Is sinusoidal obstructive syndrome a recurrent disease after liver transplantation? A case report

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OBJECTIVE: Sinusoidal obstructive syndrome (SOS) is a disease that damages hepatic sinusoidal endothelial cells, resulting in progressive occlusion and fibrosis of the lobular central vein and the occurrence of intrahepatic sinusoidal portal hypertension. However, SOS after liver transplantation (LT) is uncommon and potentially fatal. Here, we report a rare case of second-time recurrence of SOS after liver retransplantation (rLT).

CASE SUMMARY: A 22-year-old woman received a living donor LT due to SOS. Four years later, she developed abdominal distention and ascites with no apparent cause. She was diagnosed with recurrence of SOS and underwent rLT. But 2 mo post rLT, the patient suffered from aggravated jaundice and ascites again. She was diagnosed with second-time recurrence of SOS post rLT according to computed tomography and liver pathology. After treatment with warfarin anticoagulation and immunosuppressant conversion, she gradually recovered with improvement of liver function and liver pathology. During the 17-mo follow-up period, she was in good condition with normal liver function and no ascites.

CONCLUSION: SOS can be a recurrent disease after LT, and autoimmune antibody and genetic sequencing should be screened before LT. For susceptible patients, anticoagulant drugs should be used for an extended period, and tacrolimus or other pathogenic agents should be avoided. Early diagnosis and treatment can improve the prognosis of patients and avoid graft failure or death.

Key Words: Sinusoidal obstructive syndrome; Liver transplantation; Recurrence;
INTRODUCTION
Sinusoidal obstructive syndrome (SOS) is a rare disorder with a unique etiopathogenesis related to endothelial toxicity leading to fibrotic obliteration of the hepatic centrilobular veins with congestion and hemorrhage\(^1\,2\). Liver transplantation (LT) is an effective treatment for SOS patients with severe liver failure. SOS after LT is very rare with an incidence of 1.9%-2.9%, but it includes a risk for graft failure. Some cytotoxic drugs and/or immunologic responses may be associated with this entity, but the causes and pathophysiological processes of SOS after LT are not well known\(^3\). Onset of SOS is characterized by ascites, hepatomegaly and jaundice. Here, we describe an unusual case of second-time recurrence of SOS after liver retransplantation (rLT).

CASE PRESENTATION

Chief complaints
A 27-year-old woman came to our center due to aggravated abdominal distension and ascites for 1 mo.

History of present illness
Two months ago, she received rLT from a donation after cardiac death in our center for recurrence of SOS after LT. She recovered well and was discharged on postoperative day 25 under treatment with methylprednisolone, tacrolimus, mycophenolate mofetil and warfarin. One month later, she developed progressive abdominal distension and mild elevation of transaminase with no apparent cause. Abdominal ultrasound showed massive ascites without vascular abnormality.

History of past illness
Five years ago, she underwent a living donor LT for SOS (Figure 1). Initially she recovered well with an immunosuppressive regimen of cyclosporine A and mycophenolate mofetil. One year ago, she developed abdominal distension and ascites. She was diagnosed with recurrence of SOS by computed tomography (CT) and histopathology (Figures 1 and 2). She was treated with diuretics and anticoagulants, but her ascites and abdominal distension were aggravated, along with jaundice. She had no abnormal personal and family history.

Physical examination
Her body temperature, blood pressure, heart rate and breathing rate were within normal limits. Main positive signs were cutaneous and sclera icterus with abdominal bulge and shifting dullness.
Figure 1 Hepatic venography. A and B: Native liver showed marked sinusoidal dilatation and congestion in centrilobular regions and extensive bridging fibrosis and necrosis linking central to central areas; C: Explanted first liver graft characterized by massive perivenular congestion and hemorrhage with marked sinusoidal dilatation. Portal tract was not remarkable; D: Two months after liver retransplantation, liver biopsy was performed to clarify the diagnosis. The second liver graft liver pathology showed sinusoidal dilatation and congestion; E: In addition to warfarin, tacrolimus was switched to cyclosporine A. Two months after treatment, perivenular congestion and sinusoidal dilatation were alleviated and were only observed in the focal perivenular area; F: Nine months later, there was no perivenular congestion and only mild sinusoidal dilatation.

Laboratory examinations
Laboratory results suggested that alanine aminotransferase was 61 IU/L, glutamic oxaloacetylase was 39.9 IU/L, alkaline phosphatase was 90 IU/L, glutamyl transpeptidase was 103 IU/L, total bilirubin was 40.85 μmol/L, direct bilirubin was 31.7 μmol/L and creatinine was 130 mol/L. Tacrolimus trough level was 12.4 ng/mL. Testing for thrombophilia showed that she was positive for anticardiolipin antibody (ACL). Protein C, protein S and homocysteine were negative.

Imaging examinations
Abdominal ultrasound showed hepatomegaly with heterogenous echoes and seroperitoneum. CT revealed hepatomegaly with patchy enhancement and ascites (Figure 2). Then transjugular venography and liver biopsy were performed. Hepatic venography showed no stenosis of the hepatic vein or inferior vena cava, but hepatic
venous pressure gradient was 21 mmHg. Liver pathology showed sinusoidal dilatation and congestion (Figure 1).

FINAL DIAGNOSIS
On the basis of these findings, she was diagnosed with second-time recurrence of SOS post-rLT.

TREATMENT
Based on our past experience and literature review, tacrolimus was stopped and replaced with cyclosporine A, and warfarin was continued at 3 mg/d and was adjusted according to International Normalized Ratio (2-3).

OUTCOME AND FOLLOW-UP
After treatment, ascites gradually decreased with improvement of liver and renal function. Four months post-rLT, CT and histological examination were reviewed. The results showed that hepatomegaly, heterogeneous enhancement, sinusoidal dilatation and congestion were all relieved (Figures 1 and 2). During the 17 mo follow-up period, she was in good condition with normal liver function and no ascites.

DISCUSSION
SOS is a rare but fatal complication after LT, which can lead to graft failure and death. Although the pathogenesis of SOS after LT remains unknown, it is reported to be associated with azathioprine or tacrolimus, episodes of acute rejection, oxaliplatin-containing chemotherapy, irradiation and intake of pyrrolizidine-alkaloid-containing plants. In our case, the patient’s primary disease was SOS of unknown cause. After rLT, SOS recurred for the second time similar to the episode after the first LT. After withdrawal of tacrolimus, the patient experienced rapid clinical improvement, which was confirmed by imaging and histological examination. Tacrolimus may have potential cytotoxicity for endothelial cells and precipitate their dysregulation as reported.

In this case, it is strange that SOS occurred in the native liver and in the two subsequent liver allografts. We hypothesize that there may be something unusual in the patient initiating the thrombotic process. In our case, test for thrombotic disorder showed that ACL was positive. ACLs have been found in some patients with autoimmune disorder, acute infection or cardiovascular disease, and they have been associated with arterial and venous thrombosis. Therefore, the patient likely had a form of thrombotic disorder leading to recurrence of SOS. Anticoagulation therapy
with warfarin was administered at a dose of 3 mg/d. We performed a literature review and retrieved only two cases\cite{11,12} in which SOS recurred sequentially in the two liver allografts (Table 1). In the case Fiel et al\cite{12} reported, the patient also tested positive for high levels of ACL antibodies. Ansari et al\cite{13} observed that whole exome sequencing can find high-risk patients with genetic susceptibility in pediatric patients with SOS after hematopoietic stem cell transplantation\cite{13}. Some gene variants are associated with SOS in children receiving intravenous busulfan and cyclophosphamide before hematopoietic stem cell transplantation\cite{12}. Therefore, repeated relapse of SOS is probably associated with antibody-mediated autoimmune response or genetic susceptibility. In these patients, SOS may be a recurrent disease after LT, and autoimmune antibody and genetic sequencing should be screened before LT. During the post-LT period, anticoagulant drugs should be used for a long time and tacrolimus or other potential pathogenic agents should be avoided.

**CONCLUSION**

We reported a rare case of SOS that recurred twice in liver allografts. Treatment of anticoagulation and immunosuppressant adjustment can be effective in reducing the symptoms. Although the patient has remained asymptomatic after drug adjustment, close monitoring is still needed in case of a third relapse. Though this is a single case, with the greater understanding of the disease, further studies will be of great help for the investigation of pathogenesis.
| Ref.           | Year of publication | Age in yr | Gender | Primary disease              | Operation | IS         | ACR post LT | Time of first SOS occurrence | ACR post rLT | Time of second recurrence | Pathologic findings                             | Complication post third LT |
|---------------|---------------------|-----------|--------|------------------------------|-----------|-----------|-------------|-----------------------------|-------------|---------------------------|-----------------------------------------------|--------------------------|
| Martins et al | 2007               | 20        | F      | Type I autoimmune cirrhosis  | LT        | CsA/FK506  | Yes         | 2 yr                        | Yes         | 3 yr                      | Fibrous obliteration of centrilobular veins by connective tissue | Biliary stenosis; autoimmune hepatitis |
| Fiel et al    | 1999               | 37        | F      | Primary sclerosing cholangitis | LT        | FK506 + Pre + Aza | No          | 2 mo                       | No          | 20 mo                     | Obliteration of terminal hepatic venules by dense fibrosis | -                        |

ACR: Acute cellular rejection; IS: Immunosuppressant; LT: Liver transplantation; rLT: Liver retransplantation; SOS: Sinusoidal obstructive syndrome.

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