Kidney Involvement in GVHD

19

Abbie Ruth Bauer, Laura S. Finn,
and Sangeeta R. Hingorani

Clinical History

The patient is an 11-year-old boy with a past medical history of AML s/p COG AAML1031 protocol which included treatment with sorafenib, cytarabine, and etoposide. He underwent peripheral blood stem cell transplant due to relapse of his primary disease. His post-transplant course was complicated by an episode of acute kidney injury (AKI), mucositis, gut and skin GVHD, and multiple infections including aspergillosis, *Clostridium difficile*, and adenovirus viremia. He recovered

A. R. Bauer
Division of Nephrology, Seattle Children's Hospital, Seattle, WA, USA

Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA
e-mail: abbie.bauer@seattlechildrens.org

L. S. Finn
Department of Laboratories, Seattle Children's Hospital, Seattle, WA, USA

Department of Pathology, University of Washington School of Medicine,
Seattle, WA, USA
e-mail: laura.finn@seattlechildrens.org

S. R. Hingorani (✉)
Division of Nephrology, Seattle Children's Hospital, Seattle, WA, USA

Department of Pediatrics, University of Washington School of Medicine, Seattle, WA, USA

Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
e-mail: sangeeta.hingorani@seattlechildrens.org

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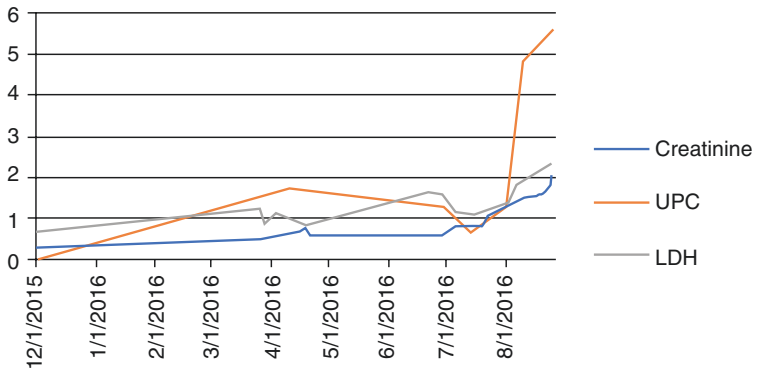

Fig. 19.1 Kidney Function tests. Soluble C5b9, CH50, and AH50 were within normal ranges

without complication and had successful engraftment 19 days after transplant. A few months after engraftment, he began to develop progressive edema and hypertension that was difficult to control despite the use of amlodipine, carvedilol, and lisinopril. He was eventually admitted roughly 6 months after transplantation due to headache and continued difficulty with blood pressure control. At that time, he was found to have significant proteinuria. He was discharged home after blood pressure was better controlled with close follow-up to monitor his blood pressure and proteinuria. In the outpatient setting, he continued to struggle with worsening proteinuria, rising creatinine, and an elevated LDH (Fig. 19.1). He developed significant abdominal pain and diarrhea of unclear etiology. Given the clinical picture and laboratory findings, a kidney biopsy was performed.

Pathology Images and Relevant Laboratory Values

Pathology: Step sections of the renal biopsy stained with H&E, PAS, Jones silver, and Trichrome stains included one core comprised predominantly of medulla and a second core that was entirely cortex. The sampled kidney contained up to 45 glomeruli which displayed a range of thrombotic microangiopathic changes including dilated blood filled capillaries with focal thrombus formation; mesangiolysis; bloodless glomeruli with fibrillary mesangial expansion; and narrowed peripheral capillary lumens due to endothelial swelling and thickened walls with basement membrane duplication, highlighted by PAS and silver stains. Occasional fragmented erythrocytes were seen and rare glomerular arterioles contained fibrin thrombi. Larger vessels were unremarkable (Figs. 19.2, 19.3, and 19.4). About half of the sampled cortex had interstitial fibrosis associated with tubular atrophy; protein casts expanded some tubules. The epithelium lining a subset of intact tubules was vacuolated and foamy, consistent with acute injury. Regenerative tubular epithelial changes were characterized by nuclear enlargement and pleomorphism but frank viral inclusions were not present.

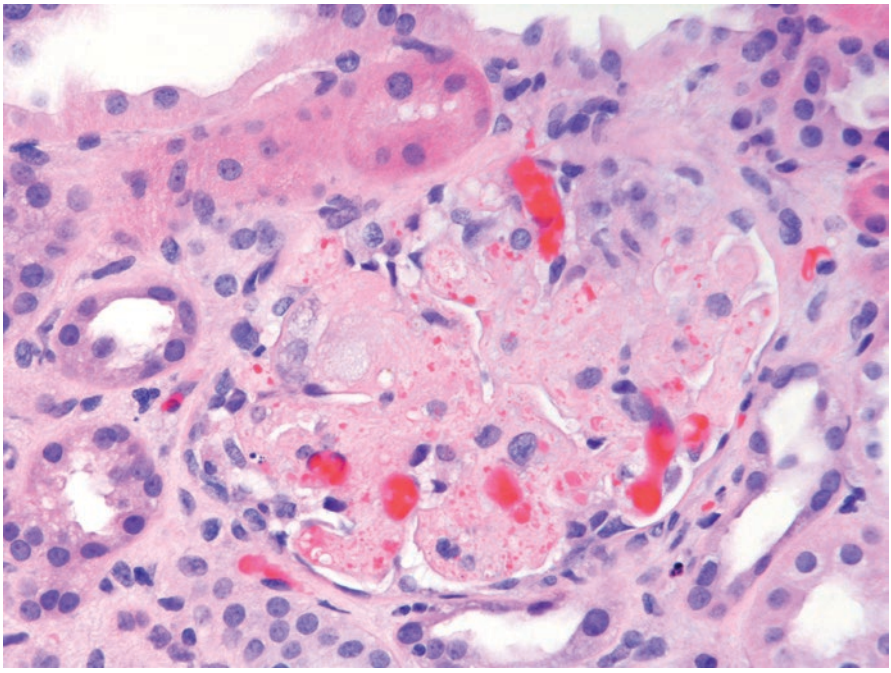

Fig. 19.2 Most lumens of this hypocellular glomerulus are occluded by markedly swollen endothelial cells, thickened capillary walls, and fibrillary mesangium with few foam cells that extend into the capillaries (H&E)

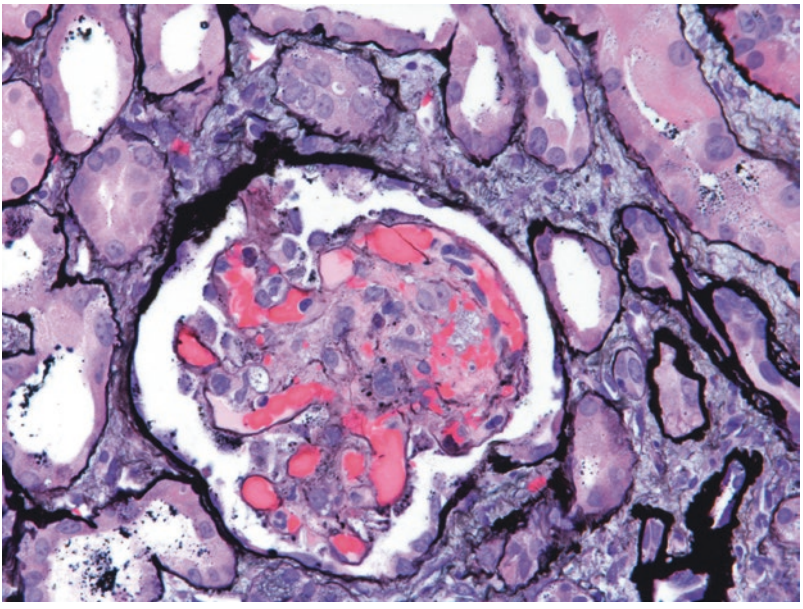

Fig. 19.3 Mesangiolysis is associated with aneurysmal dilation of the glomerular capillaries which are filled with blood and fibrin. Rare inflammatory cells are noted in the capillary lumens (Jones methenamine silver)

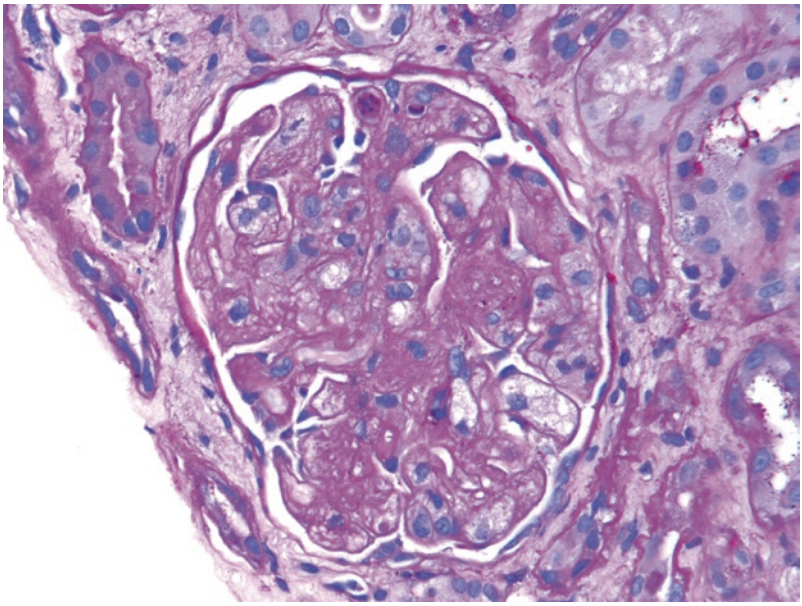

Fig. 19.4 The glomerulus has swollen endothelium, segmental membrane duplication, and expanded fibrillary mesangium with foam cells, all of which contribute to obstruction of the capillary lumens (PAS)

Diagnosis

Our patient was diagnosed with thrombotic microangiopathy (TMA) based on his pathology. He was quickly transitioned from tacrolimus to sirolimus in an attempt to halt the progression of his disease. A gut biopsy was obtained 10.5 months post-transplant which showed mild active GVHD and focal mucosal hemorrage suggestive of TMA. Unfortunately, he continued to have worsening proteinuria (UPC max of 4.64), hypertension, and declining kidney function. Over the subsequent 2 months, he had progressive loss of kidney function and eventually developed end-stage kidney disease despite increasing steroids and an 8-week course of eculizumab. He transitioned from continuous renal replacement therapy (CRRT) to hemodialysis and is now maintained on peritoneal dialysis.

Key Pathology Features and Relevant Laboratory Values

- Labs/clinical history features for TMA:
  - Anemia and thrombocytopenia
  - Hypertension requiring >2 antihypertensive medications
  - Proteinuria >/=300 mg/g creatinine

  - Schistocytes on smear
  - Elevated LDH
  - Decreased haptoglobin
  - Could have elevated C5b9 but is not required for diagnosis
- More common pathologic findings described in the kidney after HSCT
  - TMA
  - Membranous nephropathy
  - Minimal change
  - FSGS
  - BK nephropathy

Differential Discussion

The multiple causes of post-HSCT kidney injury include (but are not limited to) infections, nephrotoxic medications, GVHD, and thrombotic microangiopathy (TMA). Many of these disease processes present similarly and concurrently. Further investigation, e.g., labs and pathologic evaluation, is therefore needed to better delineate the cause of injury and to assist in guiding treatment.

Adenovirus and BK virus are common infectious causes of kidney injury after transplantation and can present with progressive elevations in serum creatinine similar to that seen in our patient [1, 2]; however, the urinalyses are often bland. Both of these infections can be monitored via serum viral load levels and further confirmed on biopsy. Antibody staining for adenovirus and BK virus shows reactivity in the nuclei of tubular epithelial cells. These infections can cause tubule epithelial cell injury, nuclear enlargement with inclusions, and subsequent interstitial inflammation. As these diseases progress, further debris and tubular damage can be appreciated. BK viremia has been associated with TMA, though the nature of this relationship is unknown. Fungal infections can also occur in patients after HCT but are distinguished by the presence of fungal elements (i.e., hyphae, spores) on biopsy, usually associated with localized necrosis.

Transplant-associated thrombotic microangiopathy (TA-TMA), as in our patient, is well described as a cause of significant kidney injury in patients after hematopoietic cell transplantation (Fig. 19.5). A strong clinical suspicion for TA-TMA is warranted in a patient with proteinuria, elevated LDH, and difficult-to-control hypertension [3–5]. Serum creatinine may or may not be elevated. The inciting mechanism is endothelial injury leading to activation of the coagulation system, formation of thrombin, and deposition of fibrin. Pathologic kidney findings include mesangiolysis, activation and injury of endothelial cells, expansion of the subendothelial space, and occlusion of the capillary lumens with debris and thrombi [6, 7]. Arteriolar C4d staining can be positive in some patients, suggesting a possible role of complement activation from endothelial injury [8].

There are many proposed etiologies of TA-TMA which include calcineurin inhibition (CNI), total body irradiation, GVHD, and complement activation [9]. CNI

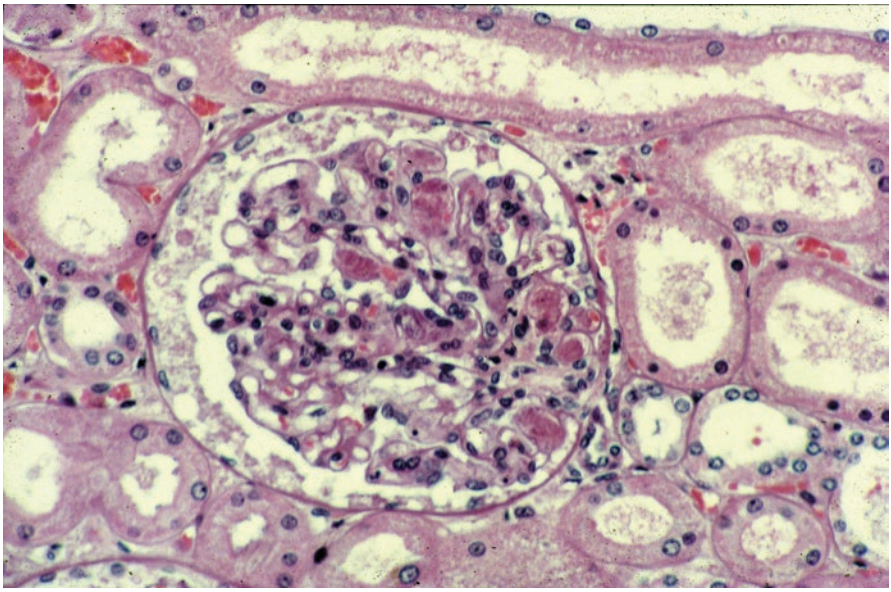

Fig. 19.5 Transplant-associated thrombotic microangiopathy: the glomerular capillary loops are distended by microthrombi

has long been considered a cause of TMA due to the vasoconstrictive effects of the pharmaceutical class leading to decreased renal blood flow and presumed thrombosis [10] (Fig. 19.6). However, TA-TMA is not consistently associated with calcineurin inhibition across all studies [9, 11]. Moreover, some patients appear to have resolution of their TA-TMA with increasing doses of calcineurin inhibitors (CNIs) used to treat their GVHD [12]. Multiple studies have shown increased incidence of TA-TMA in patients with active GVHD and in those who did not receive high-dose conditioning [3, 11, 13–15]. Beyond supportive care including avoiding further nephrotoxicity and controlling blood pressure, the best treatment for TA-TMA is unclear. There is growing interest in eculizumab as this is an effective therapy for TMA in other disease processes associated with abnormal complement activation such as atypical HUS. Initial trials with eculizumab in patients with TA-TMA have had promising results in patients with markers of complement activation such as elevated serum levels of soluble C5b9 but have not shown consistent efficacy in patients who lack these findings [16, 17]. These studies have been small; thus, far and further evaluation is ongoing. Currently, we do not recommend the use of eculizumab in patients without elevated serum levels of soluble C5b9 and clinical and/or pathologic findings consistent with TA-TMA.

In addition to TA-TMA, nephrotic syndrome is another potential manifestation of kidney injury after HSCT. Nephrotic syndrome can occur as soon as 2 months after transplantation and as late as years after transplantation. The pathologic findings in this population are most often membranous nephropathy

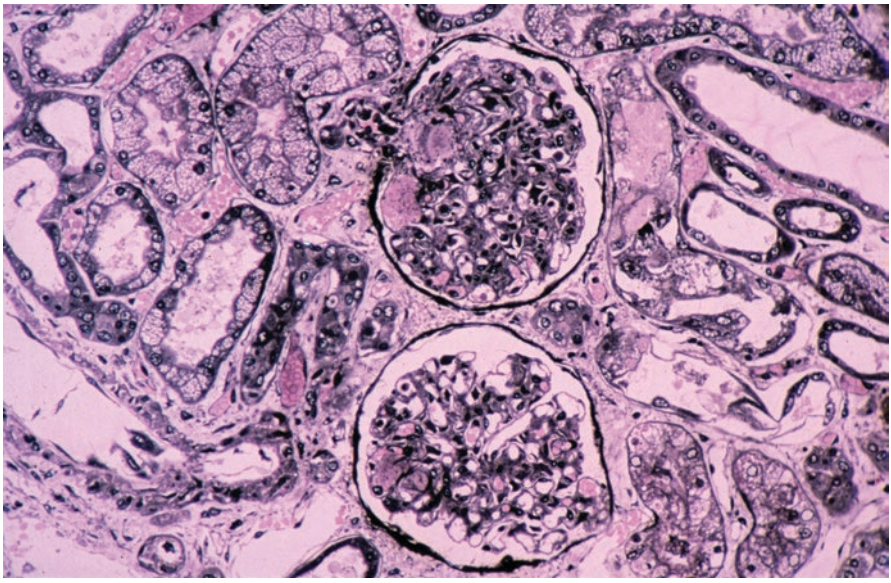

Fig. 19.6 A Jones methenamine silver stain of autopsy kidney demonstrates severe cyclosporine nephrotoxicity/transplant-associated microangiopathy (TMA). Nephrotoxicity occurred prior to the development of assays used to monitor the drug levels. The glomerular hilus and an afferent arteriole contain microthrombi. The capillary loops are small and have focal splitting of the basal layer. There is some mesangial widening or sclerosis. The markedly edematous interstitium contains dilated proximal tubules with marked cytoplasmic vacuolization. Other tubules have necrotic sloughed epithelium

(63%) and minimal change disease (MCD, 19%) [18]. In patients with membranous nephropathy, the subepithelial deposits are thought to be antibody-antigen complex deposition. MCD is thought to be T-cell mediated, though the pathophysiology in post-HSCT patients is unclear. Both disorders typically appear in conjunction with GVHD in other organ systems or when weaning immunosuppression. Less commonly, patients have also developed FSGS, proliferative glomerulonephritis (GN), cytoplasmic antineutrophil cytoplasmic antibodies (C-ANCA) GN, and IgA nephropathy. These causes of nephrotic syndrome have been associated with chronic GVHD and tapering of immunosuppression, but again, the pathophysiology remains unclear. Treatment of nephrotic syndrome after HSCT includes reinitiation of high-dose steroids, calcineurin inhibitors, or rituximab often with improvement and resolution of nephrotic syndrome [19–23].

Research to understand and to define GVHD in the kidney is ongoing utilizing mouse and rat models [24, 25]. Kidney infiltration by CD3+ cells, including CD8+ and CD4+ cells, plus CD68+ macrophages has been seen in rat models with associated peritubulitis, interstitial inflammation, capillaritis, glomerulonephritis, and renal dysfunction in the absence of immune deposition. The kidney inflammation in these rats showed temporal correlation with the appearance of GVHD in the skin,

liver, and gastrointestinal tract [24]. Mouse models have also shown increased gene expression in the kidney of proteins associated with antigen presentation and innate immune response [25].

Teaching Points

- Kidney changes associated with GVHD have a diverse array of presentations including endothelial injury in the form of TMA, interstitial nephritis, tubulitis, and nephrotic syndrome with membranous nephropathy, minimal change disease, and FSGS.
- Kidney biopsy is important to make a diagnosis and to guide therapy.
- It is important to rule out other causes of kidney injury including infectious etiologies and BK and adenovirus; viral copy numbers in the blood should be checked.
- A strong clinical suspicion for TA-TMA is needed when a patient has hypertension and proteinuria, associated with anemia, thrombocytopenia, and elevated LDH, regardless of elevations in serum creatinine. This may be a manifestation of GVHD in the kidney.
- Proteinuria, complement activation, and elevated levels of soluble C5b9 are often present in the setting of TA-TMA.
- The mechanisms by which GVHD contributes to kidney injury are not completely understood. Further investigation to elucidate the contributions of T cells, macrophages, cytokines, and gene expression of kidney proteins associated with antigen presentation and immune response is needed.
- Kidney biopsy tissue is needed to define and establish potential pathologic criteria for GVHD-associated kidney injury.

Questions

1. What are pathologic findings typical for BK nephropathy, and how would you differentiate this from TMA?
2. What are the possible presentations of GVHD in the kidney?
3. What are the potential causes of TA-TMA in the kidney?

Answers

1. Answer: Injury with BK typically manifests as tubular epithelial injury, whereas TMA causes endothelial epithelial injury. BK also has characteristic nuclear enlargement with inclusions.
2. Answer: Potential pathologic findings of GVHD in the kidney biopsy include TA-TMA, membranous nephropathy, minimal change disease, and FSGS. Clinical findings of TA-TMA include anemia, thrombocytopenia, increased LDH, proteinuria, and hypertension. In addition, edema, proteinuria, and hypoalbuminemia are the presenting symptoms of nephrotic syndrome.

3. Answer: TA-TMA etiologies include GVHD, total body irradiation, abnormal complement system activation, abnormalities in the complement pathway, and calcineurin inhibitors, primarily in combination with sirolimus.

References

1. Bruno B, Zager RA, Boeckh MJ, et al. Adenovirus nephritis in hematopoietic stem-cell transplantation. Transplantation. 2004;77(7):1049–57.
2. Haines HL, Laskin BL, Goebel J, et al. Blood, and not urine, BK viral load predicts renal outcome in children with hemorrhagic cystitis following hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2011;17(10):1512–9.
3. Laskin BL, Goebel J, Davies SM, et al. Early clinical indicators of transplant-associated thrombotic microangiopathy in pediatric neuroblastoma patients undergoing auto-SCT. Bone Marrow Transplant. 2011;46(5):682–9.
4. Jodele S, Davies SM, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. Blood. 2014;124(4):645–53.
5. Jodele S, Bleesing JJ, Mehta PA, et al. Successful early intervention for hyperacute transplant-associated thrombotic microangiopathy following pediatric hematopoietic stem cell transplantation. Pediatr Transplant. 2012;16(2):E39–42.
6. Hingorani SR, Seidel K, Pao E, Lawler R, McDonald GB. Markers of coagulation activation and acute kidney injury in patients after hematopoietic cell transplantation. Bone Marrow Transplant. 2015;50(5):715–20.
7. Jodele S, Licht C, Goebel J, et al. Abnormalities in the alternative pathway of complement in children with hematopoietic stem cell transplant-associated thrombotic microangiopathy. Blood. 2013;122(12):2003–7.
8. Laskin BL, Maisel J, Goebel J, et al. Renal arteriolar C4d deposition: a novel characteristic of hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Transplantation. 2013;96(2):217–23.
9. Hingorani S. Renal complications of hematopoietic-cell transplantation. N Engl J Med. 2016;374(23):2256–67.
10. Rosenthal J, Pawlowska A, Bolotin E, et al. Transplant-associated thrombotic microangiopathy in pediatric patients treated with sirolimus and tacrolimus. Pediatr Blood Cancer. 2011;57(1):142–6.
11. Changsirikulchai S, Myerson D, Guthrie KA, McDonald GB, Alpers CE, Hingorani SR. Renal thrombotic microangiopathy after hematopoietic cell transplant: role of GVHD in pathogenesis. Clin J Am Soc Nephrol. 2009;4(2):345–53.
12. Motoyoshi Y, Endo A, Takagi M, et al. Graft versus host disease-dependent renal dysfunction after hematopoietic stem cell transplantation. CEN Case Rep. 2014;3(2):202–5.
13. Mii A, Shimizu A, Kaneko T, et al. Renal thrombotic microangiopathy associated with chronic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. Pathol Int. 2011;61(9):518–27.
14. Kagoya Y, Kataoka K, Nannya Y, Kurokawa M. Pretransplant predictors and posttransplant sequels of acute kidney injury after allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2011;17(3):394–400.
15. Liu H, Li YF, Liu BC, et al. A multicenter, retrospective study of acute kidney injury in adult patients with nonmyeloablative hematopoietic SCT. Bone Marrow Transplant. 2010;45(1):153–8.
16. de Fontbrune FS, Galambrun C, Sirvent A, et al. Use of Eculizumab in patients with allogeneic stem cell transplant-associated thrombotic Microangiopathy: a study from the SFGM-TC. Transplantation. 2015;99(9):1953–9.
17. Jodele S, Fukuda T, Vinks A, et al. Eculizumab therapy in children with severe hematopoietic stem cell transplantation-associated thrombotic microangiopathy. Biol Blood Marrow transplant: J Am Soc Blood Marrow Transplant. 2014;20(4):518–25.

18. Beyar-Katz O, Davila EK, Zuckerman T, et al. Adult nephrotic syndrome after hematopoietic stem cell transplantation: renal pathology is the best predictor of response to therapy. Biol Blood Marrow transplant: J Am Soc Blood Marrow Transplant. 2016;22(6):975–81.
19. Petropoulou AD, Robin M, Rocha V, et al. Nephrotic syndrome associated with graft rejection after unrelated double cord blood transplantation. Transplantation. 2010;90(7):801–2.
20. Fraile P, Vazquez L, Caballero D, et al. Chronic graft-versus-host disease of the kidney in patients with allogenic hematopoietic stem cell transplant. Eur J Haematol. 2013;91(2):129–34.
21. Byrne-Dugan CJ, Collins AB, Lam AQ, Batal I. Membranous nephropathy as a manifestation of graft-versus-host disease: association with HLA antigen typing, phospholipase A2 receptor, and C4d. Am J Kidney Dis. 2014;64(6):987–93.
22. Mattei D, Sorasio R, Guarnieri A, et al. Long-term results of rituximab treatment for membranous nephropathy after allogeneic hematopoietic SCT: a case report. Bone Marrow Transplant. 2010;45(6):1111–2.
23. Hu SL, Colvin GA, Rifai A, et al. Glomerulonephritis after hematopoietic cell transplantation: IgA nephropathy with increased excretion of galactose-deficient IgA1. Nephrol Dial Transplant. 2010;25(5):1708–13.
24. Higo S, Shimizu A, Masuda Y, et al. Acute graft-versus-host disease of the kidney in allogeneic rat bone marrow transplantation. PLoS One. 2014;9(12):e115399.
25. Sadeghi B, Al-Chaqmaqchi H, Al-Hashmi S, et al. Early-phase GVHD gene expression profile in target versus non-target tissues: kidney, a possible target? Bone Marrow Transplant. 2013;48(2):284–93.