

# Successful orthotopic liver transplantation in an adult patient with sickle cell disease and review of the literature

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## Abstract

Sickle cell disease can lead to hepatic complications ranging from acute hepatic crises to chronic liver disease including intrahepatic cholestasis, and iron overload. Although uncommon, intrahepatic cholestasis may be severe and medical treatment of this complication is often ineffective. We report a case of a 37 year-old male patient with sickle cell anemia, who developed liver failure and underwent successful orthotopic liver transplantation. Both pre and post-operatively, he was maintained on red cell transfusions. He remains stable with improved liver function 42 months post transplant. The role for orthotopic liver transplantation is not well defined in patients with sickle cell disease, and the experience remains limited. Although considerable challenges of post-transplant graft complications remain, orthotopic liver transplantation should be considered as a treatment option for sickle cell disease patients with end-stage liver disease who have progressed despite conventional medical therapy. An extended period of red cell transfusion support may lessen the post-operative complications.

## Introduction

Sickle cell disease (SCD) is an inherited disorder of hemoglobin (HbS) leading to complications in multiple organ systems. Many complications are due to either recurrent vaso-occlusion or chronic hemolysis. Frequently observed manifestations of hepatic and biliary tract disease in sickle cell disease patients include vaso-occlusion of hepatic sinusoids due to the sickling process, hemosiderosis from chronic transfusions, viral hepatitis, and cholelithiasis due to chronic hemolysis.<sup>1</sup> In many patients the cause of liver dysfunction is multi-factorial.

Acute vaso-occlusion is a common event resulting from polymerization of deoxygenated HbS leading to decreased pliability of red blood cell (RBC) membrane leading to sickle shaped cells, and increasing the adhesiveness of the RBC membrane to the endothelium of small vessels. When sickling occurs in the bone, these changes result in microvascular occlusions that cause ischemia which manifest as vaso-occlusive pain crises. In the liver, vaso-occlusion of sickled RBCs occurs in the hepatic sinusoids, perhaps due to low oxygen tension.<sup>1</sup> The obstructed hepatic sinusoids generate hepatic congestion leading to hepatomegaly and hepatocyte necrosis. In addition, Kupffer cell hypertrophy from increased phagocytosis of the sickled RBCs contributes to further sinusoidal obstruction.<sup>2</sup> This phenomenon of sickle RBC induced sinusoidal obstruction has been termed *sickle cell hepatopathy*.<sup>1,3,4</sup> Sinusoidal congestion and ischemic necrosis may lead to cirrhosis. In one study by Traina *et al.*, among 20 SCD patients with liver dysfunction who underwent liver biopsy 19 patients demonstrated *sickle cell hepatopathy* from intra-sinusoidal congestion and vaso-occlusion.<sup>1</sup>

Congestion of hepatic sinusoids may manifest as a transient acute hepatic crisis associated with right upper quadrant pain, jaundice, fever, leukocytosis, increased serum aminotransferases and elevated bilirubin.<sup>3</sup> This form of sickle cell crisis often resolves without clinical consequences. However, rarely the sequestration of sickle cells in the hepatic sinusoids may lead to more severe and potentially fatal sickle cell intrahepatic cholestasis (SCIC), which usually presents as acute hepatic failure from local ischemia.<sup>3,5,6</sup> Untreated SCIC has been associated with a mortality rate of up to 40%.<sup>6</sup> While treatment with red cell transfusions improves survival over supportive management alone, it is often ineffective with a mortality of 17% in chronic intrahepatic cholestasis.<sup>6,7</sup> The role for orthotopic liver transplant (OLT) in patients with SCD and liver disease is not well defined. There have only been several cases of OLT for sickle cell disease patients with liver failure. We describe a case of a patient with sickle cell anemia and end-stage liver disease from sickle cell cholestasis who underwent a successful OLT and was maintained on perioperative transfusions with a long-term survival.

## Case Report

Our patient is a 37 year old African American male with homozygous sickle cell disease whose course included intermittent vaso-occlusive crises resulting in 1-2 hospital-

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izations per year. He has a history of cholecystectomy in 1991 and hospitalizations for acute pulmonary infiltrates in 1992 and 1998. His estimated RBC transfusion burden was ~20 units prior to his OLT. Throughout his adult course aminotransferases (AST, ALT) and bilirubin were elevated (Figure 1). Viral serologies for hepatitis B, hepatitis C and human immunodeficiency virus were negative and ferritin was 129 ng/mL. In 2005, treatment with hydroxyurea 1g daily was started and he used occasional opioids as needed.

In August 2006, 8 months prior to orthotopic liver transplant, he developed jaundice. His total bilirubin was 14.0 ng/dL, alkaline phosphatase 614, AST 176, ALT 110, and ferritin 237 ng/mL. Liver biopsy in November 2006 showed severe cholestasis, bile ductular proliferation and cirrhosis (Figure 2). RBC exchange transfusions were begun and continued every 4-6 weeks to achieve Hgb S concentrations <30%. One month prior to his transplant, he was maintained on simple RBC transfusions to maintain Hgb >7 g/dL.

In March 2007 he was admitted to the Intensive Care Unit with severe anemia, acute renal insufficiency, and deepening jaundice. Laboratory data included Hgb 5.8 g/dL, Hct 17.1, Hgb S 15.7%, bilirubin 46.5, alk phos 387, AST 223, ALT 93, and creatinine 4.5. He was evaluated and listed for OLT with a Model for End-Stage Liver Disease score of 40. Fourteen days later he underwent an orthotopic liver transplantation from an ABO matched adult cadaveric donor.

The transplantation was accomplished with minimal blood loss. During surgery the patient was transfused with 3 units of packed RBCs, 1000 mL of 5% albumin and 3 liters of crystalloid. The donor graft appeared normal;

Table 1. Review of orthotopic liver transplant cases in sickle cell disease patients.

Study citation	Sex	Age	Hb Type	Liver pathologies	Transfusion management (pre-op goal)	Transfusion management (post-op goal)	Outcome
Perini 2010 <sup>9</sup>	M	37	HbS beta thalassemia	Hepatitis C; hemosiderosis	Not stated	Post-op target HbS<30% with exchange transfusions	Death after 5 months 3 months: acute sickle hepatic crisis with elevated LFTs and RUQ pain-resolved with exchange transfusions and hydroxycarbamide 5 months: died from intracranial hemorrhage from Moyamoya disease
Greenberg 2010 <sup>10</sup>	F	30	HbSS	Extensive hepatocyte necrosis but no signs of SCIC or pregnancy related hepatopathy	RBC exchange from presenting HbS=80% to HbS=26%	Post-op: HbS<30%	Survival POD 1-3: ICU requiring mechanical ventilation POD 28: discharge home
Batchi 2005 <sup>6</sup>	F	27	HbSS	SCIC; autoimmune hepatitis; cirrhosis	Presented with HbS=69.6%, exchange transfusion to keep HbS<10%	Exchange transfusion to keep HbS<10%	Death on POD 35 from peritoneal bleed and MOF
Batchi 2005 <sup>6</sup>	F	26	HbSS	Sclerosing cholangitis; periductal fibrosis consistent with intrahepatic cholestasis	Presented initially with HbS=15.1%; exact amount of transfusion not stated	HbS<10% without any transfusions during OLT hospitalization	Death on POD 85 from septic shock and MOF
Kindscher 1995 <sup>2</sup>	F	47	HbSS	Chronic hepatitis C; cirrhosis	Exchanged 4 units to reduce HbS from 52% to 27%	Target HbS<30%	Survival: discharge home on POD 40; no signs of rejection Complication: cerebral hemorrhage POD 12 managed conservatively w/ CNS improvement after 3 months f/u
Ross 2002 <sup>11</sup>	M	49	HbSS	SCIC	Initially presented with Hb=5.2 and HbS=52%, which prompted 6 U RBC transfusion	Target HbS<20%	Death: discharge POD 33 Complication: biliary anastomosis leak repair POD 7 22 months Post-op: death from pulmonary embolus; autopsy reveals no cholestasis or rejection
Gilli 2002 <sup>5</sup>	M	22	HbS beta thalassemia	SCIC; cirrhosis	Target HbS<30%	Target HbS<20%	Survival: mild intrahepatic sickling 3 months post-op; no signs of rejection 2 years post-op
Delis 2006 <sup>12</sup>	F	19	HbSD	Hepatitis B; cirrhosis	Not stated	Exchange transfusion at 17 months post-op for elevated LFTs: decreased HbS from 33.8 to 7.8%	Survival: no rejection Complication: intrahepatic cholestasis of allograft resolved after transfusion
Van den Hazel 2003 <sup>13</sup>	M	23	HbSS	Hemochromatosis	5 U RBCs exchange decreased HbS from 32% to 19%	Intra-op: transfused 44 U RBCs HbS=4.9% 1 wk post-op (w/o transfusion)	Survival: no rejection; liver functions intact at 5.5 yrs post-OLT
Lerut 1999 <sup>14</sup>	F	42	HbS beta thalassemia	Cryptogenic cirrhosis	Target not stated	Target HbS<10%	Survival Complication: partial graft infarction/necrosis at post-op 6 month-spontaneous recovery
Emre 2000 <sup>15</sup>	M	6	HbSS	Dilated sinusoids filled with sickled RBCs	HbS=21.6% at presentation prior to first OLT; pre-op target not stated	Target HbS<20%	Death from sepsis after 3 <sup>rd</sup> transplant; 1 <sup>st</sup> graft failed due to veno-occlusive disease; 2 <sup>nd</sup> graft failed from hepatic artery thrombosis
Lang 1995 <sup>16</sup>	M	11	HbSS	Biliary cirrhosis	Not stated	HbS<20%	Survival; intact graft function
Meekel 2007 <sup>17</sup>	N/A	8, 17, 17	Not specified	3 had intrahepatic cholestasis; 1 had chronic hepatitis C	Exchange transfusions for target HbS<25% and Hb>9	Exchange transfusions for target HbS<25% and Hb>9	2 Survived 1 Death: recurrent intrahepatic cholestasis and (3 patients) chronic graft failure, and died 6 yrs post-op from subdural hematoma from fall

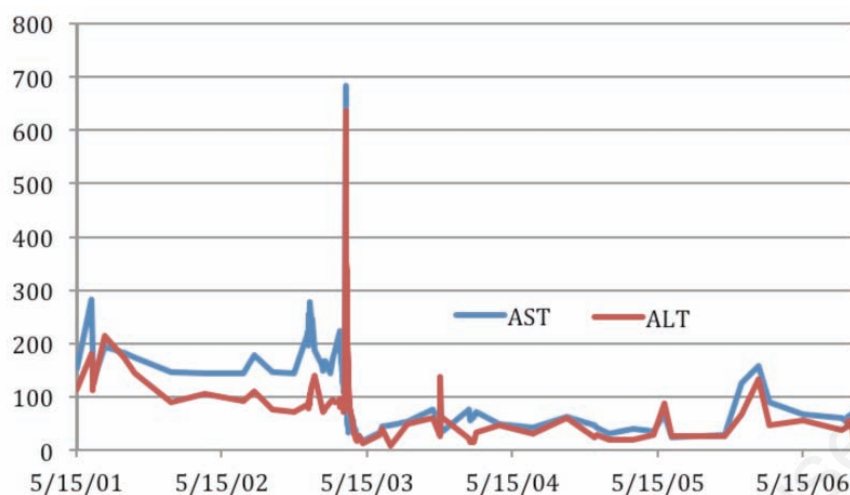
Hb, hemoglobin; SCIC, sickle cell intrahepatic cholestasis; RBC, red blood cell; OLT, orthotopic liver transplant; MOF, multiorgan failure.

the cold ischemia time was 9 hours and the warm ischemia time was 28 minutes. The graft liver was placed in a standard piggyback fashion with bile duct-to-duct anastomosis. The liver explant showed cirrhosis with marked autolysis, and cholestasis with bile duct proliferation.

The post-operative course was complicated by seizures and acute respiratory distress, which required intubation during the post-operative course. His Hgb was maintained throughout the hospital course between 7-10 and Hgb S <2% with RBC transfusions. His urine output, lung function and mental status

improved gradually, and he was discharged on the postoperative day 31 in stable condition.

The patient received immunosuppression with mycophenolate mofetil, prednisone, and tacrolimus. The prednisone was gradually tapered and he was maintained on mycophenolate mofetil and tacrolimus long-term. He was maintained on 2 units RBC transfusions every 4 weeks for target of Hgb of 10 g/dL for one year. His AST and ALT have decreased since the transplantation and liver function has improved (Figures 1 and 2). He had no post-operative sickle cell related complications and 12 months after transplant RBC treatments were stopped and he has been maintained on hydroxyurea.



### Bilirubin (mg/dL)

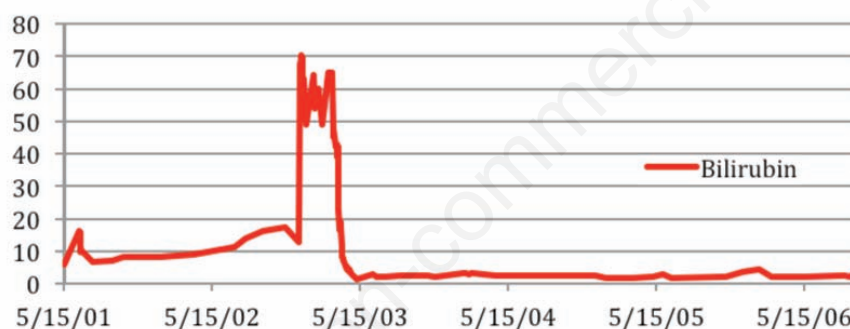


Figure 1. Aspartate aminotransferase/alanine aminotransferase (AST/ALT) (IU/L), and bilirubin (mg/dL).

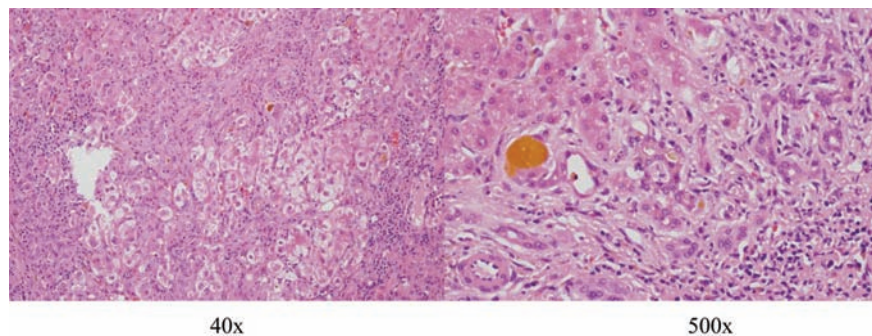


Figure 2. Liver biopsy in 2006 - severe cholestasis with fibrosis, ductular proliferation and cirrhosis (Haematoxylin and Eosin stain).

## Discussion and Conclusions

SCIC is a highly fatal complication of sickle cell disease. It has been documented that intrahepatic cholestasis has a mortality of 40% without the use of exchange transfusions.<sup>6,8</sup> In a review of 26 reported patients, Khurshid *et al.* found that with exchange transfusion therapy, the mortality from intrahepatic cholestasis was 17% suggesting that it remains a potentially fatal condition despite medical treatment.<sup>7</sup> In the patient reported here, RBC exchange transfusion therapy every 4-6 weeks for 3 months prior to liver transplantation was successful to maintain a target Hgb S <30%, but his liver function continued to decline. In these patients, OLT becomes the only therapeutic option.

There have been few reported cases of OLT in patients with sickle cell disease. A review of the literature identified 10 adult and 5 children with sickle cell disease (Table 1).<sup>2,5,6,9-17</sup> In 6 of the 10 reported adult cases, liver transplantation resulted in improved function and long-term survival. Of the 4 that resulted in post-OLT death, 2 were from causes unrelated to the OLT or liver dysfunction (1 from intracranial bleed 5 months post-op due to pre-existing vascular anomaly and 1 from pulmonary embolism 22 months post-op). Nevertheless, sickle cell related allograft complications occurred in 5 of the 6 survived cases. Among 3 of 5 pediatric cases, transplantation was successful.

There are a number of challenges in considering OLT for sickle cell disease patients. First, surgery itself presents as a procedure with high morbidity and mortality risk. Early studies show on average 10% mortality and >50% risk of perioperative complications in sickle cell disease patients undergoing a variety of surgical procedures but this can be reduced substantially with preoperative RBC transfusion.<sup>17,18</sup> Sickle cell related complications such as intrahepatic sickling and vaso-occlusion can recur in the graft causing deterioration in

function.<sup>5,12,14,15,17</sup> Preoperative transfusion therapy can be used to mitigate the post-op complications. The National Preoperative Transfusion Study evaluating the risk of cholecystectomy in SCD patients found that post-op complications of SCD were higher in the non-transfused than the transfused group.<sup>19</sup> Our patient was heavily transfused in preparation for his liver transplant to decrease sickle cell related complications. Notably, post-operative transfusion therapy has been utilized by a majority of the OLT cases to reduce risk of long-term graft sickle cell related complications. Nevertheless, the intensity and duration of transfusion therapy is not well defined and varies between studies. The experience with our patient suggests that aggressive RBC transfusion is warranted; however, chronic transfusion therapy places patients at risk for transfusion related iron overload.

Liver failure secondary to sickle cell intrahepatic cholestasis is a complicated clinical problem and in our case, medical management with hydroxyurea, and aggressive RBC transfusions were not able to reverse his declining liver function. The current experience and role for OLT in sickle cell disease patients is limited. This case had a successful outcome with OLT plus RBC support. OLT should be considered as treatment option for sickle cell disease patients with advanced liver failure.

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