**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 59562

**Manuscript Type:** CASE REPORT

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

Liu Y *et al.*SOS after LT

Ying Liu, Li-Ying Sun, Zhi-Jun Zhu, Lin Wei, Wei Qu, Zhi-Gui Zeng

**Ying Liu, Zhi-Jun Zhu, Lin Wei, Wei Qu, Zhi-Gui Zeng,** Liver Transplantation Center, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

**Li-Ying Sun,** Intensive Care Unit, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China

**Author contributions:** Liu Y was involved in concept/design, data collection, data analysis/interpretation, drafting the article and critical revision of the manuscript; Sun LY conceived and designed the study; Zhu ZJ, Wei L, Qu W and Zeng ZG participated in the performance of the research; All authors issued final approval for the version to be submitted.

**Supported by** Beijing Municipal Science & Technology Commission, No. Z181100001718220.

**Corresponding author: Li-Ying Sun, PhD, Chief Doctor,** Intensive Care Unit, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong-an Road, Beijing 100050, China. sunxlx@outlook.com

**Received:** September 20, 2020

**Revised:** October 9, 2020

**Accepted:** November 29, 2020

**Published online:**

**Abstract**

BACKGROUND

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; Sinusoidal dilatation and congestion; Patchy enhancement; Case report

Liu Y, Sun LY, Zhu ZJ, Wei L, Qu W, Zeng ZG. Is sinusoidal obstructive syndrome a recurrent disease after liver transplantation? A case report. *World J Clin Cases* 2020; In press

**Core Tip:** Sinusoidal obstructive syndrome (SOS) is a complex entity with incompletely defined pathogenesis. It is also an uncommon complication after liver transplantation. We reported a rare case of SOS that recurred twice in liver allografts. We believed that this condition is uncommon and has rarely been reported in liver transplant recipients.

**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.

***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[3], episodes of acute rejection[4], oxaliplatin-containing chemotherapy[5], irradiation[6] and intake of pyrrolizidine-alkaloid-containing plants[7]. 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[8].

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[9,10]. 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[11,12] in which SOS recurred sequentially in the two liver allografts (Table 1). In the case Fiel *et al*[12] reported, the patient also tested positive for high levels of ACL antibodies. Ansari *et al*[13] observed that whole exome sequencing can find high-risk patients with genetic susceptibility in pediatric patients with SOS after hematopoietic stem cell transplantation[13].Some gene variants are associated with SOS in children receiving intravenous busulfan and cyclophosphamide before hematopoietic stem cell transplantation[14]. 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 sequencingshould 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.

**REFERENCES**

1 **Poli E**, Kounis I, Guettier C, Verstuyft C, Coilly A, Sobesky R, Feray C, Vibert E, Ciacio O, Samuel D, Bismuth H, Duclos-Vallée JC. Post-Liver Transplantation Sinusoidal Obstruction Syndrome With Refractory Ascites Induced by Mycophenolate Mofetil. *Hepatology* 2020; **71**: 1508-1510 [PMID: 31597193 DOI: 10.1002/hep.30984]

2 **Piccin A**, Sartori MT, Bisogno G, Van Schilfgaarde M, Saggiorato G, Pierro AMD, Corvetta D, Marcheselli L, Andrea M, Gastl G, Cesaro S. New insights into sinusoidal obstruction syndrome. *Intern Med J* 2017; **47**: 1173-1183 [PMID: 28707749 DOI: 10.1111/imj.13550]

3 **Shen T**, Feng XW, Geng L, Zheng SS. Reversible sinusoidal obstruction syndrome associated with tacrolimus following liver transplantation. *World J Gastroenterol* 2015; **21**: 6422-6426 [PMID: 26034381 DOI: 10.3748/wjg.v21.i20.6422]

4 **Kitajima K**, Vaillant JC, Charlotte F, Eyraud D, Hannoun L. Intractable ascites without mechanical vascular obstruction after orthotopic liver transplantation: etiology and clinical outcome of sinusoidal obstruction syndrome. *Clin Transplant* 2010; **24**: 139-148 [PMID: 19222508 DOI: 10.1111/j.1399-0012.2009.00971.x]

5 **Choi JH**, Won YW, Kim HS, Oh YH, Lim S, Kim HJ. Oxaliplatin-induced sinusoidal obstruction syndrome mimicking metastatic colon cancer in the liver. *Oncol Lett* 2016; **11**: 2861-2864 [PMID: 27073565 DOI: 10.3892/ol.2016.4286]

6 **Fan CQ**, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). *J Clin Exp Hepatol* 2014; **4**: 332-346 [PMID: 25755580 DOI: 10.1016/j.jceh.2014.10.002]

7 **Yang XQ**, Ye J, Li X, Li Q, Song YH. Pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome: Pathogenesis, clinical manifestations, diagnosis, treatment, and outcomes. *World J Gastroenterol* 2019; **25**: 3753-3763 [PMID: 31391770 DOI: 10.3748/wjg.v25.i28.3753]

8 **Li L**, Dong Y, Li RD, Tao YF, Shen CH, Wang ZX. Sinusoidal obstruction syndrome related to tacrolimus following liver transplantation. *Hepatobiliary Pancreat Dis Int* 2020; **19**: 299-302 [PMID: 32327382 DOI: 10.1016/j.hbpd.2020.03.014]

9 **Wang D**, Lv W, Zhang S, Zhang J. Advances in the Research on Anticardiolipin Antibody. *J Immunol Res* 2019; **2019**: 8380214 [PMID: 31886311 DOI: 10.1155/2019/8380214]

10 **Tsuchimoto A**, Matsukuma Y, Ueki K, Nishiki T, Doi A, Okabe Y, Nakamura M, Tsuruya K, Nakano T, Kitazono T, Masutani K. Thrombotic microangiopathy associated with anticardiolipin antibody in a kidney transplant recipient with polycythemia. *CEN Case Rep* 2019; **8**: 1-7 [PMID: 30073489 DOI: 10.1007/s13730-018-0354-x]

11 **Martins A**, Monteiro E, Freire A, Carvalho A, Veloso J, Morbey A, Carrilho I, Martins A, Barroso E. Hepatic veno-occlusive disease after liver transplantation: an unusual case report. *Transpl Int* 2007; **20**: 1072-1073 [PMID: 17850233 DOI: 10.1111/j.1432-2277.2007.00548.x]

12 **Fiel MI**, Schiano TD, Klion FM, Emre S, Hytiroglou P, Ishak KG, Suriawinata A, Thung SN. Recurring fibro-obliterative venopathy in liver allografts. *Am J Surg Pathol* 1999; **23**: 734-737 [PMID: 10366158 DOI: 10.1097/00000478-199906000-00015]

13 **Ansari M**, Petrykey K, Rezgui MA, Del Vecchio V, Cortyl J, Ralph RO, Nava T, Beaulieu P, St-Onge P, Jurkovic Mlakar S, Huezo-Diaz Curtis P, Uppugunduri CRS, Lesne L, Théoret Y, Chalandon Y, Bartelink IH, Boelens JJ, Bredius RGM, Dalle JH, Lewis V, Kangarloo BS, Peters C, Sinnett D, Bittencourt H, Krajinovic M; Pediatric Disease Working Party of the European Society for Blood and Marrow Transplantation. Genetic Susceptibility to Hepatic Sinusoidal Obstruction Syndrome in Pediatric Patients Undergoing Hematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transplant* 2020; **26**: 920-927 [PMID: 31790828 DOI: 10.1016/j.bbmt.2019.11.026]

14 **Huezo-Diaz Curtis P**, Uppugunduri CRS, Muthukumaran J, Rezgui MA, Peters C, Bader P, Duval M, Bittencourt H, Krajinovic M, Ansari M. Association of CTH variant with sinusoidal obstruction syndrome in children receiving intravenous busulfan and cyclophosphamide before hematopoietic stem cell transplantation. *Pharmacogenomics J* 2018; **18**: 64-69 [PMID: 27779248 DOI: 10.1038/tpj.2016.65]

**Footnotes**

**Informed consent statement:** Informed written consent was obtained from the patient for publication of this report and any accompanying images.

**Conflict-of-interest statement:** The authors declare that they have no conflicts of interest.

**CARE Checklist (2016) statement:** The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** September 20, 2020

**First decision:** September 29, 2020

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

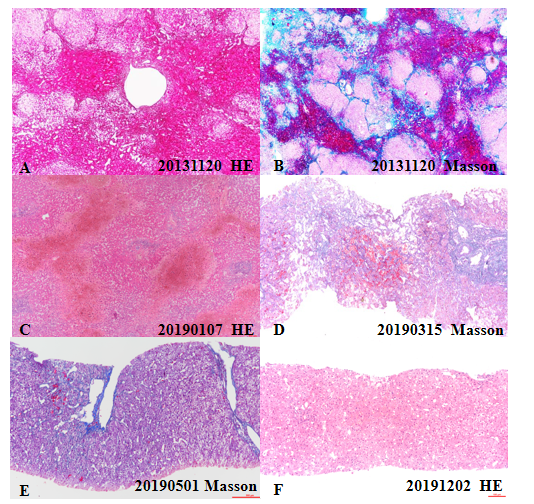
Grade C (Good): 0

Grade D (Fair): 0

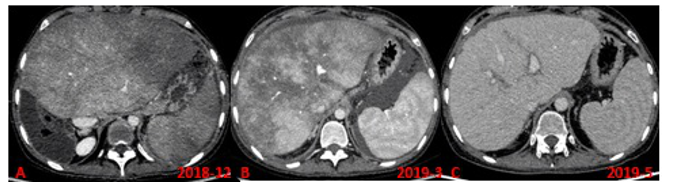
Grade E (Poor): 0

**P-Reviewer:** Rauchfuss F **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:**

**Figure Legends**



**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 dilation 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.



**Figure 2 Computed tomography image.** A: Before liver retransplantation, computed tomography (CT) showed hepatomegaly and heterogeneous, patchy enhancement; B: Two months later, the patient complained of abdominal distension. CT revealed hepatomegaly with patchy enhancement and ascites; C: Two months after treatment with anticoagulation and immunosuppressant conversion, CT showed alleviation of hepatomegaly and heterogeneous enhancement.

**Table 1 Summary of the cases reported**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| 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*[11] | 2007 | 20 | F | Type Ⅰ autoimmune cirrhosis | LT | CsA/FK506 + Pre + Aza | Yes | 2 yr | Yes | 3 yr | Fibrous obliteration of centrilobular veins by connective tissue | Biliary stenosis; autoimmune hepatitis |
| Fiel *et al*[12] | 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.