Successful Treatment of Rapid Onset, Symptomatic de novo Non-alcoholic Steatohepatitis Following Liver Transplantation: A Case Report

Justin R. Cuschieri*, Bijo K. John†, Ronald Miick‡, Jorge A. Ortiz§, Nikroo Hashemi||

*Division of Gastroenterology, Albert Einstein Medical Center, Philadelphia, PA, †Division of Gastroenterology, University of Florida College of Medicine, ‡Department of Pathology, Albert Einstein Medical Center, §Division of Transplant Surgery, Albert Einstein Medical Center and ||Division of Hepatology and Liver Transplantation, Albert Einstein Medical Center, United States

A 45 year old female with a body mass index (BMI) of 24 underwent successful liver transplantation (LT) for alcoholic cirrhosis using a donor liver from an obese woman with microvesicular steatosis (80%) and minimal macrovesicular steatosis (5–10%) on liver biopsy. Ascites and hepatosplenomegaly developed soon after LT with progressive increase of serum alkaline phosphatase to 1340 IU/L while aspartate aminotransferase (AST), and alanine transaminase (ALT), and total bilirubin remained normal. Imaging showed marked hepatomegaly, extensive fatty infiltration of the liver, and compression of the hepatic veins with narrowing of the intrahepatic inferior vena cava (IVC). Liver biopsy on post-operative day 39 revealed 90–100% macrovesicular steatosis, steatohepatitis, and portal fibrosis. A hepatic venogram showed a 10 cm segment of intrahepatic IVC stenosis that was stented, improving portal venous pressure measurements. However, portal hypertension requiring diuretic therapy and multiple paracenteses remained. By 3 months after LT, her liver had grown to 22 cm, transaminases increased 2–4 times the upper limit of normal with a 2:1 AST to ALT ratio. Liver biopsy at post-LT day 82 showed no change in steatosis and steatohepatitis despite corticosteroid withdrawal and interval periportal and perisinusoidal fibrosis. 12 weeks after LT, the patient was found to have low apolipoprotein B (65 mg/dL), high-density lipoprotein (HDL) (<10 mg/dL), low-density lipoproteins (LDL) (9 mg/dL), and total cholesterol (<50 mg/dL) levels. Therapy was started for NASH with high dose (800 IU daily) vitamin E and pioglitazone 15 mg daily, and she received topical vegetable oil and oral essential fatty acid supplements. Liver enzymes normalized after 3 months and her lipid profile improved markedly (HDL 27 mg/dL, total cholesterol 128 mg/dL), with progressive decrease in liver size and resolution of ascites after 5 months of therapy. At 2 years post-LT, the liver enzymes remain normal and lipids have normalized. (J CLIN EXP HEPATOL 2013;3:70–74)

Posttransplant NASH

Recurrent non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are known complications following orthotopic liver transplantation (LT), but rarely occur in patients without features of the metabolic syndrome. We present a case of

rapidly progressive de novo NASH leading to the development of portal hypertension soon after LT. Treatment of NASH and essential fatty acid deficiency (EFAD) was associated with marked clinical, biochemical, and radiographic improvement.

Keywords: liver transplantation, non-alcoholic fatty liver disease, portal hypertension, NAFLD, NASH

Received: 4.12.2012; **Accepted:** 15.1.2013; **Available online:** 26.1.2013

Address for correspondence: Nikroo Hashemi, Division of Hepatology and Liver Transplantation, Albert Einstein Medical Center, United States. Tel.: +1 267 421 7425

E-mail: hashemin@einstein.edu

Abbreviations: NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; LT: liver transplantation; EFAD: essential fatty acid deficiency; BMI: body mass index; IVC: inferior vena cava; HVP: hepatic venous pressure gradient; ALT: alanine transaminase; AST: aspartate aminotransferase; CT: computed tomography; PO: per os (oral); LDL: low-density lipoproteins; HDL: high-density lipoproteins; PIVENS: pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis

<http://dx.doi.org/10.1016/j.jceh.2013.01.001>

CASE REPORT

Our patient is a 45 year old Caucasian female with a pre-transplant BMI of 24 who was transplanted for biopsy proven alcoholic cirrhosis. Her MODEL FOR END-STAGE LIVER DISEASE (MELD) at transplantation was 42; she was very ill, admitted to the ICU and suitable organs for transplantation at the time were limited. The donor was a 38 year old female with a BMI of 38 who died of head trauma. A biopsy of the donor liver showed marked microvesicular steatosis (80%) and minimal macrovesicular steatosis (5–10%) (Figure 1A). The donor liver was well matched to the recipient in size, the transplant surgery was uncomplicated, and the immediate post-operative

Figure 1 Histological progression of post-transplant steatohepatitis. A: the pre-transplant donor biopsy shows minimal macrovesicular steatosis (5–10%) with marked microvesicular steatosis (80%); B: marked macrovesicular steatosis (90–100%) with steatohepatitis on post-operative day 39 (hematoxylin and eosin stain 200 $\times$).

course was uneventful. Post-LT immunosuppression consisted of tacrolimus (Astellas®, Chicago, IL), mycophenolate mofetil (Genentech®, San Francisco, CA), and corticosteroids. Four weeks after transplant, she developed ascites and hepatosplenomegaly with progressive increase of serum alkaline phosphatase to 1340 IU/L while AST, ALT, and total bilirubin remained normal. Ultrasound showed massive hepatomegaly (19 cm in the sagittal dimension) with extensive fatty infiltration and computed tomography (CT) of the abdomen revealed compression of the hepatic veins with narrowing of the intrahepatic inferior vena cava (IVC) (Figure 2). Liver biopsy on post-operative day 39 revealed 90–100% macrovesicular steatosis, steatohepatitis (NAFLD Activity Score 5/8), and portal fibrosis (Figure 1B). Hepatic venogram showed a 10 cm segment of intrahepatic IVC stenosis (Figure 3A). Three

Figure 2 Coronal CT of the abdomen and pelvis at one month post-transplant reveals diffuse, extensive fatty changes of the liver, splenomegaly, ascites, and narrowing of the IVC as it passes through the liver.

5 mm $\times$ 30 mm Z-stents were placed across the area of focal stenosis (Figure 3B). The atrio-caval gradient subsequently decreased from 23 mmHg to zero, while the hepatic venous pressure gradient (HVPg) was 4 mmHg. Two weeks later, venography and portal pressure measurements revealed an atrio-caval gradient of 3 mmHg but an increased HVPg of 21 mmHg. Over the next two months, the patient required multiple therapeutic paracenteses and diuretic therapy for recurrent ascites. By three months after transplant, her liver had grown to 22 cm on ultrasound with splenomegaly present. Transaminases increased to 2–4 times the upper limit of normal with a 2:1 AST to ALT ratio. A repeat liver biopsy at post-LT day 82 showed no change in steatosis and steatohepatitis despite corticosteroid withdrawal, and interval periportal and perisinusoidal fibrosis (stage 2/4 Brunt classification). Undetectable serum ethanol levels pre- and post-LT plus confinement to the hospital for one and a half months after transplant confirmed sobriety. Her weight had gone unchanged (pretransplant compared with post-paracentesis weight). She had bouts of noninfectious diarrhea, the etiology of which was not confirmed, but suspected to be secondary to transplant-related medications. Qualitative fecal fat was positive, quantitative test was not performed due to the patient's inability to tolerate a high-fat diet. She also did not meet her nutritional needs after transplant (estimated to be less than 75% of the recommended caloric intake), but did tolerate liquid nutritional supplementation in addition to part of a regular hospital diet. Twelve weeks after LT, essential fatty acid and apolipoprotein B deficiency was documented with low apolipoprotein B assays (65 mg/dL, normal 500–1300 mg/dL), high-density lipoprotein (HDL) (<10 mg/dL, normal 35–80 mg/dL), low-density lipoproteins (LDL) (9 mg/dL, normal 0–100 mg/dL), and total cholesterol (<50 mg/dL, normal 120–200 mg/dL). Levels of fat soluble vitamins were not processed. At no point were there signs of a rash or other clinical manifestations of a vitamin deficiency. Therapy was started for NASH with high dose (800 IU daily) vitamin E and pioglitazone 15 mg daily, and she received topical vegetable oil and oral essential fatty acid supplements in the form of fish oil capsules, 2000 mg daily. Liver

Figure 3 Hepatic and caval venograms before and after angioplasty. Fluoroscopic images of the right upper quadrant: A: the inferior portion of the SVC, right atrium, and IVC can be appreciated following injection of contrast by a 6 French catheter. A 10 cm segment of stenosis in the intrahepatic portion of the IVC is seen resulting from compression by the surrounding parenchyma of the transplanted liver; B: the intrahepatic IVC following the placement of Z-stents in the area of focal stenosis with subsequent resolution of the atrio-caval gradient.

enzymes normalized after three months and her lipid profile improved markedly (HDL 27 mg/dL, cholesterol 128 mg/dL), with progressive decrease in liver size and resolution of ascites after five months. Ten months after transplant, hepatic sonography revealed patent hepatic vasculature, absence of ascites, and a liver span of 15.9 cm with diffusely increased parenchymal echogenicity consistent with steatosis. She has remained on vitamin E, pioglitazone, and fish oil with normal liver enzymes and continued improvement in her lipid profile (HDL 64 mg/dL, cholesterol 180 mg/dL, LDL 99 mg/dL).

DISCUSSION

It is well established that the prevalence and severity of the metabolic syndrome increase along with obesity after transplant.¹ Post-LT NAFLD is somewhat common in patients with a phenotypic predisposition—that is, those who display features of the metabolic or insulin resistance syndrome. For example, the incidence of NAFLD in those transplanted for cryptogenic cirrhosis has been seen in up to 100% of patients after five years.² Up to 40% of patients transplanted for non-NAFLD related disease have been found to develop post-LT steatosis with 13% developing steatohepatitis at a mean follow up of 44 $\pm$ 4 months.³ There is a significant association with higher post-transplant BMI, with an odds ratio reported as high as 19 if the increase in BMI is greater than 10.^{3,4} Risk factors for recurrent or de novo NAFLD from cross-sectional, post-transplant studies include post-transplant weight gain, diabetes mellitus/insulin resistance, decreased HDL-cholesterol, elevated total cholesterol, and hypertension—with the use of corticosteroids and calcineurin inhib-

itors contributing to the development of these conditions in the post-transplant setting.^{2,5}

When steatosis recurs, it usually does so in an insidious fashion. Approximately 25% of patients develop steatosis within one year, and nearly 50% develop it by four years post-transplant.^{2,3} In patients whose underlying disease is alcohol, 12.5% will develop grade 2 or higher steatosis at 4 months, and 15% by 12 months.⁶ The time course of de novo NAFLD and NASH is less well defined. Seo et al documented de novo NAFLD and NASH during liver biopsy at 16 months or more post-LT. Contos et al found steatosis grades 3 and 4 only in allograft biopsies performed more than six months after LT.² To our knowledge, no trial or case report has documented such rapid development of severe, de novo NAFLD or NASH as seen in here.

Although it would have been preferable to use a donor liver with less steatosis, our patient had a very high MELD and more suitable organs at that time were lacking. However, transplantation utilizing steatotic livers is commonplace and appears to be safe. Fishbein et al in their review of 426 transplants comparing donor livers having at least 30% microvesicular steatosis with those that had <30% microvesicular steatosis found the rates of primary nonfunction, graft survival, and one year survival to be similar in both groups.⁷ In addition, graft survival does not appear to be affected by the degree of donor steatosis when other contraindications are absent and donor livers are carefully selected, even when grafts with >30% steatosis are utilized.^{1,8–10} Our patient's operation was uncomplicated, cold ischemic time was 7 h and 38 min, and although blood products were needed, there was no pressor requirement. Based on the success of the transplant by

most objective standards, we have no reason to believe that an oxidative insult secondary to poor blood flow would explain the rapid development of NAFLD.

The donor liver in this case made a remarkable transformation from having microvesicular steatosis prior to transplant to macrovesicular steatosis several weeks post transplant. We were not able to determine why this striking histologic alteration took place. The differential diagnosis for macrovesicular steatosis includes nutritional alterations such as total parental nutrition, starvation, rapid weight loss, cachexia, alcohol, and corticosteroids.¹¹ It is well established in animal models that starvation leading to hepatic steatosis can result from EFAD.¹² It has also been shown in rats that EFAD may be associated with rapid development of hepatomegaly resulting from fatty infiltration evident as early as the first day of hyperalimentation with fat-free infusate.¹³ However, it is impossible to extrapolate such findings to humans in an uncontrolled setting.

Although not previously described in humans, the possibility that EFAD led to profound macrovesicular steatosis, resultant hepatomegaly and portal hypertension is worth considering. We estimate that she was getting at least 800–1000 calories per day from her diet based on nutrition assessments. We cannot rule out the possibility of steatorrhea leading to or complicating EFAD without a quantitative fecal fat test. We know from studies on humans that malabsorption of greater than 25–50% of dietary fat leads to biochemical signs of EFAD but do not necessarily coincide with clinical effects in the short term.¹⁴ It has been shown in post-operative adult patients receiving total parenteral nutrition without fat that the development of EFAD and concomitant dermatitis can occur as early as four weeks.¹⁵ However, it is unlikely that the rapidly progressive course in our patient would have been the result of EFAD alone when the patient was taking between 25 and 50% of a balanced diet unless there was profound malabsorption of fat, in which case one would expect to find other clinical manifestations of fat soluble vitamin deficiency.

Except for the addition of topical vegetable oil and oral essential fatty acids, our patient's therapy was the same as that used in the pioglitazone versus vitamin E versus placebo for the treatment of non-diabetic patients with non-alcoholic steatohepatitis (PIVENS) trial—insulin sensitization using the thiazolidinedione—pioglitazone, and an antioxidant—vitamin E. While the PIVENS trial documented overall improvement in their patients over 96 weeks, we saw chemical and biochemical improvement in our patient in three months, with resolution of ascites and hepatomegaly by five months.¹⁶ Our findings are confounded by loose stool that tested positive for fecal fat and inadequate per os (oral) (PO) intake; both of which improved near the time our therapy for NASH was initiated. Furthermore, partial regression of fatty changes in patients with de novo NAFLD and NASH post-LT without mention of specific

medical therapy can and does occur.² It is difficult to postulate whether or not this patient would have improved had no therapy been initiated as a syndrome of this sort has not been previously described.

De novo NASH can occur in a patient transplanted for alcoholic cirrhosis. This is a rare phenomenon when it occurs in the absence of the metabolic syndrome or its components. The donor liver did have a high degree of microvesicular steatosis, but this has not been linked to the development of de novo NASH. The only identifiable risk factors were medications such as steroids and calcineurin inhibitors—which could potentiate insulin resistance and contribute to oxidative stress in the transplanted liver, and EFAD that has been linked to hepatic steatosis and hepatomegaly in animal models. However, the rapidity with which this patient developed severe macrovesicular steatosis, NASH, and portal hypertension secondary to hepatic outflow obstruction has not been described previously, regardless of the presence of risk factors. The increased atrio-caval gradient resulting from compression of the intrahepatic IVC had resolved after stent placement, but symptoms of portal hypertension persisted secondary to fatty changes in the liver. Fortunately, our patient responded to vitamin E, essential fatty acids, and pioglitazone therapy in a dramatic fashion with improvements in chemical and biochemical markers, reduction of hepatomegaly and subsequent resolution of portal hypertension. There have been no studies published to date concerning the efficacy of such therapy in patients with post-LT de novo or recurrent NASH. The success seen in this case could serve as a model for future therapy.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

1. Koehler E, Watt K, Charlton M. Fatty liver and liver transplantation. *Clinics Liver Dis.* 2009 Nov;13(4):621–630.
2. Contos MJ, Cales W, Sterling RK, et al. Development of nonalcoholic fatty liver disease after orthotopic liver transplantation for cryptogenic cirrhosis. *Liver Transpl.* 2001 Apr;7(4):363–373.
3. Lim LG, Cheng CL, Wee A, et al. Prevalence and clinical associations of posttransplant fatty liver disease. *Liver Int.* 2007 Feb;27(1):76–80.
4. Seo S, Maganti K, Khehra M, et al. De novo nonalcoholic fatty liver disease after liver transplantation. *Liver Transpl.* 2007 Jun;13(6):844–847.
5. Angulo P. Nonalcoholic fatty liver disease and liver transplantation. *Liver Transpl.* 2006 Apr;12(4):523–534.
6. Maor-Kendler Y, Batts KP, Burgart LJ, et al. Comparative allograft histology after liver transplantation for cryptogenic cirrhosis, alcohol, hepatitis C, and cholestatic liver diseases. *Transplantation.* 2000 Jul 27;70(2):292–297.
7. Fishbein TM, Fiel MI, Emre S, et al. Use of livers with microvesicular fat safely expands the donor pool. *Transplantation.* 1997 Jul 27;64(2):248–251.

8. Burke A, Lucey MR. Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis and orthotopic liver transplantation. *Am J Transplant.* 2004 May;4(5):686–693.
9. Doyle MB, Vachharajani N, Wellen JR, et al. Short- and long-term outcomes after steatotic liver transplantation. *Arch Surg.* 2010 Jul;145(7):653–660.
10. Angele MK, Rentsch M, Hartl WH, et al. Effect of graft steatosis on liver function and organ survival after liver transplantation. *Am J Surg.* 2008 Feb;195(2):214–220.
11. Yerian L. Histopathological evaluation of fatty and alcoholic liver diseases. *J Digest Dis.* 2011 Feb;12(1):17–24.
12. Werner A, Havinga R, Bos T, Bloks VW, Kuipers F, Verkade HJ. Essential fatty acid deficiency in mice is associated with hepatic steatosis and secretion of large VLDL particles. *Am J Physiol Gastrointest Liver Physiol.* 2005 Jun;288(6):G1150–G1158.
13. Keim NL, Mares-Perlman JA. Development of hepatic steatosis and essential fatty acid deficiency in rats with hypercaloric, fat-free parenteral nutrition. *J Nutr.* 1984 Oct;114(10):1807–1815.
14. Jeppesen PB, Christensen MS, Hoy CE, Mortensen PB. Essential fatty acid deficiency in patients with severe fat malabsorption. *Am J Clin Nutr.* 1997 Mar;65(3):837–843.
15. O'Neill Jr JA, Caldwell MD, Meng HC. Essential fatty acid deficiency in surgical patients. *Ann Surg.* 1977 May;185(5):535–542.
16. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. *N Engl J Med.* 2010 May 6;362(18):1675–1685.