Case Report

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Tacrolimus-induced, Transplant-associated Thrombotic Microangiopathies after Lung Transplantation

Ji Soo Choi, M.D.[1], Song Yee Kim, M.D.[1], Jin Gu Lee, M.D.[2], Soo Jeong Kim, M.D.[3], Myung Jin Song, M.D.[1], Bo Ra Yoon, M.D.[1], Moo Hyun Kim, M.D.[1], Moo Suk Park, M.D.[1] and Hyo Chae Paik, M.D.[2]

Division of Pulmonology, Department of Internal Medicine, Institute of Chest Diseases, Severance Hospital, Yonsei University College of Medicine[1], Department of Thoracic and Cardiovascular Surgery, Yonsei University College of Medicine[2], Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine[3], Seoul, Korea

We report a case of tacrolimus-induced transplant-associated thrombotic microangiopathies (TA-TMA) after lung transplantation. A 71-year-old man underwent lung transplantation secondary to idiopathic pulmonary fibrosis. After 4 months, he presented with abdominal discomfort and dyspnea, and was diagnosed with hemolytic anemia and thrombocytopenia. Tacrolimus was considered the cause of the TMA. Tacrolimus was stopped and several sessions of plasma exchange were performed immediately after diagnosis of TA-TMA. However, his platelet count did not normalize, gastrointestinal bleeding was recurrent, and severe pneumonia developed, following which he died. TA-TMA are rare but severe, life-threatening complications in lung transplant recipients. Therefore, the possibility of TA-TMA should be considered in posttransplant recipients.

Key Words: Thrombotic microangiopathies, Lung transplantation, Tacrolimus
중심 단어: 혈전미세혈관병증, 폐이식, 타크로리무스

INTRODUCTION

FK 506 (tacrolimus) is a metabolite of the fungus *Streptomyces tsukubaensis* with potent immunosuppressive activity and has been effective in preventing rejection of allografts of the liver, kidney, small intestine, and heart(1,2). This medication has many complications, including infection, cardiac damage, liver and kidney damage, hyperkalemia, and various neuropsychiatric problems such as loss of appetite, insomnia, and confusion. Among them, thrombotic microangiopathies (TMAs) is a rare but severe, life-threatening complication(3).

Many reports have described tacrolimus induced transplant-associated TMA (TA-TMA) in solid organ or bone marrow transplant patients. Most cases of this complication have been reported in kidney transplant patients(4). Development of TA-TMA following lung transplantation is rare; therefore, we report the case of a patient who developed TA-TMA with severe pneumonia and gastrointestinal bleeding after lung transplantation.

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Corresponding author: Song Yee Kim
Division of Pulmonology, Department of Internal Medicine, Institute of Chest Diseases, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: 82-2-2228-1940, Fax: 82-2-393-6884
E-mail: dobie@yuhs.ac

CASE REPORT

A 71-year-old man underwent right lung transplantation for idiopathic pulmonary fibrosis. He had a history of coronary artery occlusive disease with hypertension and diabetes mellitus. His immunosuppressive regimen included tacrolimus, 3 mg twice a day; mycophenolate 500 mg twice a day; and deflazacort 9 mg twice a day with prophylactic trime-

thoprim/sulfamethoxazole, itraconazole, and valganciclovir. His general condition was good immediately after lung transplantation.

At postoperative day 101, he visited the emergency department with progressively aggravating abdominal discomfort and dyspnea. On physical examination, there was unremarkable sign except decreased skin turgor. On initial laboratory evaluation, hemoglobin was 10.5 g/dL, leukocyte was 4,090/μL, and platelet was 199,000/mm^3. Serum creatinine was elevated (1.51 mg/dL; baseline, 0.9 mg/dL), and C-reactive protein was elevated at 67.4 mg/L. The liver function test and prothrombin and partial thromboplastin times were normal. Chest radiography showed mild pleural effusion on the right transplanted lung and diffuse reticulonodular opacities combined pneumonic consolidation on the left lung. Initial tacrolimus level was high at >30.0 ng/mL. Esophagogastroduodenoscopy (EGD) showed gastric and duodenal ulcers.

By hospital day 5, leukocyte had decreased to 2,260/μL, platelet to 51,000/μL, and hemoglobin to 7.5 g/dL, indicating normocytic normochromic anemia. On hospital day 21, leukocyte was recovered to 7,560/μL after mycophenolate and trimethoprim/sulfamethoxazole were stopped; however, anemia and thrombocytopenia persisted (hemoglobin 7.1 g/dL, platelet 23,000/μL). Lactate dehydrogenase (LDH) had increased to 2,481 IU/L, haptoglobin was markedly decreased to <10 mg/dL and reticulocyte count was elevated to 15.8%, suggesting hemolysis. Fibrin degradation products was slightly elevated to 6.14 μg/mL (normal range; 0~5 μg/mL) and d-dimer was elevated to 485 ng/mL (normal range; 0~243 ng/mL). However serum fibrinogen, thrombin time was normal range, 388 mg/dL and 18 seconds, respectively. Microscopic review of the peripheral blood smear showed the weak positive of schistocytes and the number of nucleated red blood cells was elevated 18/100 white blood cell (WBC; normal range; 0~2.3/100 WBC). Serum creatinine was elevated to 2.17 mg/dL. The test for the enterotoxigenic *Escherichia coli* was negative. The diagnosis was TMA, which included thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and microangiopathic hemolytic anemia (MAHA) associated with various systemic diseases. The findings were not consistent with other diagnosis of TMA, and other causes of TMA were not presented definitely; therefore, we established a diagnosis of TA-TMA associated with tacrolimus. We stopped tacrolimus, and plasmapheresis was initiated every alternate day with daily transfusion. After management, the laboratory findings of hemolysis were transiently recovered. LDH and reticulocyte count decreased to 545 IU/L and 2.49%, respectively. Furthermore, schistocytes were not showed on peripheral blood smear, and hemoglobin and platelet increased to 11 g/dL and 44,000/μL, respectively.

However, severe infection was co-existed. Fungal pneumonia developed in the right lung and pneumonia in the

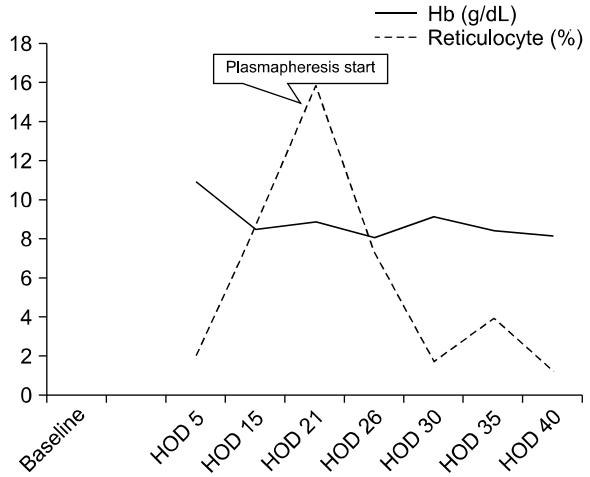

Fig. 1. Hemoglobin (Hb): baseline over 1 month prior to presentation. Plasmapheresis was started on hospital day (HOD) 21, and repeated at 12 times.

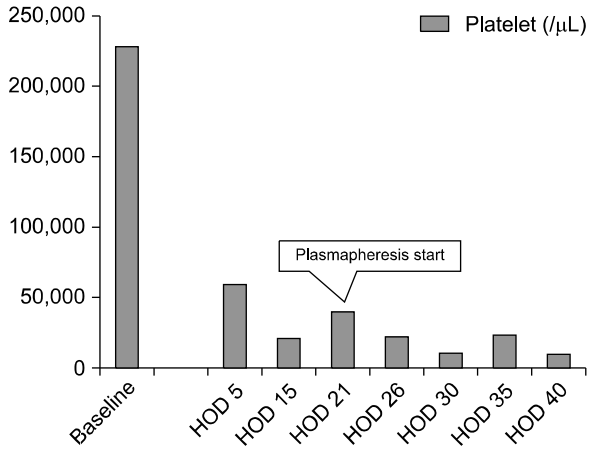

Fig. 2. Platelet: baseline over 1 month prior to presentation. Plasmapheresis was started on hospital day (HOD) 21, and repeated at 12 times.

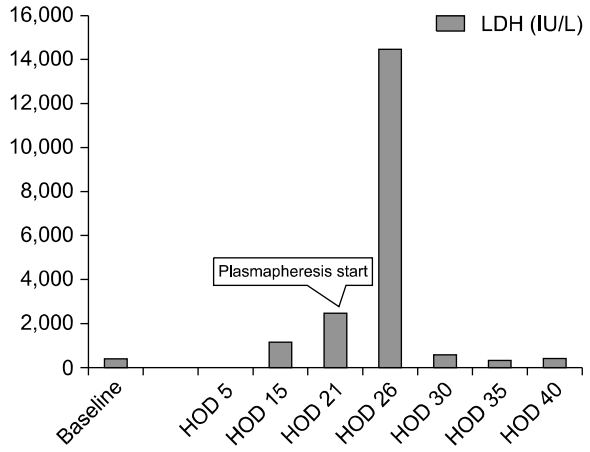

Fig. 3. Serum Lactate dehydrogenase (LDH) level: baseline over 1 month prior to presentation. LDH elevated on hospital day (HOD) 26, then decreased by taking plasmapheresis.

left lung was aggravated. Intravenous antibiotics for bacteria and fungus were administered.

On hospital day 26, his blood pressure decreased to 77/48 mmHg, and hematochezia developed. His hemoglobin decreased to 7.1 g/dL and platelet was 46,000/μL. The finding of EGD showed a gastric ulcer bleeding and a duodenal ulcer. Although hemostasis was performed through EGD, he developed recurrent gastrointestinal bleeding. His hemoglobin decreased to 6.1 g/dL, and platelet to 10,000/μL (Figs. 1, 2). Massive transfusion, daily plasmapheresis (total 12 times), and repeated hemostasis via EGD were continued. Although LDH and reticulocyte count were recovered gradually (481 IU/L and 1.21%, respectively) which showed the improvement of TA-TMA, the hemoglobin and platelet continuously decreased due to recurrent gastrointestinal bleeding (Fig. 3). Furthermore, pneumonia was not controlled and the general condition of patient was deteriorated. Ultimately, he died on hospital day 40 (postoperative day 141) due to severe infection and recurrent gastrointestinal bleeding.

DISCUSSION

TMA is a syndrome that represents endothelial injury, microvascular thrombosis, and fibrin deposition leading to MAHA and thrombocytopenia due to platelet consumption. TMA includes TTP, HUS, and MAHA associated with various systemic diseases or conditions including pregnancy, vasculitis, and other autoimmune disorders(5).

Tacrolimus is a useful immunosuppressive agent that improves the survival of organ transplant recipients, but has many complications. Trimarchi et al.(6) reported that tacrolimus could induce TMA through its direct and endothelin-1-mediated vasoconstrictor effects on the renal vasculature, leading to tissue hypoxia, endothelial cell damage, and deposition of platelets and fibrin in the glomeruli. However, the pathogenesis of tacrolimus associated TA-TMA is controversial.

Development of tacrolimus induced TA-TMA can be life-threatening; however, if detected early, they can be cured. In previous reports, tacrolimus induced TMA after solid organ transplantation developed in 0.5% to 3% of transplant patients(7). Most cases have been reported in kidney(6), liver(8), and bone marrow transplant recipients(9). However, there are few case reports in lung transplant patients. Myers et al.(10) reported a case of HUS in a lung transplant recipient receiving tacrolimus. They described that a 60-year-old woman with a history of lung transplantation for severe chronic obstructive pulmonary disease developed tacrolimus-associated HUS that resolved after discontinuation of tacrolimus(10). Boyer et al.(11) also reported that a 25-year-old woman with a history of lung transplantation secondary to cystic fibrosis had developed tacrolimus induced TA-TMA. Tacrolimus was stopped and replaced with cyclosporine, and complication was resolved with no subsequent complications(11).

A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS-13), a protease enzyme which splits ultra-large von Willebrand factor (vWF) multimers into smaller vWF fragments, prevents the entry of large multimers of vWF into the circulation(8). Idiopathic TTP is typically associated with ADAMTS-13 deficiency resulting from inherited defect, genetic mutation, or the acquisition of inhibitory antibodies to ADAMTS-13(12). TA-TMA and TTP have similar mechanisms such as endothelial damage; however, ADAMTS-13 deficiency is rarely observed in TA-TMA. We did not check the ADAMTS-13 activity level in our patient; therefore, this was a limitation in differentiating TA-TMA from TTP in this case.

We report an uncommon case of posttransplantation tacrolimus induced TA-TMA with gastrointestinal bleeding and severe pneumonia in a lung transplant recipient. Similar

to earlier studies(10,11), stopping tacrolimus plus plasmapheresis led to improvement of TMA; however, the patient died because of combined gastrointestinal bleeding and pneumonia.

TA-TMA is a rare but severe, life-threatening complication in lung transplant recipients; therefore, the possibility of TA-TMA should be considered in posttransplant recipients.

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