Fibroprogression and Cirrhosis Occurring in Living Liver Donor: First Case Report

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Background: **Limited dead donor pool paved the way for living liver donation so that waitlist mortality could be reduced. With over two decades of experience in the East as well as in the West, right lobe adult-to-adult living donor liver transplantation has become an established intervention. The short-term surgical outcomes, complications and health-related quality of life are well known. There is dearth of data on long-term health of remnant liver of donors, especially after a decade of donation.** ***Case description:*** **A 56-year-old lady who donated her right liver lobe 11 years back for her husband with end-stage liver disease. Recipient is doing well till date. She was incidentally found to have thrombocytopenia on follow-up. Her haematological evaluation was negative for blood dyscrasias. Further evaluation demonstrated biopsy-proven cirrhosis with endoscopic evidence of portal hypertension. Aetiological workup was done, which ruled out viral, autoimmune causes as well as Wilson's disease and hemochromatosis. This donor had gained weight post-donation with body mass index of 32.4 kg/m^2 and dyslipidaemia. The final diagnosis of fibro progression due to non-alcoholic fatty liver disease was made.** ***Conclusion:*** **We report the first case of cirrhosis developing in a right lobe living liver donor. While selecting living liver donors, extensive evaluation is done to rule out all potential aetiologies remaining silent but later could lead on to chronic liver disease. Although all other aetiologies, which could induce inflammation and fibrosis, are ruled out at the time of donation, lifestyle liver disease, especially non-alcoholic fatty liver disease, can occur in remnant liver post-donation. This case underscores the importance of regular follow-up of liver donors.** **(J Clin Exp Hepatol 2023;13:538–541)**

Case report

Living donor liver transplantation has curtailed waitlist mortality and has become standard of care in many countries where there are no robust dead donor programmes. With more than three decades of cumulated experience in the East as well as the West, the short-term complications and health-related quality of life (HRQOL) of living donors are well known.[1,2] There is dearth of literature on long-term health of remnant liver, especially focussing on fibro progression. As all hidden aetiologies are extensively evaluated during donor selection process, possibility of chronic liver disease in the donor or transformation into cirrhosis is unlikely. Most liver units do not engage living donors on a periodic follow-up protocol. Although most aetiologies are ruled out, the lifestyle liver disorders, namely, alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD), can progress in the donors. There is no published English literature on cirrhosis occurring in a liver donor. We present the first case of liver cirrhosis occurring in a right lobe donor. The presentation of this case is in accordance with CARE reporting checklist, and written informed consent was obtained from the patient.

CASE REPORT

A 56-year-old asymptomatic female who recently got enrolled in our liver clinic with history of right lobe liver donation for her husband who was suffering from end-stage liver disease, 11 years back. She had not undergone any periodic check-ups after donation. Before reaching the liver clinic, while getting evaluated for dyspeptic symptoms, she was found to have thrombocytopenia and hence was referred to the haematology clinic. Extensive evaluation was done by the haematologist; serum protein electrophoresis revealed the presence of M band between the alpha-2 and beta-1 chain. Bone marrow aspiration was done for evaluation of multiple myeloma and was reported as normocellular marrow with erythroid preponderance. Fluorescence in situ hybridisation for del 13q, del 17p, IgH/CCND1 translocation was done, and it was reported negative. There was no haematological diagnosis, which could explain her thrombocytopenia. Abdominal ultrasonogram revealed fatty liver disease, and hence, she attended the liver clinic. Her platelet count was 66,000/cu.mm, total bilirubin of 1.56 mg/dL with a direct fraction 0.6 mg/dL,

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Abbreviations: ALD: alcoholic liver disease; BMI: body mass index; CT: computed tomography; HRQOL: health-related quality of life; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis
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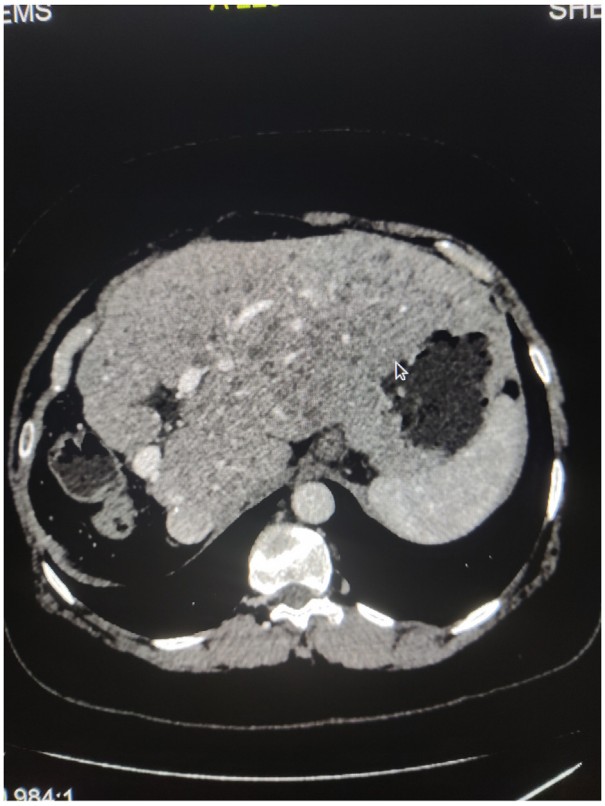

Figure 1 Axial computed tomography section of upper abdomen in venous phase. Arrow – the liver shows altered attenuation with hypertrophy of caudate and rest of remnant liver. Surface appears irregular with multiple regenerative nodules.

aspartate aminotransferase 40U/L, alanine aminotransferase 36U/L, alkaline phosphatase 80U/L, albumin of 4 g/dL, and globulin 3.4 g/dL. Computed tomography (CT) abdomen was reported as cirrhosis of remnant left lobe of liver with hypoechoic nodules and splenomegaly (Figure 1). There were no lesions enhancing in the arterial phase, and her alpha fetoprotein and prothrombin in vitamin K absence-2 were within normal limits. She had undergone right lobe liver donation in 2009 at the age of 45 years. At the time of liver donation, she did not have diabetes mellitus, systemic hypertension or dyslipidaemia. Donor evaluation protocol with serovirology panel had ruled out all aetiologies, which could potentially induce chronic liver disease. Liver steatosis assessment at the centre where she underwent donation in 2009 was radiological, plain CT to choose multiple regions of interest in spleen and liver to compare the attenuation difference; liver attenuation index before donation was +7, aspartate aminotransferase (AST) 39, platelet count 279 $\times$ 10^9/L and AST to platelet ratio index (APRI) before donation: 0.314. Although predonation liver biopsy was not performed, based on these parameters, clinically relevant fibroprogression was unlikely. Her current body mass index (BMI) is 32.4 kg/m^2, BMI at the time of donation was 26 kg/m^2; gained approximately 16 kg over 11 years. No metabolic syndrome was present at the time of donation, and she had normal liver function test, albumin to globulin ratio 1.3, fasting lipid profile and fasting blood sugar unremarkable at the time of donation. Now she has dyslipidaemia, is normotensive and has not developed type 2 diabetes.

The recipient, her husband, has an uneventful follow-up till date, enjoying good quality of life and graft health. Repeat aetiological workup was done during current liver clinic visit, which revealed negative autoimmune markers – antinuclear antibody, liver kidney microsomal antibody, antismooth muscle antibody, liver cytosol, soluble liver antigen and antimitochondrial antibody. Viral serologies for both hepatitis C and hepatitis B, including anti-hepatitis B core antibody, were negative. Serum ceruloplasmin level was 28 mg/dL, serum ferritin of 431 ng/mL with percentage transferrin saturation of 34%. Her shear wave elastography value was 14.1 Kpa. Liver biopsy was performed, which confirmed features of cirrhosis and 15–20% steatosis. There was lymphoplasmacytic inflammation at peri septal area, but her serum globulin level was normal, and autoimmune markers were negative (Figure 2a and b).

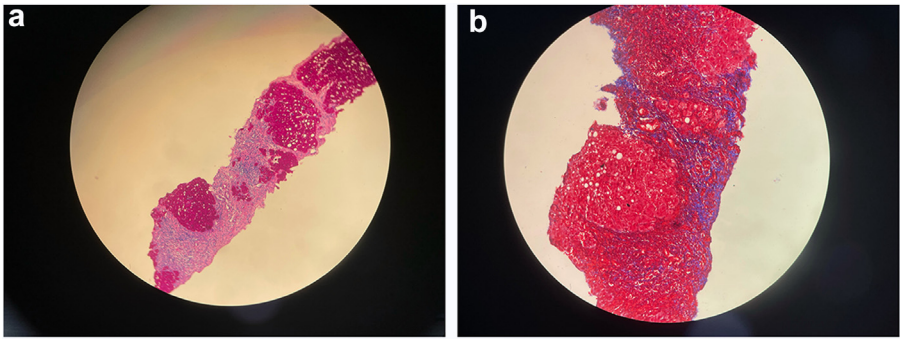

Figure 2 (a) Liver biopsy: Periodic acid–Schiff (PAS)-stained section (50×) – Hepatocytes show PAS positivity arranged in the form of nodules with widened portal tracts. (b) Masson's trichrome (MT)-stained section (100×) high lighting architectural distortion with hepatocytes arranged in nodular form and fibrotic bands.

Time since liver donation was 11 years. Her BMI is 32.4 kg/m^2, waist circumference of 87 cm. Finally, diagnoses of NAFLD-induced cirrhosis of remnant liver was made. Upper gastrointestinal endoscopy showed the presence of grade 2 oesophageal varices and mild portal hypertensive gastropathy. Hence, she was initiated on carvedilol at the dose of 3.125 mg twice daily.

DISCUSSION

The adult-to-adult living donor liver transplantation consortium observed that a subset of patient after donation demonstrated low platelet count, which was then attributed to change in spleen size rather than the possibility of underlying fibro progressive liver disease.[3] Similarly, a Chinese cohort observed that platelet count reduction from baseline evaluation to year 3 was 18.2%. Splenic volumes at the postoperative follow-up time points were significantly higher than those at baseline.[4] A study done by Murad *et al.* that followed up 97 donors observed similar findings of low platelet count and increased spleen volume.[5] All these three studies have observed a low platelet count in donors posthepatectomy on long-term follow-up and attributed it to increase in spleen size but overlooked the possibility of underlying fibro progression changes that could have led to thrombocytopenia.

Our patient had thrombocytopenia, which prompted haematological evaluation to begin with. It is a well-known fact that drop in platelet count occurs in fibro-progressed liver disease, and a value below 1.5 lakh/dL signifies clinically significant portal hypertension, which equates to the presence of grade 2 varices on esophagoscopy.[6] The noninvasive tests APRI and FIB4 are based on this phenomenon of dropping platelets in fibro progression and portal hypertension.

During the assessment of donors, before donation, all aetiologies, which induce chronic liver disease, are ruled out routinely by carrying out predonation assessment protocol, which includes a serovirology panel as well as imaging and predonation biopsy if indicated.[7] Still, two aetiologies post-donation, which could potentially induce chronic liver disease and fibro progression, are the lifestyle liver disorders, *viz*, NAFLD and ALD. Unfortunately, there is no uniform protocol for follow-up of liver donors, although societal guidelines have been put forth.[8,9] Some transplant units do not engage liver donors on a regular follow-up at all. Regarding long-term survival of donors, a recent Korean data points towards increased mortality in the long term compared with general population.[1] This first case of cirrhosis in liver donor, which we report here, stresses the importance of sticking to the existing guidelines – laboratory tests for liver function and platelet counts should be checked at follow-up for at least 1 year, all donors should be advised to have lifetime annual primary care examinations for health maintenance.[8] In the donors who do develop NAFL and Met Syndrome on follow-up may be subjected to a more meticulous evaluation.

Living donor transplantation is performed more often in Asia than in the West. The prevalence of NAFLD among Asian population is on the rise, with data pointing towards non-alcoholic steatohepatitis (NASH) turning more aggressive in recent years.[10,11] It is a common practice to optimise donors with fatty liver before donor surgery by inducing weight loss;[12,13] this facilitates perioperative outcomes and recovery but mandates meticulous long-term follow-up aiming at diet and lifestyle modifications, maintaining ideal body weight to prevent clinically significant fibro progression in the long run.

The timelines of cirrhotic transformation in our donor seem to be quite short; conventionally, it is believed that it takes 2 to 3 decades for NAFLD to evolve into cirrhosis, but recent reports suggest possibility rapid fibro progression in NASH.[14,15] There is no data till date, implicating bearing of liver donation on the progression of NASH. The question of whether accelerated fibro progression occurs in the remnant liver compared with native liver is to be addressed in large-scale biopsy-based studies.

Although short-term outcomes and HRQOL of right lobe liver donation are known, there is dearth of data on long-term liver remnant health. We report the first case of cirrhosis occurring in right lobe liver donor in published English literature. This case underscores the importance of adherence to guidelines while following up on liver donors. Biopsy-based, large-scale multicentric studies, especially on donors with metabolic syndrome beyond 10 years of donation, is warranted.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

V.K.: contributed to writing original draft, visualisation and resources.

J.J.: visualisation, writing, reviewing and editing the article.

P.G.P.: contributed to writing review and editing the article.

H.R.N.: contributed to conceptualisation, supervision, writing, reviewing and editing.

CONFLICTS OF INTEREST

The authors have none to declare.

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Case report

REFERENCES

1. Hong SK, Choe S, Yi NJ, et al. Long-term survival of 10,116 Korean live liver donors. *Ann Surg*. 2021 Aug 1;274:375–382. https://doi.org/10.1097/SLA.0000000000003752. PMID: 31850982.
2. Rela M, Reddy MS. Living donor liver transplant (LDLT) is the way forward in Asia. *Hepatol Int*. 2017;11:148–151. https://doi.org/10.1007/s12072-016-9780-z.
3. Emond JC, Fisher RA, Everson G, et al. Changes in liver and spleen volumes after living liver donation: a report from the adult-to-adult living donor liver transplantation cohort study (A2ALL): liver and spleen volumes after living liver donation. *Liver Transplant*. 2015;21:151–161. https://doi.org/10.1002/lt.24062.
4. Lei JY, Wang WT. Platelet count reduction and outcomes in living liver donors. *Hepatobiliary Pancreat Dis Int*. 2014;13:25–31. https://doi.org/10.1016/S1499-3872(14)60003-3.
5. Murad SD, Fidler JL, Poterucha JJ, et al. Longterm clinical and radiological follow-up of living liver donors: longterm Follow-Up of Living Liver Donors. *Liver Transplant*. 2016;22:934–942. https://doi.org/10.1002/lt.24442.
6. de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII - renewing consensus in portal hypertension. J Hepatol. Published online December 2021:S0168827821022996. doi:10.1016/j.jhep.2021.12.022.
7. Nugroho A, Kim OK, Lee KW, et al. Evaluation of donor workups and exclusions in a single-center experience of living donor liver transplantation. *Liver Transplant*. 2017;23:614–624. https://doi.org/10.1002/lt.24762.
8. Miller CM, Durand F, Heimbach JK, et al. The international liver transplant society guideline on living liver donation. *Transplantation*. 2016;100:1238–1243. https://doi.org/10.1097/TP.0000000000001247.
9. Manas D, Burnapp L, Andrews PA. Summary of the British transplantation society UK guidelines for living donor liver transplantation. *Transplantation*. 2016;100:1184–1190. https://doi.org/10.1097/TP.0000000000001128.
10. Chalmers J, Ban L, Leena KB, et al. Cohort profile: the Trivandrum non-alcoholic fatty liver disease (NAFLD) cohort. *BMJ Open*. 2019;9e027244 https://doi.org/10.1136/bmjopen-2018-027244.
11. Li J, Zou B, Yeo YH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999–2019: a systematic review and meta-analysis. *The Lancet Gastroenterology & Hepatology*. 2019;4:389–398. https://doi.org/10.1016/S2468-1253(19)30039-1.
12. Rose JT, Vargas P, Seay T, et al. Lose weight to donate: development of a program to optimize potential donors with hepatic steatosis or obesity for living liver donation. *Transplantation Direct*. 2021;7e702 https://doi.org/10.1097/TXD.0000000000001161.
13. Choudhary NS, Saraf N, Saigal S, et al. Rapid reversal of liver steatosis with life style modification in highly motivated liver donors. *Journal of Clinical and Experimental Hepatology*. 2015;5:123–126. https://doi.org/10.1016/j.jceh.2015.04.002.
14. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol*. 2015;13:643–654. https://doi.org/10.1016/j.cgh.2014.04.014. e9.
15. Loomba R, Wong R, Fraysse J, et al. Nonalcoholic fatty liver disease progression rates to cirrhosis and progression of cirrhosis to decompensation and mortality: a real world analysis of Medicare data. *Aliment Pharmacol Ther*. 2020;51:1149–1159. https://doi.org/10.1111/apt.15679.

APPENDIX A

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.12.004.