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CLINICAL REPORT

Thrombotic microangiopathy after living-donor liver re-transplantation

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Abstract Thrombotic microangiopathy (TMA) is a rare but potentially lethal complication encountered in solid organ and bone marrow transplant recipients that requires rapid recognition, diagnosis, and initiation of therapy. Several causes have been identified, including viral infections and various medications. We report a case of TMA after living-donor liver transplantation (LDLT). A 60-year-old man underwent LDLT for end-stage liver disease secondary to hepatitis C virus. After 6 months, he required re-transplantation because graft failure was caused by a small-for-size graft. The immunosuppressive regimen for the second transplantation consisted of tacrolimus and prednisolone; cyclosporine (CsA), mycophenolate mofetil, and prednisolone had been used for the first transplantation. Despite multiple transfusions of packed red blood cells and concentrated platelets, his hemoglobin and platelets decreased and lactate dehydrogenase increased following re-transplantation. Hematological evaluation revealed findings consistent with TMA. As soon as TMA was diagnosed, the calcineurin inhibitor (CNI) was changed from tacrolimus to CsA, and fresh frozen plasma (FFP) was given. The patient's platelets gradually increased after the CNI was changed, and no transfusions were needed. Therefore, tacrolimus was suspected as the cause of the patient's TMA. Early diagnosis, switching CNIs, and FFP supplementation allowed the TMA to resolve without the need for plasma exchange.

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Abbreviations

TMA	Thrombotic microangiopathy
LDLT	Living-donor liver transplantation
TTP	Thrombotic thrombocytopenic purpura
CNI	Calcineurin inhibitor
LDH	Lactate dehydrogenase
HCV	Hepatitis C virus
PE	Plasma exchange

Introduction

Among the various complications that occur after solid organ transplantation, thrombotic microangiopathy (TMA) stands out as an infrequent (5% of adult recipients developed TMA after living-donor liver transplantation (LDLT) as reported in the literature [1]) and severe life-threatening complication. TMA is known to be a microvascular occlusive disorder that is characterized by systemic or intrarenal aggregation of platelets and mechanical injury to erythrocytes [2]. Currently, this disorder is considered to encompass three clinical entities: thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and a third group including patients with a history of transplantation or use of certain drugs [mitomycin, cyclosporine (CsA), tacrolimus, and quinine]. To date, there are a few reports of TMA occurring in liver transplant recipients, which suggests that the discontinuation or dose reduction of the calcineurin inhibitor (CNI) was of pivotal importance, and plasma exchange (PE) also had an

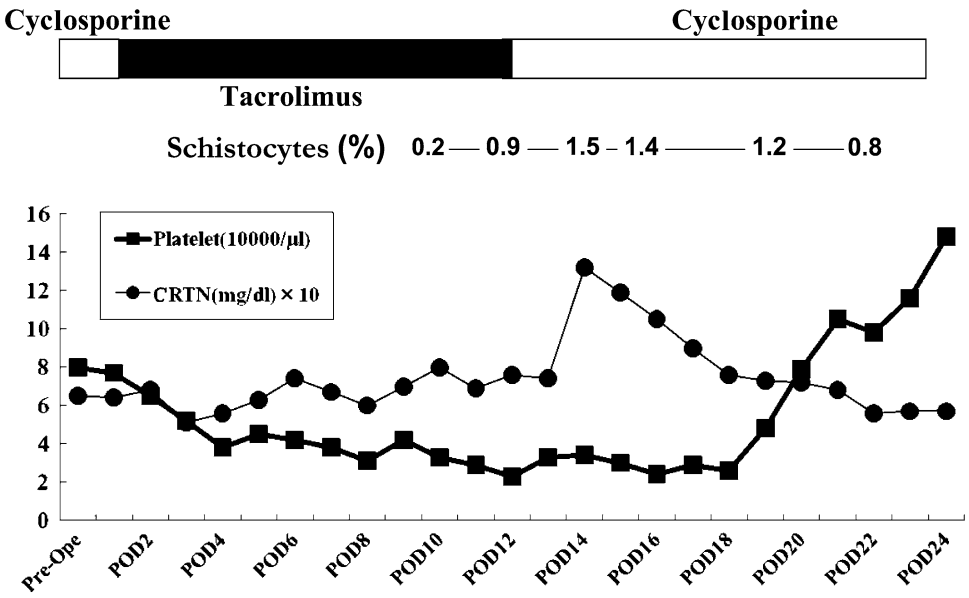

Fig. 1 Serial changes in laboratory parameters after liver transplantation (LT). Immunosuppressive agents (tacrolimus and cyclosporine, CsA) are *highlighted*. After the calcineurin inhibitor (CNI) was changed, the platelet count gradually increased and the serum creatinine was improved. The schistocytosis increased until postoperative day 14 and decreased after the change of tacrolimus. *Pre-Ope* preoperative, *POD* postoperative day, *CRTN* creatinine

important role in the management of TMA after transplantation [1]. In this article, we describe a patient who developed TMA after his second living-donor liver transplantation (LDLT).

Case report

A 60-year-old man with hepatic cirrhosis caused by hepatic C virus underwent LDLT and received a cross-match-negative and blood type-identical graft from his wife, who was healthy and had no history of previous hematological disorders or any particular family diseases. The graft weight/recipient weight ratio (GDWR) was 0.71%. The patient's liver function deteriorated as a result of biliary complications without the occurrence of acute cellular rejection or hepatitis C virus (HCV) relapse. The patient required a second transplantation because he developed secondary biliary cirrhosis 6 months after his first transplantation. He received a second living-donor graft from his son, who was healthy and had no history of previous hematological disorders. The second GDWR was 1.12%.

Posttransplantation immunosuppressive treatment was started with tacrolimus and prednisolone, although he had received CsA with his first transplantation. Tacrolimus was given orally, and the dose was adjusted to maintain a whole-blood concentration of 10–15 ng/ml until postoperative day 10. The patient was also given oral acyclovir (500 mg/day) and trimethoprim-sulphamethoxazole (1 g/day), as well as intravenous fluconazole (100 mg/day), meropenem (1 g/day), and famotidine (20 mg/day). In addition, he was given fresh frozen plasma (FFP) infusions (4–6 U daily) until postoperative day 3.

The patient was extubated on postoperative day 2. Post extubation, the patient became delirious. His renal function deteriorated; on postoperative day 14, his serum creatinine was 1.5 mg/dl, and his blood urea nitrogen was 67 mg/dl. Immediately after transplantation, there was a transient improvement in the total bilirubin (T-Bil), lactate dehydrogenase (LDH), and transaminase levels.

The patient's platelet counts declined progressively despite multiple transfusions of concentrated platelets. We gave the patient 10 or 20 U of concentrated platelets every day to maintain more than 20,000/μl until postoperative day 13. On postoperative day 14, the patient's blood cell profile showed a hematocrit of 22.5%, a white blood cell count of 12,500/μl, and a platelet count of 22,000/μl. The serial changes in laboratory parameters, including platelet counts, and serum creatinine are shown in Fig. 1.

The patient's hemostatic function was preserved, however, and the prothrombin time was 89% on postoperative day 14. A blood smear showed an increase in the number of schistocytes (1.5%) and his serum haptoglobin was also 0 mg/dl, which suggested the occurrence of hemolysis. The patient's tacrolimus trough level was not as high, and the dose was adjusted to maintain a whole-blood concentration of 5–10 ng/ml during postoperative days 10–13 for reasons of his renal dysfunction.

There was no evidence of any active infection, either viral, including cytomegalovirus (CMV), or bacterial. Thus, based on these laboratory findings and clinical features, a diagnosis of TMA was made on postoperative day 14.

The patient's subsequent management consisted of switching from tacrolimus to oral CsA microemulsion. The CsA dose was adjusted according to the whole-blood level,

with a target of 200–300 ng/ml. In addition, 4–6 U FFP was given daily for 5 days. The prednisolone dose was maintained at the same level after TMA was diagnosed, and no other medications were withdrawn or changed. The patient responded to these treatments; his platelet count and hematocrit increased steadily, and serum LDH and T-Bil levels, as well as peripheral blood schistocyte counts, decreased (see Fig. 1). The patient's renal function and delirium also improved.

On follow-up 100 days after re-transplantation, no recurrent disease was observed. Despite the CNI change, the patient did not develop acute cellular rejection.

Discussion

Tacrolimus-induced TMA was found in a patient who had a second liver transplantation. Clinically, TMA was diagnosed 14 days after re-transplantation. Early after transplantation, the patient developed a prolonged and profound thrombocytopenia and hemolytic anemia that were unresponsive to transfusion. Laboratory findings, including elevated LDH and T-Bil levels, as well as increased peripheral blood schistocyte counts, were also related to TMA. In the present case, trough tacrolimus levels were not predictive of the development of TMA, but changing CNIs resulted in improved kidney function and the hemolytic picture resolved. Because of the early diagnosis, change of CNI, and FFP supplementation, the patient developed no sequelae.

TMA must be considered in liver transplant patients treated with tacrolimus whenever persistent thrombocytopenia unresponsive to transfusion occurs. Although TMA usually responds to treatment, it may, in rare cases, lead to loss of graft function or even result in the patient's death. The development of TMA associated with CNI treatment is well documented in transplantation, especially in kidney transplant recipients [2]. In the non-transplant population, the occurrence of TMA is thought to be related to a clotting mechanism deficiency. Conversely, in transplant recipients, TMA is thought to occur as a result of direct endothelial damage caused by CNI; the hematological manifestations appear to be a secondary phenomenon [3]. However, there are few reports of TMA in living-donor liver transplant patients [1, 3, 4], and there have been no reports of TMA after re-LDLT. Thus, the present case is the first report of a patient who developed TMA after re-LDLT.

The diagnosis of TMA was based on the presence of thrombocytopenia and microangiopathic hemolytic anemia with no clinically apparent alternative etiologies [5, 6]. More specifically, microangiopathic hemolytic anemia was suggested by the sharply elevated serum LDH levels (typically >500 U/l) and the presence of fractionated erythrocytes in the blood smear. We showed that the schistocytes significantly increased after re-transplantation and were improved by the switch from tacrolimus. Two factors were considered to have caused TMA in this patient: the use of tacrolimus and his HCV infection. A zrelationship between HCV infection and TMA was recently noted in the non-transplant population [7, 8]. We gave the patients 10 or 20 U of concentrated platelets every day to maintain more than 20,000/μl, and there might be a possibility that the transfusions of concentrated platelets caused the deterioration of TMA. However, at that time, we considered a low platelet count was too dangerous for patients immediately after liver transplantation.

CNIs, such as tacrolimus and CsA, are the most likely causal agents of TMA after transplantation. The following laboratory and clinical observations support this assertion [5, 6]. First, these drugs have been shown to cause dysregulation of endothelial cells and vasoconstriction of arterioles, leading to extraordinary platelet aggregation. Second, patients with TMA improved following withdrawal of tacrolimus or CsA [1, 3–5]. Third, TMA in these settings usually occurs within 90 days of transplantation, which suggests that a relatively greater dose or blood concentration of CNI may be crucial for disease development; however, in the present case, the trough tacrolimus concentration was not high.

Thrombocytopenia is a frequent complication that usually occurs in the first week after liver transplantation [9, 10]. A correction of the early decrease in the platelet count reflects the presence of a liver that is functioning well. Several factors, such as sequestration of platelets in the reperfused liver graft, immunological reactions, increased platelet consumption, reduced platelet production, impaired production of thrombopoietin, medications, platelet transfusions, heparin-associated thrombocytopenia, hypersplenism, hemodilution, or a combination of these factors, are suspected to play a role in the development of thrombocytopenia. Nevertheless, the pathophysiology of thrombocytopenia remains unclear. Severe thrombocytopenia may lead to increased morbidity and mortality as a result of postsurgical bleeding, intracranial hemorrhage, and the inability to perform diagnostic liver and bone marrow biopsies during the early postoperative period.

The role that changing CNIs play in the treatment of TMA is not clear. It must be noted that the incidence of TMA is equivalent for both tacrolimus- and CsA-based immunosuppression. In the present case, TMA resolved immediately after the initial CNI was discontinued. This finding suggests that CNI-induced endothelial damage is a causative factor in post-LDLT TMA. Previous reports suggest that a deficiency or an inhibitor of von Willebrand factor-cleaving protease is an important factor in the occurrence of non-transplant TMA [5]. However, a recent

report suggests that post-LDLT TMA is not related to the marginal production of von Willebrand factor-cleaving protease after transplantation [4].

In conclusion, the possibility that LDLT recipients may develop TMA must be recognized. Immediate dose reduction or switching the CNI is the first-line treatment for post-LDLT TMA.

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