Graft versus host disease-dependent renal dysfunction after hematopoietic stem cell transplantation

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Abstract Nephropathy is an important complication in hematopoietic stem cell transplantation (HSCT) wherein multifactorial causes, i.e., radiation, drug toxicity, graft versus host disease (GVHD), are thought to contribute renal dysfunction. Here, we report a 10-year-old boy with high-risk acute myelocytic leukemia and severe but partially reversible renal dysfunction. The patient initially received umbilical cord blood transplantation (UCBT) with CY 120 mg/kg and kidney unshielded 12 Gy of total body irradiation. After the leukemic relapse, he received allogeneic bone marrow transplantation (BMT) 270 days after the first transplantation. Two months later, his renal function started to deteriorate and urinary protein increased gradually to 1 g/day. Four months after BMT, by the symptoms of severe GVHD, the dose of tacrolimus, utilized to avoid GVHD, was increased although his serum Cre level elevated to 2.97 mg/dL. Serum Cre level improved to 2.0 mg/dL paralleled with GVHD improvement. Renal histological findings showed severe interstitial edema, features of thrombotic microangiopathy (TMA), and C4d deposition along the glomerular capillaries and peritubular capillaries. We suggested that control of GVHD had benefitted to ameliorate renal function of the patient.

Treatment for GVHD improved renal dysfunction and TMA of our patients. Moreover, renal biopsy was powerful to elucidate the exact origin of renal dysfunction after HSCT.

Keywords Total body irradiation · Calcineurin inhibitor nephrotoxicity · Thrombotic microangiopathy · Bone marrow transplant nephropathy · Mesangiolysis · Interstitial edema

Introduction

Hematopoietic stem cell transplantation (HSCT) causes various organ complications. Renal dysfunction is one of the important complications and multiple factors may synergistically be involved in this complication. Among them, drugs utilized as conditioning regimen and some kind of antibiotics for treatment of sepsis can injure the kidney. Hepatic veno-occlusive disease caused by radiation and chemotherapy induces acute kidney injury after weight gain with edema. Engraftment syndrome reduces circulating blood volume by hyperfiltration influenced by a large quantity of cytokines and renal function is affected. Occasionally, de novo membranous nephropathy can cause renal dysfunction [1].

In the previous reports, 28 % of children who received HSCT were found to have chronic renal insufficiency 1 year after transplantation [2]. Indeed, treatment for leukemia is the only way to save the patients, renal complication occasionally restrict adequate treatment and possibly worsen the patient's condition.

Here, we report a case with acute myelocytic leukemia treated by UCBT followed by bone marrow transplantation (BMT) which caused renal dysfunction. Renal biopsy

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findings allowed us to switch the treatment resulting successful renal recovery.

Case report

The bone marrow of a 10-year-old boy with body weight loss and epistaxis was examined and diagnosed with high-risk acute myelocytic leukemia (AML)-M1 by a doctor. After remission induction therapy utilizing etoposide, cytarabine and idarubicin, he was transferred to our hospital to receive UCBT.

UCBT was performed using CY 120 mg/m² and total body irradiation (TBI) 12 Gy without kidney shielding as conditioning regimen. Low-dose methotrexate (0.5 mg/kg, three doses) was administered to avoid graft versus host disease (GVHD). His kidney condition was maintained within normal limit before and after transplantation, with the highest serum creatinine level 0.84 mg/dL.

Leukemic relapse had developed 210 days after UCBT and second transplantation was planned. Allogeneic unrelated HLA DRB1-mismatched BMT was performed 270 days after UCBT. Fludarabine 150 mg/m², melphalan 140 mg/m², and etoposide 200 mg/m² were infused as conditioning regimen, but TBI was not performed this time.

One month after 2nd transplantation, serum creatinine and cystatin C had elevated to 1.04 mg/dL and 2.11 mg/L, respectively. And his serum creatinine level ascended gradually after infectious events, such as gastroenteritis

and herpes virus infection (Fig. 1). We utilized aciclovir which might be injurious for kidney to treat herpes virus infection. Two months after second transplantation, the patient's body weight gained gradually, due to considerable pleural effusion and ascites. Soluble IL-2 receptor level was elevated to 1100 U/mL by diagnosis of manifested GVHD. Since tacrolimus seemed to suppress GVHD and renal dysfunction appeared, trough levels were kept by <3 ng/mL. Thereafter, symptoms of GVHD paralleled with renal dysfunction progressed, we increased the dosage of tacrolimus by trough level to 7.1 ng/mL. Unexpectedly serum creatinine level once improved to 2.0 mg/dL, with GVHD improvement, but renal function deteriorated again accompanied by tapering of tacrolimus. Proteinuria (1 g/day), during this course, suggested that renal dysfunction was based on the secondary glomerulonephritis, such as membranous nephropathy.

Kidney biopsy performed at 8 months after second transplantation showed partial mesangiolysis in approximately 60 % of glomeruli accompanied with diffuse double contour in glomerular basement membrane, without showing distinct mesangial proliferation. Interstitial edema was also observed in more than 80 % of the tubulointerstitial area (Fig. 2). In addition, it focally notes thickening of vascular intima and severe narrowing. IgG, IgA, IgM, C3, C4 and C1q were all negative by immunofluorescence. Additionally, C4d deposition was detected along in a part of glomerular capillaries and peritubular capillaries. Electron microscopy revealed substantial width of subendothelial widening. Collectively, we speculated that

Fig. 1 Clinical course after bone marrow transplantation. Serum creatinine level of our patient ascended gradually after infectious events. Because of renal dysfunction, tacrolimus dose was reduced gradually from 1 mg per day to 0.1 mg per day. After GVHD became obvious, tacrolimus dose was increased to 0.5 mg per day which was effective for renal function recovery

Fig. 2 Renal histological findings of the patient 8 months after second HSCT. **a** Diffuse fibrosis, edema and infiltration of lymphocytes are observed in interstitial area in Masson's Trichrome staining. Diffuse interstitial fibrosis is accompanied by lymphoid cells infiltration. Note glomeruli are diffusely collapsed with widening of urinary space. **b** Slightly thickened wall of arteriole is observed in Periodic acid-Schiff staining. **c** Segmental mesangiolysis is notable and double contour in glomerular basement membrane. Periodic acid methenamine silver staining **d**. C4d deposition was detected along the glomerular capillaries and peritubular capillaries

thrombotic microangiopathy (TMA) caused by GVHD was the base of renal dysfunction.

Thereafter, his renal function tended to change by the activity of GVHD and now, serum creatinine level was kept around 1.8–2.0 mg/dL under sufficient dose of tacrolimus.

Discussion

We experienced a case of a 10-year-old boy with high-risk AML. He underwent UCBT and BMT, and his renal dysfunction became obvious after second transplantation. From histological findings, the origin of his renal dysfunction was elucidated to be TMA with tubulointerstitial damage. Although kidney function reflects mainly on the selection of the treatment after transplantation, thrombotic microangiopathy is observed in 0.5–63.6 % of the recipients, and it influences the prognosis of renal function [3]. We speculated that TMA after GVHD induced renal interstitial edema and interruption in the circulation, and then renal dysfunction had been actualized. When severe inflammation occurs, hyperfiltration and dehydration in vessels are caused. It might reduce glomerular filtration rate. With severe pleural effusion and ascites, GVHD and hemodynamic change might have contributed to renal dysfunction.

BMT nephropathy is a multifactorial disorder, and each factor is related to others [4]. Our patient received melphalan 140 mg/m² totally before BMT, antibiotics vancomycin and antifungal agent for severe infectious disease, which might be toxic for kidney. And importantly, he received TBI 12 Gy without kidney shielding. Findings of TMA are representative in histological findings of BMT nephropathy.

Although it is generally performed to avoid radiation nephropathy, shielding for kidney during radiation in BMT has a great risk for recurrence of native disease. Recently, several issues refer to renal relapse of leukemia after radiation with kidney shielding [5–7]. Risk and benefit of kidney shielding during radiation therapy are still controversial.

Renal toxicity of tacrolimus is well known especially when it is utilized in high blood concentration. Indeed, the medication dose has to be minimized in patient with kidney dysfunction, severe GVHD led us to increase the dose of tacrolimus. Then, the general condition and renal function recovered considerably. According to kidney histological findings, glomeruli accompanied with diffuse double contour in glomerular basement membrane, thickening of vascular intima, and substantial width of subendothelial widening was observed. Moreover, C4d staining was detected in a part of glomerular capillaries and peritubular capillaries, which coincides with the symptoms of GVHD [8]. We speculated that TMA was improved by increase of tacrolimus with improvement of GVHD.

In conclusion, multifactorial causes underlie renal dysfunction after HSCT. In our case, treatment for GVHD improved renal dysfunction and TMA. Moreover, renal biopsy was powerful to distinguish the actual cause which brought benefit for the patient care.

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Conflict of interest All the authors have declared no competing interest.

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