant renal dysfunction develops, clinicians often—and appropriately—prioritize more prevalent etiologies such as calcineurin inhibitor toxicity, infections, hemodynamic insults, or transplant-associated thrombotic microangiopathy (TA-TMA). Yet renal GVHD can present outside the "classic" organ spectrum and may overlap clinically and histologically with other post-transplant renal syndromes, making timely diagnosis difficult. Reports describing renal GVHD are relatively limited, and renal pathology can be heterogeneous, ranging from glomerular disease with proteinuria to tubulointerstitial injury patterns [1-4].

We report a 49-year-old man with extramedullary myeloid sarcoma who underwent allo-HSCT from a fully matched sibling donor in December 2021 after FLAG-IDA induction. Post-transplant, he had no acute GVHD above grade 2; however, the course was complicated by hepatitis B reactivation and pulmonary embolism. Anticardiolipin antibodies were elevated (IgM >120; IgG 31), and plasmapheresis was performed for suspected secondary antiphospholipid syndrome. Despite hematologic remission, he developed progressive dyspnea; imaging in 2022 showed organizing pneumonia with evolving peribronchovascular changes that later progressed to bronchiectasis and fibrotic lung findings. Infectious evaluation, including cytomegalovirus and *Pneumocystis jirovecii*, was negative.

During follow-up, renal function deteriorated progressively (BUN 41 mg/dL, creatinine 2.34 mg/dL, clearance 27 mL/min) with proteinuria (693 mg/day). Urinalysis showed no leukocyturia but 14 red blood cells per high-power field; autoimmune serologies were negative. Given the absence of a clear alternative explanation and the persistence of kidney injury, a renal biopsy was pursued. Histopathology demonstrated chronic tubulointerstitial damage with extensive interstitial fibrosis and tubular atrophy (>50% cortical involvement) and mild-to-moderate arteriolar hyalinosis; immunofluorescence was nonspecific, arguing against classic immune complex–mediated glomerulonephritis. Overall, the findings supported a diagnosis of renal GVHD with concurrent

thrombotic microangiopathy. Eculizumab (900 mg weekly) was initiated but discontinued after eight doses due to lack of response. The patient remains in hematologic remission with stable (though impaired) renal function under nephrology/hematology follow-up.

Discussion

This case is clinically instructive for three reasons: (1) renal GVHD may be overlooked when kidney dysfunction evolves gradually and does not mirror conventional GVHD phenotypes; (2) coexisting TMA can obscure the diagnostic picture and complicate therapeutic decisions; and (3) kidney biopsy is often the decisive step that converts a broad differential into a specific, actionable diagnosis.

Renal GVHD: Uncommon, heterogeneous, and easy to miss

Renal manifestations attributed to GVHD have historically been considered rare, and many clinicians encounter them infrequently. Proteinuria in association with chronic GVHD has been recognized for years, but the renal pathology and clinical trajectories vary widely, including glomerular diseases (e.g., membranous nephropathy/minimal change disease) and tubulointerstitial injury patterns [1,5]. Contemporary biopsy series in allo-HSCT recipients emphasize that post-transplant kidney injury frequently reflects mixed or unexpected pathology, underscoring why "presumptive" diagnoses based on labs alone can be misleading [2,6]. In our patient, the combination of modest proteinuria, progressive reduction in clearance, and an otherwise unrevealing autoimmune/infectious evaluation could easily be attributed to drug toxicity or chronic post-transplant kidney disease; indeed, chronic kidney disease after HSCT is common and multifactorial [7]. What shifted the case from "probable" to "proven" was histology.

Why concomitant TMA matters

TA-TMA is an endothelial injury syndrome occurring after allo-HSCT, with reported frequencies that vary by diagnostic criteria and population [8,9]. TA-TMA can present with renal impairment and proteinuria and may overlap with exposures common in transplant care (conditioning toxicity, calcineurin inhibitors, infections, inflammation) [9]. Recent consensus efforts have aimed to standardize definitions and improve early recognition, reflecting the real-world difficulty in diagnosing TA-TMA promptly [10]. In practice, this means that when renal dysfunction appears post-transplant, "TMA vs. drug toxicity vs. infection" tends to dominate the differential—often appropriately. However, as this case illustrates, anchoring on more common etiologies may delay recognition of renal GVHD, particularly when systemic GVHD features are absent or mild.

When biopsy becomes the turning point: Timing matters

Renal biopsy is sometimes deferred in transplant recipients due to bleeding risk, thrombocytopenia, and competing acute issues. Nevertheless, available biopsy series after allo-HSCT consistently show that histology frequently changes management—either by confirming TMA patterns, revealing glomerular disease, or identifying dominant tubulointerstitial injury [2,6]. In renal GVHD specifically, biopsy not only supports diagnosis but also helps exclude immune complex diseases and clarifies the degree of chronicity, which has prognostic and therapeutic implications [2,11]. In our patient, the extent of chronic tubulointerstitial injury (>50% cortex) suggested a limited reversibility window—an important context when interpreting subsequent treatment response.

Therapeutic implications and the eculizumab question

Complement activation plays a role in many TMA syndromes, and complement blockade with eculizumab has been increasingly reported for TA-TMA, including prospective and observational data in high-risk settings [10,12,13]. However, responses are not uniform—particularly when substantial chronic kidney damage is already established or when multiple injury mechanisms coexist [10,13]. Our patient did not respond clinically to eculizumab after eight doses, which may reflect advanced chronicity on biopsy, ongoing non-complement drivers of endothelial injury, or the possibility that renal GVHD–associated damage was the dominant determinant of kidney function at that stage. Importantly, a lack of response to complement blockade should prompt reassessment of (i) chronicity and irreversibility, (ii) concurrent drivers (drug toxicity, hemodynamics, occult infection/inflammation), and (iii) whether the primary pathology is better targeted by GVHD-directed immunomodulation rather than TMA-focused therapy—decisions that are best anchored in pathology and multidisciplinary review.

Conclusion

Clinical takeaway

The central message of this case is not that renal GVHD is common, but that it is clinically plausible and diagnostically consequential—especially when kidney dysfunction progresses despite remission and when standard serologic/infectious evaluations are unrevealing. Clinicians should maintain a high index of suspicion and consider early renal biopsy in unexplained post-allo-HSCT kidney injury, because delayed recognition allows chronic tubulointerstitial remodeling to accumulate, narrowing therapeutic options and limiting reversibility.

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