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자가조혈모세포이식 후 Ganciclovir로 거대세포바이러스 감염 치료시 발생한 혈전성 미세혈관병증 1예

이명수[1] • 배기수[1] • 박세진[1] • 임현이[2] • 박준은[1]

아주대학교 의과대학 [1]소아과학교실, [2]병리학교실

Thrombotic Microangiopathy during Ganciclovir Treatment for Cytomegalovirus Infection in a Patient with Autologous Hematopoietic Stem Cell Transplantation

Myung Soo Lee, M.D.[1], Ki Soo Pai, M.D.[1], Se Jin Park, M.D.[1], Hyun Ee Yim, M.D.[2] and Jun Eun Park, M.D.[1]

Departments of [1]Pediatrics, and [2]Pathology, Ajou University School of Medicine, Suwon, Korea

Thrombotic microangiopathy (TMA) is a known complication of hematopoietic stem cell transplantation (HSCT). Here, we describe a case of TMA after autologous HSCT, which was associated with ganciclovir treatment. A 5-year-old boy presented with Coombs-negative hemolytic anemia, thrombocytopenia, gross hematuria, massive proteinuria, and hypertension during ganciclovir treatment after autologous HSCT. TMA was confirmed by renal biopsy which showed swelling of endothelial cells, occlusion of the glomerular lumina, duplication of glomerular basement membranes, and mesangiolysis. There was complete resolution of TMA in both laboratory and clinical manifestations after ganciclovir cessation only with supportive cares and hydration.

Key Words: Thrombotic microangiopathy, Cytomegalovirus, Ganciclovir

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책임저자: 박 준 은
경기도 수원시 영통구 원천동 산 5
아주대학교 의과대학 소아과학교실, 443-721
Tel: 031-219-5168
Fax: 031-219-5169
E-mail: pedpje@ajou.ac.kr

Introduction

Thrombotic microangiopathy (TMA) is a significant complication of hematopoietic stem cell transplantation (HSCT). The reported incidence of TMA in patients after HSCT varies enormously between 0.5 and 76% [1,2]. In the transplant setting, various conditions may contribute to the injury of microvascular endothelial cells. Factors such as total body irradiation, high-dose chemotherapy, use of immunosuppressants (especially calcineurin inhibitors (CNI)), sepsis, and severe graft-versus-host disease (GVHD) are related to transplantation-associated TMA (TA-TMA). In the nontransplant setting, TMA has been associated with Escherichia coli 0157 : H7, human immunodeficiency virus, pregnancy, and drugs such as ticlopidine, quinine [1,3].

The majority of post-HSCT patients manifest TMA by a slight rise in lactate dehydrogenase (LDH) and increase in fragmented RBCs in circulation. However, the disease spectrum includes a life-threatening disorder, thrombotic thrombocytopenic purpura (TTP) [1,3]. The classic 'pentad' describing the disease process, which are fever, hemolytic anemia, thrombocytopenia, neurological complications and renal impairment, is not always present to the same extent

in every patient [4].

Here, we describe a patient with a rare case of HSCT-associated TMA due to ganciclovir, who did not present the classic manifestations of TTP and achieved complete resolution after ganciclovir cessation without any other treatment options of TMA.

Case Report

A 5-year-old boy was diagnosed with Wilms' tumor (stage II) in January 2009 and underwent the left radical nephrectomy. The chemotherapy regimen consisted of dactinomycin (0.045 mg/kg) and vincrinstine (0.05 mg/kg) continued for 18 weeks in remission. However, one month after completion of chemotherapy, a follow-up computed tomography (CT) scan showed the recurrence of Wilms' tumor (Fig. 1A). Positron emission tomograpy (PET) revealed metastasis to the upper lobe of left lung (Fig. 1B). *En bloc* adrenalectomy and distal pancreatectomy were performed, and the biopsy specimen also showed metastasis to pancreas, adrenal gland, and skeletal muscle of diaphragm. After surgery, he was treated with radiotherapy (21.4 Gy at abdomen, 10.5 Gy at whole lung field) and with 2 courses of chemotherapy consisted of ifosfamide (1.2 g/m^2), carboplatin (400 mg/m^2) and etoposide (100 mg/m^2). High dose chemotherapy and autologous HSCT were performed; Carboplatin, 400 mg/m^2 and etoposide, 100 mg/m^2 for 5 days (from D-7 to D-3) were used for conditioning regimen, and 5×10^6/kg CD34 positive cell was infused to the patient for hematopoietic rescue.

Apparently, 5 weeks after autologous HSCT, CMV antigenemia was observed in the patient with detection of 7 peripheral blood lymphocytes per 200,000 that are expressing the pp65 protein. Ganciclovir was started and maintained for 3 weeks (5 mg/kg every 12 hour for 2 weeks, and then every 24 hour for 1 week). During the last 3rd week of ganciclovir treatment, the leukocyte count was 4,200/μL, whereas the hemoglobin and platelet level dropped to 6.9 g/dL and 8,000/μL, respectively. Concurrently, hypertension (more than 140/90 mmHg), three-positive proteinuria, and gross hematuria occurred. Other laboratory findings were as follows: blood urea nitrogen (BUN), 28.2 mg/dL; serum-creatinine (S-cr), 1.1 mg/dL; lactate dehydrogenase (LDH), 667 U/L; total bilirubin, 0.6 mg/dl; direct bilirubin, 0.2 mg/dL; and haptoglobin, <10 mg/dL. Fragmented RBCs were found in the blood smear and Coombs' test was negative. Twenty-four hour urine protein collection showed the nephrotic range proteinuria (40.1 mg/m^2/hr). The spot urine protein to creatinine ratio was 9.1 (normal ratio, <0.2; nephrotic ratio, >3.5). There was no evidence of viral infection such as Ebstein-Barr virus or BK polyoma virus, and CMV antigen has not been detected since the onset of the clinical presentation of TMA in this patient.

Renal biopsy was done to rule out other possible renal injuries that may cause massive proteinuria and hematuria in this patient rather than TMA. The biopsy finding revealed swelling of endothelial cells, occlusion of the glomerular lumina, duplication of glomerular basement membranes, and mesangiolysis, which is seen in TMA (Fig. 2).

Monitoring of BUN, S-cr, LDH, haptoglobin, hemoglobin, and platelet counts along with blood pressure and urine output was continued. Clinical symptoms and laboratory findings had recovered with proper hydration and anti-hypertensive agent. Fever, oliguria and hypertensive symptoms such as headache, neck pain and eye discomfort were not present. Seven days after completion of ganciclovir, blood pressure was normalized and gross hematuria dis-

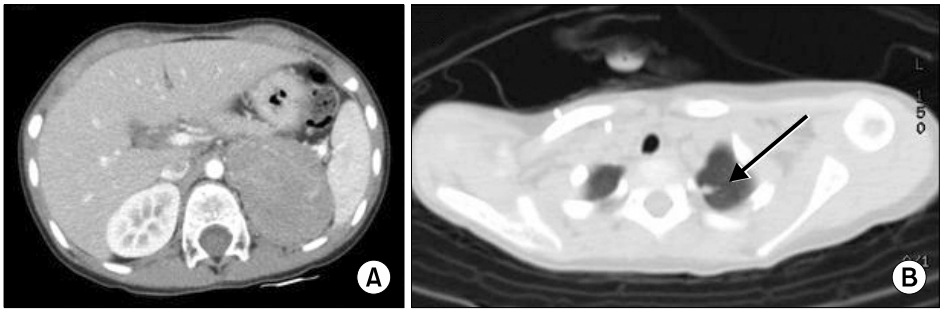

Fig. 1. (A) Abdominal CT scan shows recurrence of Wilms' tumor and (B) PET-CT shows a metastatic nodule in the upper lobe of the left lung.

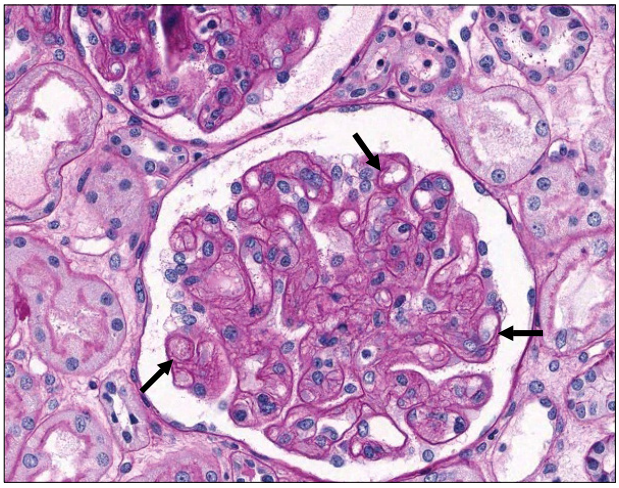

Fig. 2. Mesangiolysis and duplication (arrows) of glomerular capillary walls are noted (×400, PAS stain).

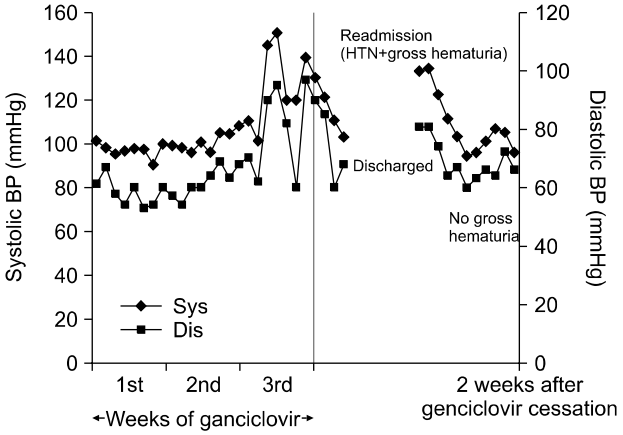

Fig. 3. This illustration displays the changes in blood pressure and hematuria.

appeared (Fig. 3). Two weeks after completion of ganciclovir, the spot urine protein to creatinine ratio was decreased to 0.2 and RBCs were not detected in urine analysis. Hemoglobin level reached up to 8.3 g/dL and platelet level was 68,000/μL.

Discussion

In this case report, we present a patient with autologous HSCT who developed TMA due to ganciclovir treatment after CMV infection. Both TMA (presenting Coombs-negative hemolytic anemia) and Evans syndrome (thrombocytopenia and Coombs-positive hemolytic anemia) after HSCT rarely occur [5], but they could be life-threatening. Although the exact pathogenesis of TMA after HSCT remains elusive, recent literature addresses the roles of cytokines, the coagulation cascade, and complement [6]. The kidney is most commonly affected, and injury has rarely been reported elsewhere in the body [6,7]. In its most severe form, mortality rates are often high, whereas milder cases have an increased risk of resulting in chronic kidney disease (CKD) [8].

The following three major categories of renal diseases have been described in patients with post-HSCT CKD: (i) immune complex type glomerulonephritis, (ii) non-immune complex type glomerular diseases, (iii) TMA and mesangiolytic glomerulopathy [9,10]. Renal TMA is morphologically defined as fibrin thrombi in glomeruli, mesangiolysis, and/or thrombi in arterioles or interlobular arteries, regardless of clinical information [11]. Mesangiolytic glomerulopathy which shows severe endothelial injury, various degrees of mesangiolysis, and accumulation of mesangial matrix is identical to renal TMA [11].

Despite the high prevalence of renal disease after HSCT, <2% of patients underwent a renal biopsy [6,12,13]. Rather than TMA, given concerns for other lethal injuries of remaining single kidney in this patient, confirmative diagnosis was needed by renal biopsy. With the histopathologic features of mesangiolytic glomerulopathy, we were able to exclude other life-threatening renal diseases that may cause massive proteinuria and hematuria.

According to the report by Waiser et al., TMA developed in two renal allograft recipients with acute CMV infections (biopsy-proven CMV esophagitis and generalized febrile illness with leucopenia), after receiving intravenous ganciclovir. Treatment with intravenous ganciclovir was continued. Consequently, plasmapheresis was initiated in both patients. CMV was thought to be a main cause of TMA in both cases, but with the time course of event, ganciclovir was suggested only as a trigger factor [14]. In this case, CMV viral load had decreased with intravenous ganciclovir and finally, the antigen was not detected at the end of second week of ganciclovir infusion. Then the TMA developed during the last 3rd week of ganciclovir treatment. After two weeks of ganciclovir cessation, the patient fully recovered from TMA. Therefore, we could conclude that TMA in this patient was due

to ganciclovir treatment rather than CMV infection.

Treatment options of TA-TMA have been variable and range from discontinuation of causable medication to the employment of plasmapheresis, use of intravenous immunoglobulin or steroids along with control of blood pressure with antihypertensive medications. Some case reports have also highlighted a potential role of the anti-CD20 antibody rituximab in the treatment of TMA [15]. Unlike the situation in idiopathic TTP, the efficacy of plasmapheresis in TA-TMA has never been proved and its role remains controversial. Reported response rates vary between 0-49% [16,17], compared with 78-91% in patients with idiopathic TTP [15]. Plasmapheresis was not necessary to be employed in our case. According to A. Bren et al., 14 of 15 patients had good resolution of CSA-associated TMA after CSA dose reduction or temporary discontinuation [18].

The risk factors that are related to worse outcome of TA-TMA are early onset, age >18 years, use of CSA or tacrolimus, kidney or central nervous system involvement, and the use of unrelated or haploidentical donors [19]. The patient had no factor indicating poor prognosis of TA-TMA other than nephropathy in this case. Consequently, without plasmapheresis, there was complete and sustained resolution of all laboratory and clinical manifestations of TMA after ganciclovir avoidance. Thus, in our opinion, early identification of TMA with frequent monitoring in the patient who receives ganciclovir treatment is necessary for instituting proper treatment.

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