An autopsy case that manifested no convincing histological changes of severe renal failure after hematopoietic stem cell transplantation

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Abstract A 48-year-old Japanese woman, who had been diagnosed with smoldering adult T-cell leukemia, was admitted to our hospital for hematopoietic stem cell transplantation (HSCT) because of an acute exacerbation of her disease. After myeloablative conditioning procedures, comprising cytarabine with cyclophosphamide and total body irradiation, the HLA-matched unrelated bone marrow stem cells were infused (day 0). Her serum creatinine concentration, having been 0.6 mg/dL at baseline, began to increase from day 1 and was 2.3 mg/L on day 7. Hemodialysis was required to treat fluid overload and worsening uremia on days 8 and 9. On day 10, she presented with refractory hypotension and died due to multi-organ failure on day 12. Renal pathology at autopsy showed no specific histological changes to which her clinically severe acute kidney injury (AKI) was attributable. This case suggests that post-HSCT AKI is not necessarily accompanied by apparent renal histologic damage, even if it is clinically serious.

Keywords Acute kidney injury · Adult T-cell leukemia · Urinary biomarker · Cytokine · Acute graft-versus-host disease

Introduction

Hematopoietic stem cell transplantation (HSCT) is a notable treatment that provides a radical cure for hematological malignancies and, as such, has contributed greatly to improving the quality of life and survival of patients with these disorders. Transplanted patients experience various kidney diseases throughout the clinical course following HSCT [1, 2]. Among them, acute kidney injury (AKI) develops in the early phase of HSCT and represents one of the most critical complications, as it largely governs the fate of the patients [3–6]. At present, there are three major HSCT modalities: autologous HSCT, myeloablative allogeneic HSCT, and non-myeloablative allogeneic HSCT, with selection depending on disease status and comorbidity. AKI is a common complication of all these HSCT modalities, although the incidence, severity, and impact on mortality differ among them [7–10].

A recent report from our hospital showed that 62–66 % of patients receiving myeloablative allogeneic HSCT developed AKI, which was defined according to the criteria of either RIFLE (risk, injury, failure, loss of kidney function, end-stage kidney disease) or AKIN (Acute Kidney Injury Network) [11, 12]. Risk factors for myeloablative allogeneic HSCT-associated AKI are numerous and the pathogenesis is usually complex. Preexisting kidney disease, use of liposomal amphotericin, sinusoidal obstruction syndrome, acute graft-versus-host disease (GVHD), hemorrhagic cystitis, and sepsis, etc. were documented as risk factors for AKI related to HSCT [12]. From the clinical point of view, the administration of high-dose nephrotoxic drugs in the period of myeloablative conditioning is most likely associated with AKI developing in the early phase of HSCT. However, the renal pathology of such AKI is almost unknown, as renal biopsy examination is practically

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unfeasible due to the perceived risks of the procedure in the early period after HSCT. El-Seisi et al. [13] studied the renal pathology at autopsy after HSCT; however, their histological conclusions were based on the tissues obtained from a mixed population, including subjects with AKI or chronic kidney disease (CKD) or both.

We report here an autopsy case of severe AKI that occurred in the early post-HSCT period, suggesting that there may be a large clinical and pathological dissociation in AKI following HSCT.

Case report

A 48-year-old Japanese woman, who had been diagnosed with smoldering adult T-cell leukemia (ATL) 2 years ago, was referred to our affiliated hospital, as she had developed an acute exacerbation 4 months previously. She was given Lymphoma Study Group 15 (LSG15) therapy, comprising four cycles of VCAP (vincristine, cyclophosphamide, doxorubicin, and prednisone), AMP (doxorubicin, ranimustine, and prednisone), and VECF (vindesine, etoposide, carboplatin, and prednisone), and then transferred to our hospital for HSCT using an HLA-matched unrelated donor. Her height and weight were 158.5 cm and 48.4 kg, respectively. Her blood pressure was 105/75 mmHg, body temperature 36.5 °C, pulse rate 96 beats per min, and room air oxygen saturation 98 %. Her conjunctiva was pale but not jaundiced; otherwise, there were no particular abnormalities in the physical examination. Her laboratory data on admission are shown in Table 1. She appeared to have normal kidney function according to conventional examinations, such as serum Cr concentration (0.6 mg/dL), serum urea nitrogen (UN) concentration (10 mg/dL), and estimated glomerular filtration rate (eGFR) (82.5 mL/min/1.73 m²); however, she had abnormalities in urinalysis: proteinuria (1+) on dipstick test and elevated urinary N-acetyl-β-D-glucosaminidase (NAG) (17.2 U/gCr), α₁-microglobulin (α₁M) (68.7 mg/gCr), and β₂-microglobulin (β₂M) (4422 μg/gCr). She was conditioned using 8 g/m² cytarabine, 120 mg/kg cyclophosphamide, and 12 Gy TBI. She received antibiotics, antifungals, and antiviral drugs, including meropenem, vancomycin, micafungin, trimethoprim-sulfamethoxazole, and acyclovir for infection prophylaxis before the HSCT. In addition, tacrolimus and short-term methotrexate were given for acute GVHD prophylaxis. She complained of no particular symptoms during the conditioning therapy. The serum concentrations of new sensitive tubular biomarkers, such as cystatin C and neutrophil gelatinase-associated lipocalin (NGAL), markedly increased in the morning of day 0 (Fig. 1). On day 1, the serum Cr concentration increased to 0.9 mg/dL and continued to increase over time (Fig. 2). Meanwhile, as she

Table 1 Laboratory data on admission

Urinalysis		ALT (IU/L)	28
Protein	1+	LDH (IU/L)	364
Occult blood	–	CK (IU/L)	32
Sediments		BUN (mg/dL)	10
RBC (/HPF)	1–3	Cr (mg/dL)	0.6
Urinary chemistry		Na (mEq/L)	139
NAG (IU/L)	17.2	K (mEq/L)	5.1
β ₂ M (μg/g)	4422	Cl (mEq/L)	103
α ₁ M (mg/g)	68.7	Ca (mg/dL)	8.1
ACR (mg/g)	5.8	iP (mg/dL)	6.4
Blood cell count		Glu (mg/dL)	97
WBC (/μL)	4.8 × 10 ³	HbA1c (%)	5.0
Neu (%)	19.5	CRP (mg/dL)	0.2
Lym (%)	15	IgG (mg/dL)	836 (871–1700)
RBC (/μL)	269 × 10 ⁴	IgA (mg/dL)	91 (110–410)
Hb (g/dL)	8.5	IgM (IU/mL)	75 (11–580)
Hct (%)	25.4	sIL2R (U/mL)	4540 (220–530)
Platelet (/μL)	6.8 × 10 ⁴	Infection test	
Serum chemistry		HBs-Ag	Negative
TP (g/dL)	6.9	HCV-Ab	Negative
Alb (g/dL)	4.7	β-DG (pg/ml)	3.9 (3.9–20.0)
AST (IU/L)	24	eGFR	82.5
		(mL/min/1.73 m ²)	

The numbers in parentheses indicate normal ranges

HPF high-power field, *NAG* N-acetyl-β-D-glucosaminidase, *β₂M* β₂-microglobulin, *α₁M* α₁-microglobulin, *ACR* albumin creatinine ratio, *WBC* white blood cell, *Neu* neutrophil, *Lym* lymphocyte, *RBC* red blood cell, *Hb* hemoglobin, *Hct* hematocrit, *TP* total protein, *Alb* albumin, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *LDH* lactate dehydrogenase, *CK* creatine kinase, *BUN* blood urea nitrogen, *Cr* creatinine, *Na* sodium, *K* potassium, *Cl* chloride, *Ca* calcium, *iP* inorganic phosphorus, *Glu* glucose, *HbA1c* hemoglobin A1c, *CRP* C-reactive protein, *sIL2R* soluble interleukin 2 receptor, *HBs-Ag* hepatitis B surface antigen, *HCV-Ab* hepatitis C virus antibody, *β-DG* β-D-glucan, *eGFR* estimated glomerular filtration rate

manifested oliguria on day 2, intravenous infusion of dopamine hydrochloride was initiated in addition to the administration of furosemide. Tacrolimus was started for acute GVHD prophylaxis from day 2 according to the usual HSCT protocol. On day 7, her serum Cr concentration was elevated to 2.3 mg/dL and her urine output decreased to 269 mL/day, despite the increased amount of furosemide. On day 8, hemodialysis therapy was required to reduce uremia and fluid overload. From the morning of day 9, her systolic blood pressure dropped and she became refractory to treatment, which resulted in cessation of hemodialysis treatment on day 10. No specific bacteria were identified in 3 consecutive blood cultures. On day 12, she developed multi-organ failure and died. Serum C-reactive protein (CRP) levels varied greatly in the peri-HSCT period: 7.95 at day –2, 12.02 at day –1, 12.29 at day 0, 8.99 at day 1, 6.76 at day 2, 10.39 at day 3, 14.73 at day 4, and remained constant at a value of more than 30 mg/dl after day 5.

Fig. 1 Changes of urinary biomarkers before and after HSCT. *HSCT* hematopoietic stem cell transplantation, *NAG* N-acetyl- β -D-glucosaminidase, α_1M α_1 -microglobulin, *NGAL* neutrophil gelatinase-associated lipocalin, *CyC* cystatin C

Fig. 2 Changes of serum Cr and UN levels and urine volume in the clinical course of HSCT. *HSCT* hematopoietic stem cell transplantation, *UN* urea nitrogen, *Cr* creatinine

Serum concentrations of interleukin 6 (IL-6) and tumor necrosis factor- α (TNF- α) increased over time: IL-6 was 305 pg/ml on day 0, 584 pg/ml on day 1, and 792.0 pg/ml on day 5; TNF- α was 0 pg/ml on day 0, 7.32 pg/ml on day 1, and 9.23 pg/ml on day 5 (Fig. 3). Autopsy was performed 36 h after death. Renal pathology showed some tubular dilatation and flattening of the epithelium, but there were no specific changes indicating hypoxia and ischemia in glomeruli and no inflammatory cellular infiltration in

tubulointerstitial areas (Fig. 4a, b). There were no findings suggesting disseminated intravascular coagulopathy and thrombotic microangiopathy (TMA), a well-recognized disorder related to HSCT. Several glomeruli contained small fibrin thrombi; however, they were not considered to be attributable to the severe oliguric AKI that required hemodialysis treatment (Fig. 4c). Slight interstitial scarring was otherwise identified around the other 3 glomeruli, but it failed to explain the marked elevation of biomarkers

suggesting tubular injury. In addition, immunofluorescence and electron microscopic analyses showed no specific abnormalities in glomeruli, tubules, and arterioles.

Discussion

We present the autopsy findings of a patient who developed severe AKI in the early phase after bone marrow stem cell

Fig. 3 Increase in serum levels of proinflammatory cytokines after HSCT. *HSCT* hematopoietic stem cell transplantation, *IL-6* interleukin 6, *TNF-α* tumor necrosis factor-α

infusion. Considering the definite changes of the laboratory data, including urinary biomarkers, serum Cr concentration, and urine output, some renal histological changes were assumed; however, the renal pathology at autopsy failed to manifest any convincing causes for the severe AKI.

The patient developed severe AKI requiring hemodialysis therapy; that is, ‘loss’ in the RIFLE criteria [14]. The increase in urinary tubular markers indicated that some kidney tubular damage had occurred during the conditioning period, prior to the infusion of stem cells on the day of HSCT. As is to be expected, serum Cr had begun to increase over time from then. This clinical course allowed us to speculate that there was a chain of events leading to severe AKI. First, ‘conditioning-associated tubular injury’ occurred, possibly due to the administration of a high amount of cyclophosphamide, as it is known to impair the uroepithelium through its toxic metabolite, acrolein [15]. Next, the inflammatory and cytokine cascade that accompanies the infused allogeneic stem cells affected kidney function [2, 16, 17], as the serum proinflammatory cytokine levels were highly increased in parallel with the increasing serum Cr levels. The pathophysiologic nature of the increased CRP remained conjectural, infectious inflammation or non-infectious inflammation or both, in this case. We are skeptical that sepsis played a key role in the

Fig. 4 Renal pathology at autopsy. **a** Periodic acid-Schiff stain. In some areas, exfoliation of tubuloe epithelial cells was confirmed; however, there were some tubular dilatation and flattening of the epithelium, but no specific findings of hypoxia and ischemia in glomeruli and no cellular infiltration in the tubulointerstitial areas.

b Hematoxylin and eosin stain of a glomerulus. The glomerulus had no convincing pathological findings of oliguric acute renal failure. **c** Hematoxylin and eosin stain of a glomerulus. The arrows show that some of the glomeruli had small fibrin thrombi, as shown here

development of AKI, as no microorganisms were identified in 3 consecutive blood cultures.

Renal pathology at autopsy failed to reveal a convincing intrarenal cause for the severe AKI in this case. The pathology showed no specific findings relevant to histological tubular injury, including acute tubular necrosis (ATN) and a lack of cellular infiltrates in the interstitium and peri-glomerular areas. Although there were solitary small fibrin thrombi in several glomeruli, which might indicate early injury to the glomerular capillary endothelium, this lesion was not adequate for explaining the emergence of oliguric severe AKI. Zager et al. [18] have already reported that autopsy kidney specimens provided no clear explanation for AKI in the vast majority of 36 post-HSCT AKI patients who required hemodialysis, and, thus, they speculated that the renal functional impairment is usually hemodynamic, rather than structural, in nature. In fact, we speculate that the acute loss in renal function is associated with a decrease in renal perfusion in this case; however, indices of systemic perfusion including body weight changes and serum levels of human atrial natriuretic peptide and brain natriuretic peptide were not measured before and after the development of AKI. In addition, the typical morphological ATN is rare and often shows physiological and pathological dissociation in usual AKI [19]. The data of increased proinflammatory cytokines following HSCT in this case suggest that glomerular and tubular functional changes may have preceded the emergence of renal structural changes, as loss or omission of the polarity of a glomerular loop wall and a decrease in water permeability of a glomerular loop wall may occur in AKI accompanying systemic inflammation [20, 21].

The histological changes that accompany AKI after HSCT are less well known, as renal biopsies are rarely undertaken in the peri-transplantation period because of the perceived risks of the procedure in this patient population. El-Seisi et al. [13] reported the renal pathology of 26 consecutive recipients of HSCT who died and underwent autopsy at a single transplant center. They described that abnormalities of renal pathology at autopsy were common: glomerular sclerosis in 73 %, tubular epithelial atypia in 73 %, tubular calcification in 69 %, tubulitis in 67 %, and thrombotic microangiopathy in 46 % of the patients. However, the study included patients who developed AKI and those who developed CKD, and did not clarify the differences in pathology between the AKI and CKD following HSCT. Those pathological findings are likely to represent the comprehensive postmortem features of kidney failure after HSCT, but unlikely to represent specific abnormalities of *de novo* AKI that occurred soon after HSCT. Further studies are warranted in order to elucidate whether a discrepancy between physiological and pathological findings can exist in severe post-HSCT AKI.

In summary, we have presented an autopsy case of ATL who developed severe post-transplant AKI. The patient showed marked elevations of new sensitive urinary biomarkers before stem cell infusion and serum proinflammatory cytokines over time after infusion. In contrast, renal histology at autopsy failed to reveal convincing intrarenal causes for AKI. Further comparative assessments between renal pathology and function are warranted to resolve the critical issues posed by this case.

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Conflict of interest None declared.

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