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

Received: 14 September, 2018; Accepted: 28 November, 2018

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). A bronchoscopic biopsy showed the lung arteriole was nearly occluded by large amount of debris, which supported the diagnosis 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
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
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. 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.7,8 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

| 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        | Seizures                       | Seizures and ARF               | Yes                            | Yes                            | No                             |
| neurologic dysfunction          |                                |                                |                                |                                |                                |
| 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.
nervous system involvement, MAHA, hypertension, and thrombocytopenia.\textsuperscript{1,2}

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.\textsuperscript{13} Defibrotide, a polydeoxyribonucleotide salt, has been used to treat hepatic veno-occlusive disease. A retrospective study reported by Corti et al\textsuperscript{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.\textsuperscript{5} 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.

ACKNOWLEDGMENTS

The authors would like to thank doctor Chunju Zhou provided pathological image, Jihang Sun provided imaging data.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Ho VT, Cutler C, Carter S, et al. Blood and marrow transplant clinical trials network toxicity committee consensus summary: Thrombotic microangiopathy after hematopoietic stem cell transplantation. \textit{Biol Blood Marrow Transplant.} 2005;11:571.
2. Goldberg RJ, Nakagawa T, Johnson RJ, et al. The role of endothelial cell injury in thrombotic microangiopathy. \textit{Am J Kidney Dis.} 2010;56:1168-1174.
3. 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. \textit{Blood.} 2013;122:2003-2007.
4. Jodele S. Complement in pathophysiology and treatment of transplant-associated thrombotic microangiopathies. \textit{Semin Hematol.} 2018;55:159-166.
5. Jodele S, Davies S, Lane A, et al. Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults. \textit{Blood.} 2014;124:645-653.
6. Ye Y, Zheng W, Wang J, et al. Risk and prognostic factors of transplantation-associated thrombotic microangiopathy in allogeneic haematopoietic stem cell transplantation: a nested case control study. \textit{Hematol Oncol.} 2017;35:821-827.
7. Siami K, Kojouri K, Swisher KK, et al. Thrombotic microangiopathy after allogeneic hematopoietic stem cell transplantation: an autopsy study. \textit{Transplantation.} 2008;85:22-28.
8. Ruutu T, Barosi G, Benjamin RJ, et al. Diagnostic criteria for hematopoietic stem cell transplant-associated microangiopathy: results of a consensus process by an International Working Group. \textit{Haematologica.} 2007;92:95-100.
9. Fuge R, Bird JM, Fraser A, et al. The clinical features, risk factors and outcome of thrombotic thrombocytopenic purpura occurring after bone marrow transplantation. \textit{Br J Haematol.} 2001;113:58-64.
10. Cho BS, Yahng SA, Lee SE, et al. Validation of recently proposed consensus criteria for thrombotic microangiopathy after allogeneic hematopoietic stem-cell transplantation. \textit{Transplantation.} 2010;90:918-926.
11. Peyvandi F, Siboni SM, Lambertenghi Deliliers D, et al. Prospective study on the behaviour of the metalloprotease ADAMTS13 and of von Willebrand factor after bone marrow transplantation. \textit{Br J Haematol.} 2006;134:187-195.
12. Kim SS, Patel M, Yum K, et al. Hematopoietic stem cell transplant-associated thrombotic microangiopathy: review of pharmacologic treatment options. \textit{Transfus.} 2015;55:452-458.
13. Kennedy GA, Kearey N, Bleakley S, et al. Transplantation-associated thrombotic microangiopathy: effect of concomitant GVHD on efficacy of therapeutic plasma exchange. \textit{Bone Marrow Transplant.} 2010;45:699-704.
14. Corti P, Uderzo C, Tagliabue A, et al. Defibrotide as a promising treatment for thrombotic thrombocytopenic purpura in patients undergoing bone marrow transplantation. \textit{Bone Marrow Transplant.} 2002;29:542-543.
15. Jodele S, Fukuda T, Mizuno K, et al. Variable eculizumab clearance requires pharmacodynamic monitoring to optimize therapy for thrombotic microangiopathy after hematopoietic stem cell transplantation. \textit{Biol Blood Marrow Transplant.} 2016;22:307-315.

How to cite this article: Jia C, Qin M, Wang B, et al. Variable clinical manifestations of hematopoietic stem cell transplant-associated thrombotic microangiopathy. \textit{Pediatr Invest.} 2018;2:253-256. https://doi.org/10.1002/ped4.12100