63: 407.
7. Battaglia SE, Pretto JJ, Irving LB, et al. Resolution of gas exchange abnormalities and intrapulmonary shunting following liver transplantation. Hepatology 1997; 25: 1228.
8. Abrams GA, Jaffe CC, Hoffer PB, et al. Diagnostic utility of contrast echocardiography and lung perfusion scan in patients with hepatopulmonary syndrome. Gastroenterology 1995; 109: 1283.
9. Krowka MJ, Tajik J, Dickson ER, et al. Intrapulmonary vascular dilatations (IPVD) in liver transplant candidates: screening by two-dimensional contrast-enhanced echocardiography. Chest 1990; 97: 1165.
10. Donovan CL, Marcovitz PA, Punch JD, et al. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. Transplantation 1996; 61: 1180.
11. Barbe T, Losay J, Grimon G, et al. Pulmonary arteriovenous shunting in children with liver disease. J Pediatr 1995; 126: 571.
12. Wolfe JD, Tashkin DP, Holly FE, et al. Hypoxemia of cirrhosis: detection of abnormal small pulmonary vascular channels by a quantitative radionuclide method. Am J Med 1977; 63: 746.
13. Genovesi MG, Tierney DF, Taplan GV, et al. An intravenous radionuclide method to evaluate hypoxemia caused by abnormal alveolar vessels: limitations of conventional techniques. Am Rev Respir Dis 1976; 114: 59.

Received 11 January 1999.
Accepted 10 June 1999.

LIVER TRANSPLANTATION IN A PATIENT WITH ACUTE LIVER FAILURE DUE TO SICKLE CELL INTRAHEPATIC CHOLESTASIS

SUKRU EMRE,[1,2] KAZU KITIBAYASHI,[1] MYRON E. SCHWARTZ,[1] JIYONG AHN,[3] AUDREY BIRNBAUM,[4] SWAN N. THUNG,[5] AND CHARLES M. MILLER[1]

The Recanati/Miller Transplantation Institute and the Departments of Radiology, Pediatrics, and Pathology, Mount Sinai Hospital of Mount Sinai–New York University Health, New York, New York

Background. **Sickle cell intrahepatic cholestasis is a potentially catastrophic complication of sickle cell anemia. Once acute liver failure develops, transplantation is the only option. We describe a patient with sickle cell intrahepatic cholestasis who underwent liver transplantation.**

Methods. **Data were obtained from the chart. Serial hemoglobin S levels were monitored, and measures were taken to maintain hemoglobin S <20% to prevent sickle cell crisis.**

Results. **Although the allograft functioned well initially, the patient developed veno-occlusive disease and required repeat transplantation at 5 months after transplant. Histologic examination of the explant revealed occlusion of the terminal hepatic venules due to fibrosis and packed red cells. Repeat transplant was complicated by thrombosis of the intrahepatic portion of the hepatic artery, and sepsis. The patient died of sepsis after a third transplant.**

Conclusion. **Liver transplantation for sickle cell disease involving the liver may carry a high risk of graft loss due to vascular problems. Repeat transplantation may not be feasible if disease recurs.**

Patients with sickle cell anemia (SCA) are at risk for perioperative vascular complications. Liver transplantation is a complex procedure, and intra-operative insults, such as ischemia reperfusion injury, hypothermia, and acidosis, can induce sickling. In addition, the flow of blood through the cold allograft upon reperfusion can promote sickling in the sinusoids. Therefore, liver transplantation in patients with SCA remains a challenge.

CASE HISTORY

SK was a 6-year-old black male who was transferred to our hospital with the picture of acute liver failure. Physical examination demonstrated a moderately encephalopathic 6-year-old boy with jaundice. The liver functions were: prothrombin time, 35.5 sec; partial thromboplastin time, 44.5 sec; aspartate aminotransferase, 1,800 U/L; alanine aminotransferase, 3,395 U/L; total bilirubin, 29.4 mg/dl; ammonia, 265 μg/dl. Viral serologies were negative for hepatitis A, B, and C. Hemoglobin S (HbS) was 21.6%.

On July 13, 1996 he underwent living related donor liver transplantation using his mother's left lateral segment. The level of HbS at the transplantation was 10.3%.

The operative course was uneventful. Although careful attention was given to oxygenation, fluid balance, and body temperature to decrease the risk of sickle cell crisis during surgery, postperfusion biopsy showed prominent aggregation of erythrocytes in sinusoids. Microscopic examination of the explanted liver revealed submassive hepatic necrosis with prominent lymphoid follicles in portal tracts and giant cell transformation of hepatocytes. Clusters of sickled erythrocytes were also seen in dilated sinusoids (Fig. 1).

His postoperative course was complicated by bilateral pneumonia and line sepsis with *Candida*. He also developed clinically evident ascites and anasarca; liver biopsy findings were consistent with a vascular outflow problem. Vena cavagram revealed a patent vena cava and hepatic vein, and the child was relisted for a second liver transplantation with the diagnosis of veno-occlusive disease.

Repeat transplantation was done 3 months after the first transplant. His HbS level at repeat transplantation was 3.3% and was maintained at <10%. Histologic examination of the explanted liver showed severe centrilobular congestion, hepatocyte dropout, and fibrosis. The terminal hepatic venules were either occluded by fibrosis or packed with sickled erythrocytes.

His postoperative course was complicated with intra-abdominal sepsis requiring surgical exploration. During this procedure, patchy necrosis of segments 4 and 5 was noted. Although the extrahepatic

[1] Recanati/Miller Transplantation Institute.
[2] Address correspondence to: Sukru Emre, M.D., Mount Sinai Hospital, Box 1104, One Gustave L. Levy Place, New York, NY 10029-6574. E-mail: sukru_emre@smtplink.mssm.edu.
[3] Department of Radiology.
[4] Department of Pediatrics.
[5] Department of Pathology.

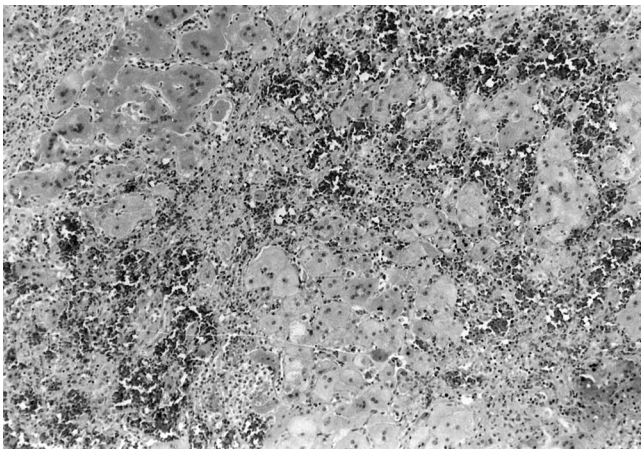

FIGURE 1. Explanted native liver showing multinucleated giant hepatocytes and dilated sinusoids filled with sickled erythrocytes (hematoxylin and eosin stain; original magnification, ×100).

portion of the hepatic artery was patent, intra-operative ultrasound revealed thrombosis of the segmental hepatic arteries.

After his intra-abdominal infection cleared and his condition stabilized, on December 23, 1996, he received a third liver graft. Although the initial graft function was good, he again became septic and died of overwhelming sepsis on January 3, 1997.

DISCUSSION

The liver is frequently involved in SCA. In 26 liver biopsy specimens from patients with SCA, Charlotte et al. (*1*) noted sinusoidal dilatation in 23, perisinusoidal fibrosis in 19, and acute ischemic necrosis in 5.

Sudden trapping of sickled red cells may occur in the liver in a fashion similar to acute splenic sequestration in patients with SCA, which may result in significant morbidity and mortality. The sickle cell intrahepatic cholestasis (SCIC) was described as a very severe form of hepatic crisis marked by the sudden onset of severe right upper quadrant pain, progressive hepatomegaly, coagulopathy with hemorrhage, and extreme hyperbilirubinemia with poor prognosis (*2*, *3*). Exchange transfusion and transfusion of hemoglobin A erythrocytes have been reported to be effective at reversing SCIC (*4–6*), but in our case, the patient's condition worsened despite exchange transfusions, and he lapsed into stage 4 coma.

Among kidney recipients, survival is similar in patients with and without SCA, with no increased risk of vascular complications (*7*, *8*). There are only two reported cases of liver transplantation in patients with SCA (*9*, *10*): an 11-year-old boy with secondary biliary cirrhosis and a 47-year-old woman with hepatitis C cirrhosis. In neither patient was SCA primarily responsible for the chronic liver disease. The case we describe here is the first in which transplantation was done for acute liver failure from SCIC.

Although we made great efforts to prevent sickling, our patient's postperfusion biopsy showed sickling in the sinusoids, even with an HbS level <11%. Unfortunately, despite careful management, the first graft was lost secondary to occlusion of small hepatic veins and the second graft to thrombosis of the intrahepatic portion of the hepatic artery. Based on the histologic findings in the explanted allografts, we believe the vascular events that resulted in failure of allografts originated from the trapping and accumulation of sickled cells within sinusoids and/or tiny peripheral arteries. The present case thus demonstrates the difficulty in preventing recurrent intrahepatic sickling in patients with SCIC.

Another possible problem in managing posttransplant patients with SCA is the clinical diagnosis of acute rejection. Sludging of sickled cells within sinusoids together with the enlargement of Kupffer cells after active phagocytosis of sickled cells can cause mild congestion, which may cause mild elevations of liver enzymes. It is also common for patients with SCA to have hyperbilirubinemia, elevated white blood cell counts, and low-grade fever. These combined factors can confuse the clinical evaluation of acute rejection in patients with SCA. Moreover, it may be the case that the change of intrahepatic environment caused by acute rejection might facilitate/trigger intrahepatic sickling, leading to graft failure. As we did not have biopsy-proven acute rejection episodes in this case, we cannot discuss this issue.

Although our experience is limited to one case, it suggests that transplantation for sickle cell disease involving the liver may carry a high risk of graft loss and death due to vascular problems. Repeat transplantation does not appear to be indicated once the disease recurs.

REFERENCES .

1. Charlotte F, Bachir D, Nenert M, et al. Vascular lesions of the liver in sickle cell disease: a clinicopathological study in 26 living patients. Arch Pathol Lab Med 1995; 119: 46.
2. Sheehy TW. Sickle cell hepatopathy. South Med J 1977; 70: 533.
3. Schubert TT. Hepatobiliary system in sickle cell disease. Gastroenterology 1986; 90: 2013.
4. Shao SH, Orringer EP. Sickle cell intrahepatic cholestasis: approach to a difficult problem. Am J Gastroenterol 1995; 90: 2048.
5. Sheehy TW, Law DE, Wade BH. Exchange transfusion for sickle cell intrahepatic cholestasis. Arch Intern Med 1980; 140: 1364.
6. Stephan JL, Merpit GE, Richard O, et al. Fulminant liver failure in a 12-year-old girl with sickle cell anaemia: favorable outcome after exchange transfusions. Eur J Pediatr 1995; 154: 469.
7. Chatterjee SN. National study on natural history of renal allografts in sickle cell disease or trait. Nephron 1980; 25: 199.
8. Chatterjee SN. National study in natural history of renal allografts in sickle cell disease or trait: a second report. Transplant Proc 1987; 19: 33.
9. Lang T, Berquist WE, So SK, et al. Liver transplantation in a child with sickle cell anemia. Transplantation 1995; 59: 1490.
10. Kindscher JD, Laurin J, Delcore R, et al. Liver transplantation in a patient with sickle cell anemia. Transplantation 1995; 60: 762

Received 9 February 1999.
Accepted 30 June 1999.