The Overview of Diagnostic Criteria and Treatment Options of Transplantation Associated Thrombotic Microangiopathy with Two Case Reports

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ABSTRACT

Transplantation associated thrombotic microangiopathy has been considered to be a severe complication of hematopoietic stem cell transplantation. Although there has been an agreement in terms of transplantation associated thrombotic microangiopathy criteria, treatment options has not been clarified yet. Therefore we want to present two patients aged 5 years and 13 years who developed transplantation associated thrombotic microangiopathy after allogenic peripheric stem cell transplantation and to discuss both diagnostic criteria and treatment options of transplantation associated thrombotic microangiopathy.

Keywords: Transplantation, Microangiopathy, Childhood

ÖZET

Transplantasyon İlişkili Trombotik Mikroanjiopati Tanı Kriterleri ve Tedavi Seçeneklerinin İki Olgu Nedeniyle Gözden Geçirilmesi

Transplantasyon ilişkili trombotik mikroanjiopati, hematopoetik kök hücre naklinin en ciddi komplikasyonlarındandır. Tanı kriterleri açısından fikir birliğine varılmış olmasına rağmen tedavi konusunda henüz bir uzlaşı bulunmamaktadır. Bu nedenle biz burada, hematopoetik kök hücre nakli sonrası transplantasyon ilişkili trombotik mikrianjiopati gelişen 5 ve 13 yaşındaki hastalarımızı sunarak, transplantasyon ilişkili trombotik mikroanjiopati tanı kriterleri ve tedavi seçeneklerini gözden geçirmek istedik.

Anahtar Kelimeler: Transplantasyon, Mikroanjiopati, Çocukluk çağı

INTRODUCTION

Transplantation associated thrombotic microangiopathy (TAM) was firstly described in 1980 and was a complication of hematopoietic stem cell transplantation (HSCT).[1] TAM is a syndrome characterized by thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever and renal dysfunction. Prognosis is poor and there has been no consensus regarding the approach to the treatment of TAM yet.

CASE 1

Thirteen year-old male patient diagnosed with Fanconi aplastic anemia underwent allogeneic periferic stem-cell transplantation from HLA full-match sibling donor. Before transplantation both donor and patient had positive CMV IgG antibody titer. The conditioning regimen consisted of fludarabine 30 mg/m^2/d (4 days, total dose of 120 mg/m^2), cyclophosfamide 10 mg/kg/d (4 days, total dose of 40 mg/kg) and antithymocyte globulin (ATG) 20 mg/kg/d (3 days, total dose of 60 mg/kg). Short course methotrexate (mtx) and cyclosporine A (CsA) were given for the prophylaxis of graft versus host disease (GVHD). Leukocyte engraftman occurred on day 12. His liver and renal function tests elevated abnormally on day 41. Plasma lactic dehydrogenas (LDH) level and haptoglobulin level were 1123 U/L and 8.3 mg/dl, respectively. Reticulocyte count was 10%. Peripheral blood smear revealed anisocytosis, poikilocytosis and schistocytes more than 4%. Direct coombs test was negative. On the basis of these results, TAM was diagnosed. Thirty mg/kg/d steroid was given for 5 days, and steroid dose was begun to decrease on continuing days. Defibrotide treatment was placed and plasma exchange was performed on day 47 due to progression of TAM. On day 48, the status of patient was deteriorated after plasma exchange. The patient had tachypnea and dyspnea. Although lung sounds were normal, there was bilateral reticular appearance on his chest radiography. Acute respiratory distress syndrome (ARDS) was diagnosed. Since blood CMV-PCR was 67500 copy/ml, gancyklovir was given. Steroid, acyclovir and fluconazole were stopped. Trimetoprim was increased to the tratment dose. CMV-IgG was began on day 51. Defibrotide was ceased. Severe allergic reaction occured due to albumin during the third plasmapheresis. In case of secondary graft failure due to CMV pneumonia and gancyclovir treatment, peripheric stem cell was retransplanted again on day 55. After the transfusion, hypotension, reduction in oxygen saturation and pulmonary hemorrhage occurred respectively. Consequently assisted ventilation was applied. On day 58, pulmonary improvement was observed and he was weaned from the ventilator. He continued to receive oxygen with baloon-mask. Gancyclovir and weekly CMV-IgG treatment were continued. Oxygen saturation was decreased although he received oxygen with bloon-mask. Positive pressure ventilation was begun again. On day 64, bilaterally intensive ground-glass appearance was seen on his chest tomography. CMV-PCR copy was decreased to 26200 copy/ml on day 71. LDH and haptoglobulin levels became normal. A dramatic decreasing in red blood cell systocytes and poikilocytosis were observed. CMV related TAM findings were disappeared. White blood cell (WBC) count of 1000/mm^3, hematocrit of 23% and a platelet count of 23.000 /mm^3 were found secondary to infection and gancyclovir was given 81 days after the transplantation. It was thought that graft failure was occurred and the patient was additionally transplanted with peripheric stem cell third times. Clinical and laboratory improvement were recorded at follow-up. Since CMV DNA was detected at a low copy number (584 copy/ml) in peripheral blood, gancyclovir was ceased on day 60. After complete recovery, he was discharged on day 122.

CASE 2

Five year-old boy with thalassemia major was underwent allogenic transplantation from HLA full-match sibling donor. The conditioning regimen consisted of busulfan 14 mg/kg and cyclophosfamide 120 mg/kg. Short course mtx and CsA were given for GVHD prophylaxis. Engraftment was provided on the 18th day of after transplantation. On day 33, the patient progressively developed cognitive deficits. Anemia and trombocytopenia were found. Plasma LDH and indirect bilirubin levels were 934 U/L and 3.7 mg/dl, respectively. Haptoglobulin level was low (10.8 mg/dl), but reticuloctocyte was high (8%). Anisocytosis, poikilocytosis and schistocytes above 4% were seen on peripheric blo-

Table 1. Potential TMA risk factors

	Case 1	Case 2
Female gender recipient	-	-
Older age	-	-
Advanced primary disease	-	-
Unrelated donor transplant	-	-
Nonmyeloablative transplant (fludarabine based regimens)	+	-
High-dose busulfan (16 mg/kg)	-	+
Acute GVHD ≥ 2	-	+
Total body irradiation	-	-
Cyclosporine / Tacrolimus	+	+
Antithymocyte globulin	+	-
CMV	+	-
Other infections	-	+
Neuroblastoma (usage of cisplatin based regimen)	-	-

od smear. Direkt coombs was negative. Renal, hepatic and pulmonary systems were within normal limit. TAM was diagnosed with these findings. Thirty mg/kg/d pulse steroid was begun and plasma exchange was performed. CMV DNA was not detected in peripheral blood. Steroid's dose was begun to decrease after 5 days. On day 54, haptoglobulin and LDH levels were 87.2 mg/dl and 379 U/L, respectively. Despite to transfusions, anemia and trombocytopenia persisted. Because of reticulocytosis and schistocytosis, defibrotide (25/mg/kg/d) was begun. By reason of growing of Candida Parapsilosis in Hickman catheter and his being febrile, the catheter was removed and amphotericin B was given. On day 71, TAM was under partial remission, but the patient had diarrhea and ALT (243 U/L) AST (163 U/L) and total bilirubin level (4.5 mg/dl) increased. Because of developing acute GVHD, steroid was added. When the amount of stool increased to 95 ml/kg in a day, octreotid was given. The patient received daclizumab because of being unresponsive to steroid. We decided to isolate mesenchymal stem cells (MSC) from donor. In follow up, total bilirubin level and the amount of stool were found as 18.8 mg/dl and 125 ml/kg/d, respectively. Cultured MSC was infused on day 95. No acute complication was seen. After 48 hours of MSC infusion, total bilirubin level and the amount of stool decreased. However multiple organ dysfunctions developed and patient died because of pulmonary hemorrhage on day 99.

DISCUSSION

The frequency of TAM varied in the reports from 0.5 to 63.6%, the median frequency of diagnosis being 7.9%. The mean beginning time is on days 44 and 171 after HSCT. The mortality in the different series ranged from 0 to 100%, and the overall mortality rate was 61%.[2] The pathogenesis is not well understood. While initiating of conditioning regimen for stem cell transplantation, vascular endothelium is injured by toxic chemicals. Microtrombi develop in both small arteriol and capillaries and cause obstruction partially. Because red blood cells undergo mechanical trauma, they were resulted in hemolysis and fragmentation. The potential risk factors of TAM[3] and the distribution of it in our cases were presented in Table 1. Diagnostic criteria for TMA were varying for different clinical processes untill 2007. International Working Group described a new consensus for TMA diagnostic criteria

Table 2. Diagnostic criteria for HSCT-associated thrombotic microangiopathy (International Working Group Definition)

> 4% schistocytes in blood
De novo, prolonged or progressive thrombocytopenia (< $50x10^9$/l or greater reduction from previous counts)
Sudden and persistent increase in LDH
Decreased hemoglobin concentration or increased transfusion requirement
Decrease in serum haptoglobin

Table 3. Agents reported for the management of TAM

Agent	Number Treated	Treatment	Response	Overall survival	Comment
Daclizumab[9]	13	1 mg/kg/ 4 weekly (2 mg/kg loading dose); discontinuation of calcineurin inhibitor and sirolimus	5 CR, 2 PR	4/13 infection	Treatment started after diagnosis of TAM; most deaths due to
Rituximab[10]	5	375 mg/m^2/ week x 4	4 CR	3/5	All patients failed at least 7 days plasma exchange and high-dose cortico-steroids before rituximab
Eicosapentaenoic acid[11]	7	1.8 g orally per day	Not applicable	7/7	Treatment started 3 weeks before transplant; no TAM in treated group, TAM devoloped in 4 of 9 untreated patients
Transdermal isosorbide[12]	1	20 mg daily	1	1/1	No side effects observed
TNF-α inhibitors (Etanercept, Infliximab)	None of the studies of TNF-α inhibitors in TAM				TNF-α inhibitors is an increased risk of opportunistic infections, including invasive fungal and viral infection.

at 2007.[2] This criterias were avaible in our both two cases and shown on Table 2.

There is no consensus on treatment currently. Potential culprit medications, such as CsA, tacrolimus and sirolimus should be withdrawn immediately if TMA is suspected. In the setting of the need for continuing immunosuppression, alternative agents, such as corticosteroids, mycophenolate mofetil, azathioprine or others are instituted.[3]

Plasma exchange, despite limited data, many centers employs plasma exchange as part of the management of TAM. Response rates to plasma exchange in TAM are significantly lower (less than 50%). Furthermore, major complications associated with pheresis catheters or plasma exposure, including systemic infection, thrombosis, hemorrhage, pneumothorax, pericardial tamponade, hypoxia, hypotension, serum sickness and anaphylaxis occur in approximately 28% of patients treated with plasma exchange.[3]

Defibrotide is a single-stranded polydeoxyribonucleotide that protects the vascular endothelial cells, particularly those of small vessels, from damage and activation. After binding to endothelial cells, defibrotide decreases cell adhesion and pro-coagulant activity of activated endothelial cells, and increases the fibrinolytic potential of endothelial cells. Defibrotide's effects are predominately local within the vascular bed, and there is no significant effect on systemic coagulation. Its beneficial pharmacological effects are due to its anti-thrombotic, anti-inflammatory and anti-ischemic properties.[4-6] Defibrotide, which has been shown to improve outcome in patients with hepatic veno-occlusive disease[6,7], also prevents TNFα-induced endothelial cell apoptosis in vitro.[8] In a recently reported case series nine responses were seen in a group of 12 patients with moderate to severe TAM after prolonged treatment, suggesting the need for randomized trials of defibrotide in this disorder.[5] Other treatment options are shown on Table 3.

When TAM was diagnosed, CsA was ceased in our both cases. Steroid was given for maintaining of immunosupression and plasma exchange was applied. Both cases also received defibrotide. Complet remission was achieved by the treatment of CMV infection in case 1 diagnosed with TAM. In Case 2, TAM was partially controlled by defibrotide treatment, and acute GVHD accompanied to the scene.

Although we used daklizumab and MSC, the patient died due to acute GVHD.

In conclusion, there is no consensus regarding the approach to the treatment of TAM currently and no randomized clinical trials exist. Therefore multicenter studies are needed.

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