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Complete resolution of transplantation-associated thrombotic microangiopathy and hepatic veno-occlusive disease by defibrotide and plasma exchange

Transplantasyona bağlı mikroanjiopati ve karaciğerin veonoklusif hastalığında plazma değişimi ve defibrotide ile tam düzelme

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Transplantation-associated thrombotic microangiopathy has been associated with significantly reduced survival following allogeneic bone marrow transplantation. We describe here the course of Transplantation-associated thrombotic microangiopathy and hepatic veno-occlusive disease, and response to plasma exchange therapy. A 19-year-old male patient underwent hematopoietic stem cell transplantation (HSCT) from his HLA-matched brother for lymphoblastic lymphoma in the first complete remission. Transplantation-associated thrombotic microangiopathy was diagnosed 17 days after transplantation. At that time, neurological abnormalities were not present. Cyclosporin A (CsA) was discontinued. Hematological stabilization was recorded. On day +20, abdominal distention, painful hepatomegaly and ascites complicated the clinical picture. With a high hepatic venous pressure gradient (18mmH_20), veno-occ lusive disease of the liver was diagnosed and defibrotide was started, which resulted in a dramatic cessation of pain and increase in urinary output. However, transplantation-associated thrombotic microangiopathy-related symptoms progressed and plasma exchange was instituted, which resulted in worsening of veno-occlusive disease symptoms. He was referred to the Intensive Care Unit due to respiratory compromise and was intubated. Plasma exchange was continued in order after hemofiltration. In three days, fever resolved, hemofiltration could be stopped, and ventilator dependence ended. After 19 aphereses, serum LDH level returned to normal and schistocytes were minimal on microscopic examination of the blood film. Platelet count increase was more gradual. Plasma exchange was discontinued. On the 40th day of defibrotide, all symptoms related with veno-occlusive disease were resolved and defibrotide was stopped. We think that our case is important to establish the relation and management strategy of these two small vessel complications of HSCT.

Key words: Hepatic veno-occlusive disease, cell transplantation, thrombotic microangiopathy, defibrotide

Transplantasyon ile ilişkili trombotik mikroanjiopati kliniği oldukça kötü seyretmektedir. Bu yazıda, transplantasyon ile ilişkili trombotik mikroanjiopati ve ardı sıra venooklusif hastalık gelişmiş bir vakada defibrotid ve tedavi amaçlı plazmaferez ile tam düzelme elde edilen bir olgu sunuldu. 19 yaşında bir erkek hasta lenfoblastik lenfoma birinci remisyon tanısı ile HLA tam uyumlu erkek kardeşinden hematopoetik kök hücre nakli oldu. + 17.günde transplantasyon ile ilişkili transplantasyon ile ilişkili trombotik mikroanjiopati gelişti. Nörolojik bulgu saptanmadı. Siklosporin A kesildi. Kan değerlerinin stabilize olması elde edilmiş iken +20. günde karında gerginlik, asit, ağrılı hepatomegali ve idrar miktarında azalma yakınması gelişti. Hepatik ven wedge basıncı yüksek bulundu (>18mmH_20). Venooklüsif hastalık tanısı ile defibrotid (defibrotid, 10mg/kg/gün, 4 doza bölünmüş olarak, 2 saatlik infüzyon halinde) başlandı. Ağrısı dramatik şekilde geriledi, idrar çıkışı arttı. Ancak, sık eritrosit transfüzyon ihtiyacı ile Transplantasyon ile ilişkili trombotik mikroanjiopati kliniği progresyon gösterdi. Bu durumda tedavi amaçlı plazmaferez başlandı. Takiben yeniden ciddi kilo artışı, asit ve solunum yetmezliği gelişen hasta entübe edildi. Hemofiltrasyonu takiben plazmaferez ile ateşi düşen hastanın mekanik solunum desteği ortadan kalktı. Plazmaferezin 19. günü transplantasyon ile ilişkili trombotik mikroanjiopati belirgin geriledi. Venooklüsif hastalık belirti ve bulgularının tamamen kaybolması ile defibrotid+40. günde kesildi. Olgu, hematopoetik kök hücre transplantasyonu sonrası iki ölümcül seyirli küçük damar hastalığının tedavi yaklaşımlarının etkileşiminin netleştirilmesine yardımcı olabileceği düşüncesi ile sunuldu.

Anahtar kelimeler: Karaciğerin venooklusif hastalığı, kök hücre nakli, trombotik mikroanjiopati, defibrotid

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INTRODUCTION

Hepatic veno-occlusive disease (VOD) is a potentially lethal complication of both allogeneic and autologous hematopoietic stem cell transplantation (HSCT). The pathogenesis of VOD involves injury to the sinusoidal endothelial cells, leading to occlusion of small vessels with fibrin deposition and disruption of hepatic function. Previous attempts at therapy using either heparin or tissue plasminogen activator have been unsuccessful (1, 2). Defibrotide is a single-stranded polydeoxyribonucleotide that has effects on the vascular endothelial cells, particularly those of small vessels. After binding to endothelial cells, defibrotide enhances factors that contribute to fibrinolysis and suppresses those that promote coagulation. These effects are predominately local within the vascular bed, and there is no significant effect on systemic coagulation, which was seen during treatment with tissue plasminogen activator. Previous pilot trials of defibrotide for VOD have suggested both efficacy and lack of significant toxicity (3, 4). Transplantation-associated thrombotic microangiopathy (TA-TMA), another serious complication of HSCT, is characterized by arterial hypertension, microangiopathic hemolytic anemia, thrombocytopenia, elevated LDH level, proteinuria, microscopic hematuria, and severe renal failure within six weeks of HSCT (5). It has no generally accepted detailed diagnostic criteria, and many HSCT-related complications mimic different components of TA-TMA. The diagnosis of TA-TMA, therefore, relies on the clinical suspicion of the treating physician, and the outcome of patients diagnosed as TA-TMA is poor (6). The use of defibrotide has been reported with some promise (7). Here, we describe the course and response to defibrotide and plasma exchange of the two serious transplant-related complications, TA-TMA and VOD, in an HSCT patient.

CASE REPORT

A 19-year-old boy underwent allogeneic peripheral blood stem cell transplantation from his HLA-identical ABO compatible brother, while in the first complete remission of B cell lymphoblastic lymphoma (stage IVB). Busulfan and cyclophosphamide were used as conditioning regimen. He received phenytoin to prevent busulfan-induced seizures and ursodeoxycholic acid (UDCA; 250 mg ***bid*** one day prior to the start of cytotoxic therapy and continuing for 21 days) to reduce the incidence and/or severity of hepatic complications. Graft-versus-host disease (GVHD) prophylaxis was with cyclosporine (CsA) and short-term methotrexate. He was treated in a Hepa-filtered positive pressure HSCT facility. Low bacterial diet was used. Antimicrobial prophylaxis consisted of ciprofloxacin, metronidazole, acyclovir, fluconazole and trimethoprim–sulfamethoxazole. The latter was used for *Pneumocystis carinii* prophylaxis and was ceased during cytopenic period. As a transplant-related complication, he experienced cyclophosphamide-induced hemorrhagic cystitis, which resolved in a short time after hyperhydration and intensified platelet transfusions. On the 8th day of HSCT, he experienced a febrile neutropenic episode for which he received cefepime with isepamicine. Disappearance of fever and engraftment occurred concurrently, on the +11th day, following the addition of vancomycin. On the 17th day of HSCT, hemoglobin level decreased from 12.7 g/dl to 10.1 g/dl. Blood films highlighted the presence of more than 10% of fragmented red cells. Lactic dehydrogenase level was three-fold above the normal range. Blood pressure showed a mild increase and the blood CsA level proved to be high (788 ng/ml, normal range 200-400 ng/ml) with a normal serum creatinine level (0.7 mg/dl) (Figure 1). CsA-associated nephrotoxicity with microangiopathic hemolytic anemia (MAHA) was diagnosed. CsA was stopped and replaced subsequently by methylprednisolone at a dose of 1 mg/kg/day. In three days, a sudden onset of severe abdominal pain and distention with a gradual increased fever up to 38∞C complicated the clinical picture. Physical examination revealed hepatomegaly and ascites, which was confirmed by abdominal ultrasonography. The rapid fall of platelet level from 102, 000/µL to 27, 000/µL was striking. Routine infection evaluations including cytomegalovirus (CMV) antigenemia failed to demonstrate evidence of infection elsewhere, despite normal neutrophil count. Hepatic venography revealed a high hepatic venous pressure gradient (18mmHg). Hepatic VOD was diagnosed. Fluid restriction, spironolactone and narcotic analgesics were commenced as symptomatic treatment. In two days, defibrotide (DF), which is not yet available in Turkey, was obtained and administered by iv infusion in a crystalloid solution at a dose of 10 mg/kg/day in 4 divided doses, each infused over 2 hours, which resulted in dramatic cessation of pain (Figure 1). However, the severity of microangiopathic anemia increased and he had to receive frequent blood transfusions, which contributed to clinical deterioration with increased abdominal distension, dyspnea, progressive azotemia (serum creatinine le-

vel increased from 0.9 mg/dl to 2.5 mg/dl), and oliguria (Figure 1). Chest roentgenogram followed by computed tomography showed bilateral segmental atelectasis and a moderate pleural effusion. On day +26, plasma exchange was initiated with infusion of 45 ml of fresh frozen plasma/kg/exchange (Figure 1). After 19 phereses, serum LDH level returned to normal and schistocytes were minimal on microscopic examination of the blood film. Platelet count increase was more gradual (Figure 1). Plasma exchange was discontinued. Defibrotide was given for 40 days until clinical improvement with fluid mobilization, decrease in bilirubin, and reduction in hepatomegaly. The patient is now in the second year of HSCT, and remains well without any organ dysfunction.

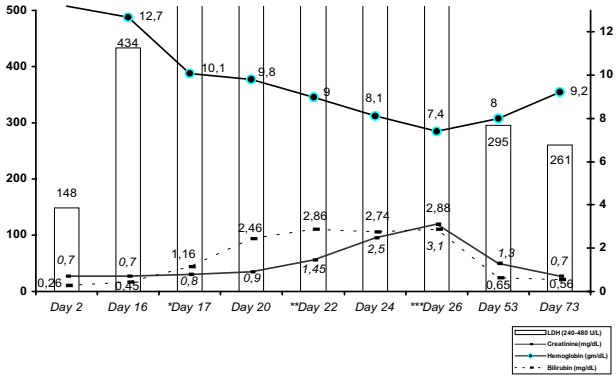

Figure 1. Serum LDH, bilirubin, hemoglobin and creatinine levels of the patient. With the increasing LDH levels, hemoglobin level showed a decrement and microangiopathic hemolytic anemia occurred. With the development of VOD symptoms, serum LDH and creatinine levels increased. After defibrotide treatment and multiple plasmaphereses, serum creatinine and LDH levels returned to the normal range. *On day +17, cyclosporine was ceased. **On day +22, defibrotide treatment was started. ***On day +26, plasmapheresis was started

DISCUSSION

Hepatic VOD is a regimen-related toxicity after ablative preparative therapy. It is characterized clinically by fluid retention that manifests as weight gain more than 2% above baseline and/or ascites, and painful hepatomegaly early in the course of disease, followed by elevated bilirubin and, sometimes, transaminases. Because clinical signs of portal hypertension follow those of hepatic parenchymal injury and because not all patients with this clinical syndrome have hepatic venular occlusion on biopsy or autopsy material, a more appropriate name for this toxicity, sinusoidal obstruction syndrome (SOS), has been suggested rather than the more commonly used VOD (8). Sudden severe thrombocytopenia that becomes refractory to transfusion can be a striking feature, as can dyspnea due to tense ascites and concomitant pleural effusions (9, 10). Hepatic veno-occlusive disease (HVOD) shares many clinical features with Budd-Chiari syndrome, including tender hepatomegaly, jaundice, and ascites. A transvenous approach allows the measurement of the hepatic wedge pressure. A gradient > 10 mmHg between the wedged hepatic and free hepatic venous pressures has a greater than 80% positive predictive value for the histological diagnosis of VOD. A variety of risk factors for the development of VOD have been identified (10). For our case, the known risk factors would be the allogeneic HSCT and the use of busulfan as a part of the conditioning regimen. However, multivariate analyses suggest that autologous transplants are not associated with a lower incidence of VOD compared to allogeneic transplants, and we do not know the pharmacokinetics of busulfan (area under curve, AUC) in our patient (11). Patients with SOS-VOD may recover spontaneously. For patients with severe illness, there are to date no treatment strategies proven in prospective, randomized, and controlled studies in the published literature. Some clinical signs may predict outcome. Fewer than 20% of patients with mild or moderate disease and about half of patients with severe disease develop ascites. Patients who demonstrate early rapid increases in weight and bilirubin are likely to die (12). Approximately 30% of patients appear to respond to tissue plasminogen activator, but almost as many develop significant hemorrhagic complications (2, 10). Defibrotide, a large, single-stranded polydeoxyribonucleotide, is derived from mammalian tissue (porcine mucosa) by controlled depolymerization, and has been found to have anti-thrombotic, anti-ischemic, anti-inflammatory, and thrombolytic properties, without significant systemic anticoagulant effects (3-13). In a small treatment group, complete response occurred in 36% of patients (4), and there was no significant toxicity associated with its use. The clinical spectrum that presents in a similar manner to that of thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) during HSCT is another small-vessel-related complication of HSCT referred to as transplantation-associated thrombotic microangiopathy (TA-TMA). It encompasses a spectrum of related and overlapping syndromes: multifactorial fulminant thrombotic microangiopathy, conditioning regimen-associated HUS, CsA-associated nephrotoxicity with MAHA, and CsA-associated neurotoxicity with MAHA (14). The pathogenesis

of classical TTP is thought to involve a plasma factor leading to endothelial cell apoptosis. These patients have a deficiency in von Willebrand's factor (vWF) cleaving metalloprotease leading to larger than normal von Willebrand's factor multimers, which causes platelet aggregation. However, in TA-TMA, the vWF cleaving metalloprotease activity is generally preserved (15). The high-risk group commonly consists of allogeneic HSCT patients, who have received CsA or tacrolimus for GVHD prophylaxis, and who have had a superimposed event such as hepatic VOD, CMV infection, or GVHD (16). The outcome of this form of TTP-HUS-like syndrome is poor and mortality is high (17). Although there are some reports of remission achieved with plasma exchange using fresh frozen plasma or cryosupernatant fraction of plasma, the management with plasmapheresis has not generally been found to be very effective (18). Because CsA or tacrolimus has been linked to its pathogenesis, many physicians choose to reduce the dose of the drug, or discontinue it, as we did. There are some reports regarding the beneficial effect of defibrotide in chemotherapy-related hemolytic-uremic syndrome (HUS)/TTP or TTP during HSCT and liver transplantation (20, 21) [4, 19]. In our case, discontinuation of CsA seemed to provide some response whereas the glucocorticoid could have contributed to this. In the following days, the superimposed VOD aggravated TA-TMA. On the other hand, management of TA-TMA by frequent packed red cell transfusion followed by plasma exchange worsened the course of VOD by facilitating fluid retention. Institution of defibrotide, which contributed to the gradual improvement in the VOD-related process, might also have played a part in the remission of TA-TMA. We think therefore that our case is important to establish the relation and management strategy of these two small vessel complications of HSCT.

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