CASE REPORT

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Variable clinical manifestations of hematopoietic stem cell transplant-associated thrombotic microangiopathy

Chenguang Jia | Maoquan Qin | Bin Wang | Guanghua Zhu | Yan Yan

Beijing Key Laboratory of Pediatric Hematology Oncology; National Key Discipline of Pediatrics (Capital Medical University); Key Laboratory of Major Diseases in Children, Ministry of Education; Department of Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Maoquan Qin, Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, Beijing 100045, China.
Email: qinmq3966@qq.com

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INTRODUCTION

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a complication of hematopoietic stem cell transplantation (HSCT) characterized by small vessel endothelial damage leading to thrombosis and fibrin deposition resulting in hemolytic anemia and thrombocytopenia. The severity of TA-TMA varies from mild self-limited disease to a fulminant variant resulting in death. Here, we review two rare cases and review the literature of TA-TMA.

CASE REPORT

Case 1

A 5-year-old girl was admitted to our hospital with a 4-month history of fever and cytopenia. She had been diagnosed with very severe aplastic anemia. There was no HLA-matched unrelated donor, so the patient underwent a haploidentical HSCT (fludarabine, cyclophosphamide, antithymocyte globulin preparative regimen) from her father, with excellent early post-transplant neutrophil recovery and 100% donor chimerism in the peripheral blood. On day +25, she developed grade II acute graft-versus-host disease of the skin, and was successfully treated with steroid and tacrolimus instead of cyclosporine. On day +35, the patient developed symptoms of polypnea and tachycardia without fever, and rale of lung was found. A computed tomography (CT) scan showed an interstitial infiltrating shadow area occupying the left lower lobe (Figure 1A). There was no positive pathogenic test, except for a mild elevation of CMV-DNA (1.1×10^3 copies/ml). Ganciclovir and anti CMV immunoglobin were administered as treatments, but the patient's respiratory status continued to be deteriorative until nasal continuous positive airway pressure was used. The patient developed seizures on day +42, and the blood levels of tacrolimus were markedly elevated. Brain magnetic resonance imaging (MRI) showed characteristic images of posterior reversible encephalopathy syndrome (PRES) (Figure 1B). A diagnosis of TA-TMA was established based on the Blood and Marrow Transplants Clinical Trials Network (CTN) diagnostic criteria, which included the clinical picture of elevated lactate dehydrogenase (LDH), thrombocytopenia, the presence of schistocytes (2/HPF) on peripheral blood smear, and negative direct antiglobulin test (Table 1).[1] A bronchoscopic biopsy showed the lung arteriole was nearly occluded by large amount of debris, which supported the dignosis of TA-TMA (Figure 1C). Then, we treated her with basiliximab instead of tacrolimus, and the clinical symptoms improved significantly on day +70 (Figure 1D).

Case 2

An 8-year-old boy was diagnosed with chronic active

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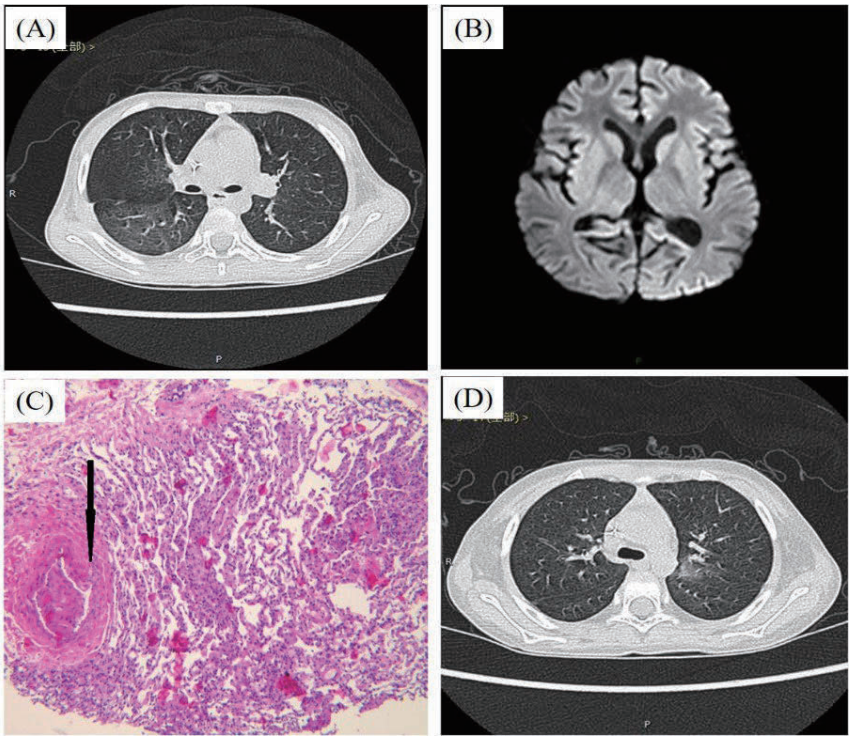

FIGURE 1 Imaging and histologic features of transplantation-associated thrombotic microangiopathy affecting organs. (A) Initial chest CT scan on day +35 shows an interstitial infiltrating shadow area occupying the left lower lobe; (B) Magnetic resonance imaging on day +42 shows characteristic images of posterior reversible encephalopathy syndrome (PRES); (C) The bronchoscopic biopsy shows the lung arteriole was nearly occluded by a large amount of debris (arrows). (HE stain; magnification ×200); (D) Repeated chest CT scan shows the almost normal appearance of the lung on day +70.

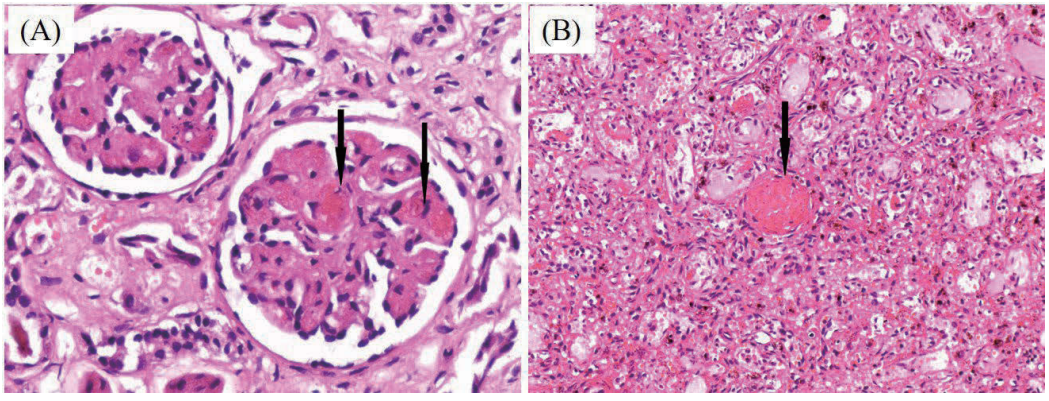

FIGURE 2 Photomicrographs of the autopsy specimens. (A) Glomeruli have thickened capillary walls and occluded vessel lumens (arrows). (HE stain; magnification ×400); (B) Arterioles of the splenic sinus show injured endothelial cells and red blood cell extravasation (arrows). The vessel lumen is occupied by schistocytes. (HE stain; magnification ×400).

Epstein Barr virus infection, and underwent haploidentical HSCT with reduced intensity conditioning consisted of fludarabine, cyclophosphamide, antithymocyte globulin and low-dose total body irradiation. On day +6, he developed diarrhea with oliguria and jaundice, and weight and abdomen circumference increased. On day +7, the condition was continuously deteriorative, so the patient was transferred to the ICU for acute renal failure (ARF). Blood tests showed elevated LDH, and a peripheral smear at that time showed 4 schistocytes/HPF (Table 1). TA-TMA was diagnosed with CTN-TMA criteria, but it was difficult to differentiate from hemolytic uremic syndrome (HUS) and/or thrombotic thrombocytopenic purpura (TTP). Therapeutic plasma exchange (TPE) and drugs (such as low molecular heparin, prostaglandin E1, and defibrotide) were initiated empirically. We used basiliximab instead of cyclosporine, but his condition did not improve. Continuous renal replacement therapy (CRRT) was used to treat his ARF. Laboratory findings showed that his stools were negative for Escherichia coli O157:H7 and that his von Willebrand factor cleaving protease (ADAMTS13) level was normal. On day +11, he

TABLE 1 Important findings and diagnostic criteria of TA-TMA

Important findings and tests	Case 1	Case 2	CTN-TMA	IWG-TMA	Probable-TMA
Diagnostic criteria					
Coagulation assays	Normal	Normal	Normal	Normal	Normal
Schistocytosis	2/HPF	4/HPF	≥2/HPF	≥4/HPF	≥2/HPF
Serum LDH	Increase	Increase	Increase	Increase	Increase
Renal dysfunction and/or neurologic dysfunction	Seizures	Seizures and ARF	Yes	Yes	No
Coombs' test	Negative	Negative	Negative	-	Negative
Platelet	Normal	Decrease	-	Decrease	Decrease
Hemoglobin	Normal	Decrease	-	Decrease	Decrease
Serum haptoglobin	NA	NA	-	Decrease	Decrease
Other findings					
ADAMTS 13 level	NA	Normal	-	-	-
Hypertension	Yes	Yes	-	-	-
Proteinuria	No	Yes	-	-	-

CTN, Blood and Marrow Transplants Clinical Trials Network; IWG, International Working Group; TMA, thrombotic microangiopathy; HPF, high power field; LDH, lactose dehydrogenase; ARF, acute renal failure; ADAMTS 13, von Willebrand factor cleaving protease; NA, not available; -, not applicable.

developed seizures, then fell into a coma, and brain CT scan did not observe intracranial hemorrhage with normal coagulation assays. After treatment with defibrotide for 1 week, his consciousness was restored but anuria remained. On day +30, he suffered from a massive hemorrhage of the gastrointestinal tract, so we had to stop treatment with defibrotide and other anticoagulation drugs. On day +35, he died of shock during CRRT. An autopsy showed that microangiopathy was present in multiple organs (Figure 2A, B).

DISCUSSION

TA-TMA occurs when endothelial injury leads to microangiopathic hemolytic anemia (MAHA), platelet activation, thrombosis, and fibrin deposition in the organ microcirculation, which causes widespread tissue injury.[2] The mechanisms involved in endothelial injury in patients with TA-TMA remains unclear. Recent research has focused on complement system abnormalities in the pathogenesis of TA-TMA.[3,4]

The incidence of TA-TMA ranges from 4% to 39% and usually occurs about 60 days after HSCT, but can also occur in the early (day +4) or late stage (2 years) after transplantation.[5,6] Clinical manifestations can range from a mild, self-limited form to an uncontrolled condition leading to death, as demonstrated in the two cases presented here. Patients usually present with MAHA, and thrombocytopenia not explained by other complications, as well as manifestations of multiple or single organic lesions. The kidney and brain appear to be the most common organs affected by TA-TMA, although the lung, bowel, and heart can be involved.[7]

The diagnosis of TA-TMA lacks a gold standard, and it is formed based on clinical diagnosis. At present, two diagnostic criteria, the CTN and International Working Group (IWG), are the most widely used for TA-TMA with some differences (Table 1).[1,8] However, it is difficult to make a diagnosis in the early stage by using these criteria. Fuge et al reported a case series of 22 TA-TMA patients, where all patients with up to five diagnostic criteria died.[9] A retrospective study by Cho et al suggested the limitations of previous criteria and proposed the concept of "probable TMA", which is of value for the pre-emptive therapy of TA-TMA (Table 1).[10] Testing for ADAMTS13 and soluble membrane attack complex (sC5b-9) level are strongly suggested, as they might benefit from TPE or complement blocking therapy.[4,11] Currently, some single centers are conducting clinical trials of the integral diagnostic system, which is valuable for the early diagnosis and treatment of TA-TMA.

The prognosis of TA-TMA is variable because of different pathogenetic mechanisms. Calcineurin inhibitor (CNI) (such as tacrolimus, and cyclosporine) -associated cases are usually not severe, and most patients can be cured by CNI discontinuation. Fulminant TA-TMA occurring early post-HSCT is lethal because it has an aggressive clinical course with poor response to treatment, an unfavorable prognosis, usually complicated with ARF, with central

nervous system involvement, MAHA, hypertension, and thrombocytopenia.[4,12]

There are no universally agreed treatment strategies for TA-TMA. In case 2, we used TPE for treatment, but the response was poor. Kennedy et al retrospectively analyzed the efficacy of TPE for 11 cases of TA-TMA. Only 3 cases (27%) showed complete remission after treatment, demonstrating that TPE is not a good choice for cases with normal ADAMTS13 activity.[13] Defibrotide, a polydeoxyribonucleotide salt, has been used to treat hepatic veno-occlusive disease. A retrospective study reported by Corti et al[14] demonstrating a 55% response rate with defibrotide. Eculizumab, a monoclonal antibody directed towards sC5b-9, showed promise as a targeted therapy. The response rate of treatment for TA-TMA was up to 72% based on data from Jodele et al at Cincinnati Children's Hospital Medical Center.[15] However, because of its high cost, it has limited availability in developing country. Prospective studies should be carried out to develop pretransplant screening tests, and other novel targeting agents should be investigated for TA-TMA.

We reported two rare cases of TA-TMA with complete clinical and pathological data. However, even with this data, it is difficult to make a diagnosis in the early stage. Clinicians should be alert to the unexplained manifestations post-HSCT, and focus on early treatment rather than following the guidelines step-by-step. Pathology is not essential for diagnosis, but it can help for the early diagnosis of TA-TMA.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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