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A Case Report of Drug-Induced Thrombocytopenia after Living Donor Liver Transplantation

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There are few descriptions of severe thrombocytopenia during the early postoperative period after liver transplantation, and these have not been fully documented in the literature. Here, we report a case of drug-induced thrombocytopenia requiring transfusion of blood products after living donor liver transplantation. We determined that this was not caused by the interferon-free anti-viral therapy but by tacrolimus A 61-year-old woman with hepatitis C-related cirrhosis and hepatorenal syndrome underwent living donor liver transplantation using a left lobe graft from her son. After transplantation, immunosuppression consisted of tacrolimus and steroid. Seven weeks after transplantation, interferon-free therapy with daclatasvir and asunaprevir was started. Thirteen days thereafter, hepatitis C virus tested negative. However, the platelet count had begun to gradually decrease just before starting anti-viral therapy. Daclatasvir and asunaprevir were stopped because this was suspected to be a side-effect of these drugs, but the patient nonetheless went on to develop severe thrombocytopenia (platelet count 17,000/μL), which needed transfusions. Now suspecting tacrolimus as the inducer of this side effect, we changed to cyclosporin, after which the platelet count gradually recovered. Viral markers were still not detectable up to 2 months after discontinuation of the antiviral drugs. We conclude that when severe thrombocytopenia occurs, possible drug-induced thrombocytopenia as well as other disorders must be investigated.

Mild to moderate thrombocytopenia early after living donor liver transplantation (LDLT) is a common complication (1). Although many factors can contribute to thrombocytopenia after LDLT, most do not usually cause severe thrombocytopenia needing transfusion (1, 2). Few cases of severe thrombocytopenia during the early postoperative period after liver transplantation (LT) have been recorded, and they have not been fully described in the literature (1, 3-5).

Drug-induced thrombocytopenia (DIT) is a relatively uncommon adverse reaction caused by drug-dependent antibodies that react with platelet membrane glycoproteins only when the implicated drug is present (6). The incidence of DIT is not well known but is estimated to occur in 10 cases per million people per year (7). More than 100 drugs have been associated with causing DIT (8).

Here, we report a case of DIT requiring transfusion of blood products after LDLT.

CLINICAL CASE

A 61-year-old woman was considered for liver transplantation at our facility. In January 2014, she had been referred to a local hospital because of liver dysfunction and was diagnosed with hepatitis C-related cirrhosis (hepatitis C virus (HCV)-RNA 6.3 Log IU/mL, antigenicities of group 1). Although alleviation therapy was administered, the HCV load did not decrease and she was routinely followed at the outpatient clinic. In March 2015, she was hospitalized because of sepsis caused by pyelonephritis. Although antibiotic treatment improved the infection, hepatorenal syndrome could not be controlled, and she was referred to our facility for liver transplantation. A Model for End-Stage Liver Disease score of 23 was established. In June 2015, she received LDLT using a left lobe graft from her son who had the identical blood type.

The weight of the liver graft was 375g, and the graft-to-recipient body weight ratio was 0.63%. The operating time was 677 min, and blood loss was 4380 mL. The patient received 14 Units of matched arterial platelets, 34 units of fresh frozen plasma, and 10 units of platelets.

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After transplantation, immunosuppression consisted of tacrolimus and steroid. Seven weeks after LDLT, interferon-free therapy with the direct-acting antiviral (DAA) drugs daclatasvir and asunaprevir was started. Side effects of liver dysfunction remained absent and she was discharged from the hospital 7 days after the introduction of interferon-free anti-viral drug therapy. After a further 6 days, HCV became negative. However, the platelet count had gradually begun to decrease just before starting the DAA regimen. A peripheral blood smear showed normal RBCs, WBCs, but absent platelets. At this point, excluded differential diagnoses included idiopathic (autoimmune) thrombocytopenia (ITP), thrombotic microangiopathy, disseminated intravascular coagulation (DIC), consumptive coagulopathy, and acute liver graft failure. Platelet-reactive antibodies were not found and we therefore suspected drug-induced thrombocytopenia. We hypothesized that DAA were causing these side effects, and so they were stopped. However, the patient went on to develop severe thrombocytopenia (platelet count 17,000/μL), which needed transfusion. Now suspecting tacrolimus, we substituted it with cyclosporin, after which her platelet count gradually recovered. Despite discontinuing the antiviral drugs, viral markers were not detectable up to 2 months later (Figure).

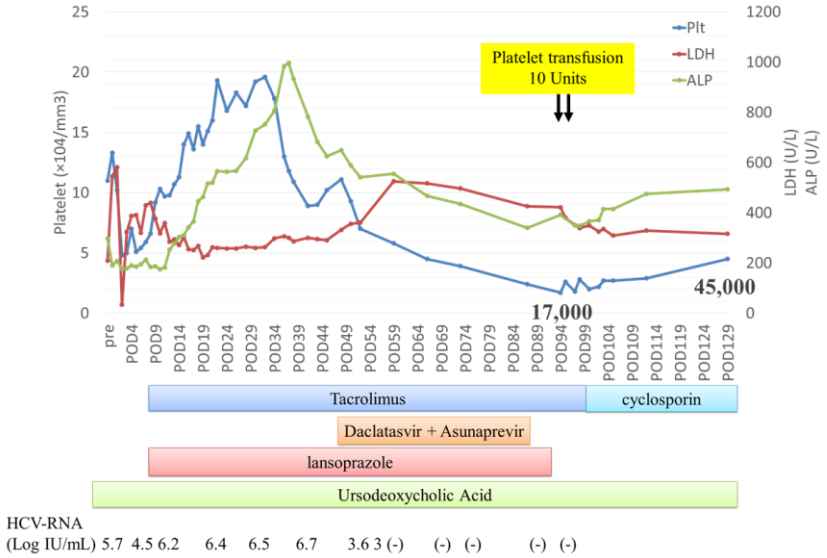

Figure. Postoperative clinical course after LDLT. After transplantation, moderate thrombocytopenia developed in the early period, and then improved. After starting the immunosuppressive regimen and interferon-free anti-viral therapy, severe thrombocytopenia developed. After discontinuing the drugs, and changing tacrolimus to cyclosporin, her platelet count gradually recovered.

DISCUSSION

Thrombocytopenia after LT can be caused by many factors, including reduced hepatic thrombopoietin production, allograft sequestration, hypersplenism, hemorrhage, heparin-induced thrompocytopenia, immunologic reactions, hemolysis, drugs, infections, platelet consumption secondary to DIC and sepsis (1, 9, 10). However, most of these factors usually cause mild to moderate, but not severe, thrombocytopenia.

Several cases of severe thrombocytopenia in the early postoperative period of LT have been described in the literature, caused by acute liver graft failure (5), thrombotic microangiopathy (3, 4), ITP transmitted by the donor (9, 11), and post-transfusion purpura (1). However, in the case reported here, all these causes of thrombocytopenia could be excluded. The temporal sequence of the development of thrombocytopenia led us to diagnose drug-induced thrombocytopenia.

The diagnosis of DIT is complicated by its similarity to other non-drug-induced immune thrombocytopenias and must be differentiated by temporal association of exposure to a candidate drug (8). Although the diagnostic criteria (Table) for drug-induced thrombocytopenia have been described (6, 12), it was difficult to determine which drug was responsible in the present case. The most effective treatment for DIT is to stop the causative drug (12, 13). We discontinued the drugs one by one and found that DAA and lansoprazole were probably irresponsible whereas changing tacrolimus to cyclosporin resulted in the platelet count gradually recovering. It is said that the platelet counts of patients with DIT typically 5 to 10 days after taking the causative agent for approximately one week, and begin to recover within 1 to 2 days after stop (6). However, the lengths of time to development or recovery vary with each case (14, 15). Although many drugs are indispensable for LDLT

recipients, it is important to avoid any future exposure to potentially thrombocytopenia-causing drugs and substitute adequate alternatives.

Criterion or Level of Evidence	Description
Criterion	
1	1) Therapy with the candidate drug preceded thrombocytopenia and 2) recovery from thrombocytopenia was complete and sustained after therapy with the drug was discontinued
2	1) The candidate drug was the only drug used before the onset of thrombocytopenia or 2) other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug with a sustained normal platetet count
3	Other vauses for thrombocytopenia were excluded
4	Re-exposure to the candidate drug resulted in recurrent thrombocytopenia
Level of evidence	
I	Definite: criteria 1, 2, 3, and 4 met
II	Probable: criteria 1,2,and 3 met
III	Possible: criterion 1 met
IV	Unlikely: criterion 1 not met

Table. Evaluation of published reports on drug-induced thrombocytopenia. The information is adapted from references 6, 12.

The recent application of DAA therapy against HCV after LT has shown good efficacy and tolerability (16-18), but cases of thrombocytopenia >Grade 3 have been reported in patients treated with asunaprevir and daclatasvir hydrochloride. For this reason, “thrombocytopenia” was added to the clinically significant adverse reactions section in the drug prescription literature in Japan.

To the best of our knowledge, this is the first report of a case of drug-induced severe thrombocytopenia after LDLT. Although the frequency of DIT caused by DAA or tacrolimus has been reported to be relatively rare, most such instances did lead to severe thrombocytopenia and accordingly further investigation is mandatory in this context.

In conclusion, although severe thrombocytopenia is not well described in liver transplant recipients, once it occurs, possible drug-induced thrombocytopenia as well as other disorders must be investigated.

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