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Editorial Comment

EDITORIAL COMMENT

Glomerular diseases post-hematopoietic stem cell transplantation: pathologic spectrum and plausible mechanisms

Tiffany N. Caza[1] and Kenar D. Jhaveri[2]

[1]Arkana Laboratories, 10810 Executive Center Drive #100, Little Rock, AR, USA and [2]Division of Kidney Diseases and Hypertension at Hofstra/Northwell and the Glomerular Center at Northwell Health, Lake Success, NY, USA

Correspondence to: Tiffany N. Caza; E-mail: tiffany.caza@arkanalabs.com

ABSTRACT

Glomerular disease is an important complication in patients undergoing hematopoietic stem cell transplantation (HSCT), impacting approximately 1%–2% of all HSCT recipients and equating to 700–1400 cases per year worldwide. Development of kidney disease in HSCT recipients is often multifactorial and a kidney biopsy is required to identify the underlying disease etiology and pathology. While glomerular disease is an important toxicity following HSCT, there are few kidney biopsy studies examining this complication, with the majority being limited to small series and case reports. A range of glomerular diseases may occur in association with HSCT. The study by Yap *et al.* defines this disease spectrum, which includes (in descending order) thrombotic microangiopathy (38.7%), membranous nephropathy (25.8%), mesangial proliferative glomerulonephritis (12.9%), minimal change disease (9.7%), focal segmental glomerulosclerosis (9.7%) and membranoproliferative glomerulonephritis (3.2%). In this editorial, we summarize the study and prior studies looking at glomerular diseases associated with HSCT.

Keywords: glomerular disease, graft-versus-host disease, hematopoietic stem cell transplantation

INTRODUCTION—NEPHROTOXICITY IN HEMATOPOIETIC STEM CELL TRANSPLANT RECIPIENTS

Haematopoietic stem cell transplantation (HSCT) can be a life-saving, curative treatment for patients with hematologic malignancies and hematologic disorders, with approximately 1 million transplants performed to date [1]. However, nephrotoxicity is a common complication, with acute kidney injury (AKI) affecting between 15% and 73% of patients [2] and 1%–2% of patients developing *de novo* glomerular disease. This prevalence of glomerular disease is approximately 1000-fold higher in individuals who underwent HSCT than the general population. In this issue of *CKJ*, a study by Yap *et al.*, titled 'Clinico-pathological correlations and outcomes of *de novo* glomerular diseases in patients after haematopoietic stem cell transplantation', examines glomerular disease in HSCT recipients [3].

In this study, the authors examined a series of 2204 patients who underwent HSCT over a 22-year period from a single center in Hong Kong, of which 1.4% developed *de novo* glomerular disease [3]. Forty-five percent of these cases were associated with graft-versus-host disease (GVHD), diagnosed prior or concurrent with the onset of glomerular disease. Not surprisingly, patients receiving HSCT from unrelated donors were at increased risk compared with matched siblings, haploidentical individuals or autologous transplants. This is associated with increased numbers of HLA mismatches, which increases the

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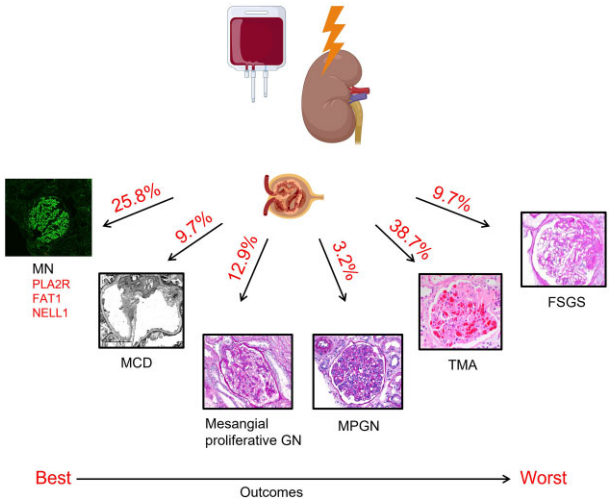

Figure 1: Types and frequencies of glomerular diseases associated with HSCT.

risk of development of GVHD. Patients come to clinical attention with AKI, proteinuria, or both.

Kidney disease in a patient with HSCT can arise from varied causes leading to both AKI and chronic kidney disease (CKD). The etiologies include chemotherapy toxicities, BK virus nephropathy, antibiotics, other drugs, hepatic sinusoidal obstruction, tumor lysis syndrome, high-dose conditioning regimens, total body irradiation and long-term immunosuppression with cumulative exposure to calcineurin inhibitors [2, 4]. Kidney damage can also occur secondary to recurrence of the native disease with lymphomatous/leukemic infiltration into renal parenchyma or monoclonal gammopathies of renal significance. CKD post-HSCT usually is related to thrombotic microangiopathy (TMA) and that could be in turn associated with chronic GVHD. Chronic GVHD is a very common complication of HSCT, impacting 30%–80% of individuals [5, 6], predominantly with extra-renal manifestations (skin, gastrointestinal tract), with approximately 1% of patients demonstrating renal involvement [5]. Some researchers consider TMA as an endothelial variant of GVHD [7].

GLOMERULAR DISEASES IN HSCT RECIPIENTS

A range of glomerular diseases may occur in association with HSCT. The study by Yap *et al.* defines this disease spectrum, of which includes (in descending order) thrombotic microangiopathy (38.7%), membranous nephropathy (25.8%), mesangial proliferative (GN) (12.9%), minimal change disease (MCD) (9.7%), focal segmental glomerulosclerosis (FSGS) (9.7%) and membranoproliferative GN (3.2%) [3] (Fig. 1).

The most common glomerular disease post-HSCT was TMA. High-dose total body irradiation was associated with development of TMA, as radiation induces endothelial injury. The TMA in HSCT patients was predominantly glomerular, with less involvement of the renal vasculature. While broad etiologies of TMA may be possible, post-HSCT hemolytic uremic syndrome is the most prevalent. Vascular microangiopathic changes are less common, although accelerated arteriosclerosis and arteriolar hyalinosis are not uncommon with HSCT recipients having an increased frequency of systemic hypertension and cardiac events [8, 9]. Other causes such as infections, calcineurin inhibitors and chronic GVHD all have been identified as risk factors for post-HSCT-TMA. Recognition is critical, as HSCT-associated TMA has a high mortality rate [10] and also comprises the most common manifestation of kidney disease post-HSCT in autopsy studies [11].

Membranous nephropathy was identified in multiple prior reports to occur post-HSCT and, in some series, is the most common glomerular disease in stem cell transplant recipients [12, 13]. While the pathogenesis is incompletely understood, recently protocadherin FAT1 was identified as the main target antigen in membranous nephropathy associated with HSCT [14]. Less commonly, PLA2R- and NELL1-associated MN occur in this setting [15]. Podocytopathies, including both MCD and primary FSGS, can occur post-HSCT, but also can occur as a paraneoplastic phenomenon in hematologic malignancies [16–20]. Workup for recurrence of the native disease is indicated, particularly cases that resistant to corticosteroid therapy [21]. Mesangial and membranoproliferative GN have been described in the setting of HSCT, but infrequently and limited to case reports [22, 23].

ROLE FOR A KIDNEY BIOPSY

Due to the diversity of diseases that can cause renal dysfunction post-HSCT, a definitive diagnosis through a kidney biopsy is necessary [4]. Kidney biopsy may also predict response to therapy based on the chronicity of renal lesions. While multiple glomerular diseases may benefit from immunosuppressive therapy, thrombotic microangiopathy, which is the most common pathology related to HSCT, would not benefit from immunosuppression and may even be contraindicated. Monoclonal gammopathies of renal significance can also be a source of proteinuric kidney disease with recurrence of the underlying hematologic cancer.

Tubulointerstitial diseases occurring after HSCT include (but are not limited to) acute tubular injury, acute or chronic tubulointerstitial nephritis, nephrocalcinosis and urate nephropathy. The most common risk factor among all of these is acute or chronic GVHD. End-organ involvement by GVHD often involves mononuclear infiltration within multiple organs, which incites collagen deposition and induces fibrosis, for which the kidney is no exception [24].

Renal dysfunction can occur prior to recognition of recurrence of the hematologic disease, which may have not otherwise come to clinical attention by a hematologist or oncologist due to a lack of systemic manifestations. Disease recurrence can induce direct infiltration of leukemic cells into the kidney, which is not uncommon in the setting of acute lymphocytic leukemia, lymphoma, myeloid sarcoma or non-hematopoietic neoplasms. AL amyloidosis, as well as other monoclonal gammopathies of renal significance, can cause renal damage, including, but not limited to light chain cast nephropathy, light chain deposition disease, light chain proximal tubulopathy, C3 GN and proliferative GN with monoclonal immunoglobulin deposits. Such diseases may require aggressive clone-based therapy, where AKI or proteinuric kidney disease may serve as harbinger of recurrence of the underlying neoplasm.

PATHOGENESIS OF KIDNEY DYSFUNCTION FOLLOWING HSCT

The most common trigger of glomerular and tubulointerstitial disease following HSCT is the development of chronic GVHD. In both human studies and animal models, a close temporal association exists between development of glomerular disease and occurrence of GVHD. The etiopathogenesis underlying GVHD includes several clinical and immunologic factors influenced by

both the donor and recipient. Demographic differences play a role in development of GVHD, including increased age of either the donor or recipient, sex differences, and HLA incompatibility. Exposures to total body irradiation or *de novo* cytomegalovirus infection increase risk [5]. Sensitization can occur from previous transplantation, making those with a prior HSCT at greater risk. Additionally, non-myeloablative conditioning regimens could result in chimerism between the host and donor bone marrow, allowing T cells that survival conditioning to precipitate graft-versus-host responses [25]. In a large study of 281 patients who underwent HSCT, 4.3% developed proteinuria, compared with 0% with myeloablative conditioning [25].

Induction of chronic GVHD involves both alloimmune and autoimmune responses. The pathogenesis is primarily T cell mediated, with T cell activation leading to production of pro-inflammatory cytokines and B cell help for autoantibody production. Multiple donor-derived $CD4^+$ T cell subsets influence development and progression of GVHD [26]. The T cell repertoire is shifted with skewing of $CD4^+$ T cell populations into pro-inflammatory T helper 17 (Th17) and Th2 subsets [27]. Donor-derived T cell clones were found to be "nephritogenic" when they induce excessive production of proinflammatory cytokines in response to major histocompatibility complex (MHC) class II determinants, which include Th2-dervied cytokines [interleukin (IL)-4, IL-10, and IFN-γ] [28]. The MHC class II molecules through which induce $CD4^+$ T cell responses are shared by both the graft and the host, acting autoimmune in nature. The Th2 and Th17 specification reduces lineage commitment to regulatory T cells (Tregs) that mediate peripheral tolerance, and therefore depletion of this population results in a loss of tolerance that promotes autoimmunity [29]. Treg lineage commitment is reduced when there is activation of the mechanistic target of rapamycin (mTOR) signaling pathway, and therefore, mTOR inhibition can promote commitment to the Treg lineage for tolerance induction [30].

In addition to a reduction in peripheral tolerance, "nephritogenic" T cells can provide help to autoreactive B cells, which results in B cell activation, expansion and autoantibody production [31]. Follicular helper T cells (T_{FH}) promote prolonged survival of activated B cells that is mediated by activation of the pro-survival transcription factors Bcl-2 and BAFF [32, 33]. T_{FH} cells also promote class-switching of immunoglobulin genes at germinal centers to induce antibody production and stimulate commitment of naïve B cells to the memory B cell lineage [32]. These factors can induce production of multiple autoantibodies, including those against DNA, histones, platelet-derived growth factor and laminin proteins, among others [31, 33].

The pathophysiology of chronic GVHD and associated glomerular disease elucidated new treatment targets with promising results in animal models and/or clinical trials. These include extracorporeal photopheresis to increase peripheral tolerance and promote T cell anergy [34], mTOR inhibition (sirolimus), [35] BAFF inhibition (belimumab) [36], B cell depletion to decrease autoantibody production (rituximab) and [37] inhibition of pro-inflammatory cytokine production (tumor necrosis factor and IL-6) [38], among others.

HOW DOES RECOGNITION OF KIDNEY DISEASE POST-HSCT IMPACT CLINICAL PRACTICE?

Recognition of glomerular disease is critical in HSCT recipients and impacts long-term outcomes. Patients who undergo HSCT in general have an increased risk of mortality compared with the general population in the first decade post-transplant; however, those developing glomerular and other kidney disease are at higher risk. The risk is the most significant for those who require dialysis during their disease course (approximately 5% of patients) [39]. In the study by Yap *et al.*, the overall 5-year survival of patients who develop GN secondary to HSCT was 83.5% [3], compared with the total HSCT population with an overall survival of 89%–97% [40, 41]. For renal outcomes, MN and MCD had the best prognosis, while TMA and steroid-dependent/resistant FSGS had the worse outcomes.

A challenge for clinical recognition is that the onset of glomerular disease following HSCT is often delayed, with a mean interval of 2.8 years post-transplantation [3]. GVHD manifestations are often not renal-limited and can be discovered concurrently with other disease manifestations, although not all glomerular disease is related to GVHD. Measurement of renal function and proteinuria at routine follow-up intervals in HSCT patients could improve recognition to initiate early treatment. In a study of patients with post-HSCT glomerular disease, treatment of acute or chronic GVHD (with prednisone and cyclosporine) led to resolution of proteinuria through mitigation of the graft-versus-host response [12]. Therefore, we can improve both patient and renal outcomes through early and specific diagnosis of glomerular disease, which often requires a kidney biopsy.

CONFLICT OF INTEREST STATEMENT

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K.D.J. is a founder and co-president of the American Society of Onco-Nephrology; and reports consultancy agreements with Secretome, GSK, George Clinicals, PMV pharmaceuticals and Calliditas. K.D.J reports honoraria from the American Society of Nephrology, the International Society of Nephrology and UpToDate.com; reports serving on the editorial boards of *American Journal of Kidney Diseases*, *CJASN*, *CKJ*, *Journal of Onconephrology*, *Kidney International* and *Nephrology Dialysis Transplantation*; and reports serving as Editor-in-Chief of ASN Kidney News and section editor for onconephrology for *Nephrology Dialysis Transplantation*.

(See related article by Yap et al. Clinico-pathological correlations and outcomes of de novo glomerular diseases in patients after haematopoietic stem cell transplantation. *Clin Kidney J* (2023) 16: 976–984.)

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