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Prof. Ke-Qin Hu, Koo, MD, FAASLD

Prof. Jeong Kang, MD, PhD

Prof. Nikolaos Pyrsopoulos, FACP, FRCP (C), MD, PhD

Editor-in-Chief, Editorial Office

Re: Manuscript NO: 51183 – Manuscript revision

Title: Successful Liver Transplantation for Acute Sickle Cell Intrahepatic Cholestasis: A Case Report and Review of the Literature

Dear Editorial Board and Reviewers,

Thank you for your thoughtful review of our manuscript, "Successful Liver Transplantation for Acute Sickle Cell Intrahepatic Cholestasis: A Case Report and Review of the Literature".

Below are our responses to review and explanation of manuscript alterations. Changes to the manuscript and tables are highlighted in yellow. We hope you agree with us that the revised manuscript incorporating the reviewer's comments makes for a much better report.

Sincerely,

Christina Lindenmeyer, MD

Title:

We would like to change the title into clearer format as below.

“Successful Liver Transplantation for Acute Sickle Cell Intrahepatic Cholestasis: A Case Report and Review of the Literature”

Corresponding author:

The new corresponding author will be: Christina C. Lindenmeyer, MD

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Reviewers' comments:

Reviewer #1: “It is an interesting case report of successful orthotopic liver transplantation for acute sickle cell intrahepatic cholestasis. Minor corrections are needed especially in the references section.”

Reply: Thank you for your feedback. The manuscript has been revised as presented; the references section was updated and formatted using Endnote X9, PubMed and DOI hyperlinks were added.

Reviewer #2: “General comments The authors reported a case of a 29 year-old male with history of vaso-occlusive pain crisis, who presented with clinical and laboratory features suggestive of acute liver injury and acute kidney injury. Within two weeks of hospitalization (inferred from the authors’ stated time frame), patient had undergone a successful orthotopic liver transplantation from a HCV donor, and received post-operative medications for the positive HCV RNA testing. Clinical outcome was said to be satisfactory on follow-up. Although the report was an interesting evidence of an apparently- successful therapeutic intervention for a potentially-fatal complication in sickle cell disease, I have the following concerns about the manuscript”

Reply: Thank you very much for your feedback. We are happy to address all concerns as following:

“Major concerns 1. In the Abstract, the second sentence under Case Summary read ‘On examination, he had jaundice with soft non-tender abdomen, initially he was alert and oriented then later became confused.’ I think the statement is ambiguous. The reader would like to understand the time frame within which the change in sensorium had occurred. The clinical progression should be captured well. See also a similar statement under Case Report viz ‘He was jaundiced and initially was alert and oriented to person, place and time. His abdomen was soft with no tenderness or organomegaly and had normal bowel sounds. He later became confused.’

Reply: Thank you for raising this valid point. We edited the following to highlight the time frame for clinical progression.

Page 4 line 59-61: “A 29-year-old male with a past medical history of SCD presented with vaso-occlusive pain crisis. On examination, he had jaundice and a soft, non-tender abdomen. Initially he was alert and fully oriented; within 24 hours he developed new-onset confusion.”

Page 6 lines 108-111: “ On initial examination, his vital signs were within normal limits. He was markedly jaundiced and was alert and fully oriented. His abdomen was soft without tenderness or organomegaly and with normal bowel sounds. Within 24 hours of presentation, he developed new-onset confusion attributed to hepatic encephalopathy.”

“2. Pre-surgery, it appeared the patient was in a critical state as stated by the authors thus: ‘He was admitted to the medical intensive liver unit (MILU) for further management. He received 2 units of platelets and 4 units of fresh frozen plasma (FFP). He was intubated for acute respiratory failure secondary to acute chest syndrome.....’ Since OLT is a complex procedure requiring painstaking pre-operative preparation and intra-operative meticulous implantation, one wonders how the patient successfully underwent the procedure within the reported short time frame. Was a total organ transplantation done? From a cadaveric or from a live donor?”

Reply: Thank you for raising this valid point. We have clarified the evaluation and listing process as below:

Page 7-8 lines 133-144: “He was admitted to the medical intensive liver unit (MILU) for further management. He required intubation and mechanical ventilation for acute hypoxic respiratory failure secondary to acute chest syndrome; for this he was treated with empirical vancomycin and meropenem. An exchange transfusion was initiated with subsequent decrease of hemoglobin S (HbS) level from 56.3 to 8.2 g/dL. Despite the exchange transfusion, his hepatic synthetic function did not improve; he was rapidly evaluated and subsequently listed with a MELD-Na score of 40 for urgent LT for acute sickle cell intrahepatic cholestasis.

The pre-operative evaluation was coordinated by a multidisciplinary team involving hepatology, infectious disease, dermatology, dentistry, anesthesiology, transplant surgery, critical care and apheresis

specialists. Nine days after initial presentation, the patient underwent LT from a brain dead, hepatitis C virus (HCV) nucleic acid test (NAT) positive donor utilizing standard piggyback technique and a duct-to-duct biliary anastomosis.”

3. Based on the objective of this review, I think the Discussion section should have started with this paragraph: ‘There is a total of 22 reported liver transplant cases in SCD patients. Majority of transplant cases are indicated for liver failure secondary to acute sickle cell intrahepatic cholestasis. 1 Only two case series about OLT in SCD patients are present in the literature. The first included six transplanted patients with 1-, 5- and 10-year survival rates of 83.3%, 44.4% and 44.4% respectively. 6 The other series reported 3 pediatric patients who were followed up for a mean of 4.3 years and survival rate was 66% 9. Indeed, these results are not too far from survival rates of non SCD patients undergoing OLT with 5- and 10-year survival rates of 71% and 61% respectively. 11’ The authors can now bring in their own experience with the current case report for comparison.....”

Reply: Thank you for raising this valid point, starting with the literature review about the liver transplant cases would be more consistent with the objective of the case report.

Pages 9 Lines 167-172: “Only 22 cases of LT for SCH have been reported in the literature. The majority of transplants have been performed for acute liver failure (ALF) secondary to acute sickle cell intrahepatic cholestasis. We report the 23rd LT for SCH; the first reported case of an HCV NAT positive donor that facilitated urgent LT for an HCV NAT negative patient with acute sickle cell intrahepatic cholestasis. Our patient subsequently achieved sustained virologic response after being treated with 3 months of glecaprevir/pibrentasvir.”

“4. Overall, the Discussion section was not presented in a logical fashion. There was a lot of redundant information occupying several paragraphs. The authors should have presented a more concise prose focusing on the objective of this case report which was to highlight the role of OLT as a therapeutic measure for acute liver failure secondary to sickle cell intra-hepatic biliary cholestasis.”

Reply: Thank you for this important feedback. The Discussion has been revised and rephrased; we hope to highlight the role of LT and post-operative surveillance.

“ Only 22 cases of LT for SCH have been reported in the literature. The majority of transplants have been performed for acute liver failure (ALF) secondary to acute sickle cell intrahepatic cholestasis. We report the 23rd LT for SCH; the first reported case of an HCV NAT positive donor that facilitated urgent LT for an HCV NAT negative patient with acute sickle cell intrahepatic cholestasis. Our patient subsequently achieved sustained virologic response after being treated with 3 months of glecaprevir/pibrentasvir.

Sickle cell hepatopathy (SCH) is an inclusive term referring to any liver dysfunction among patients with SCD. SCH can present with both acute or chronic liver dysfunction, but has primarily been used in the literature to describe the acute hepatic manifestations of SCD. At times, SCH has been used to denote acute intrahepatic cholestasis specifically¹⁻⁶.

Acute intrahepatic cholestasis related to SCD is the most severe, and often fatal, form of SCH, associated with a mortality rate approaching 40%. Patients may present with severe acute hepatic crisis with fever, right upper quadrant pain and leukocytosis; however, this condition is characteristically accompanied by significant jaundice and can rapidly progress into ALF. Patients typically experience a dramatic increase in conjugated bilirubin with reported levels ranging between 30 and 273 mg/dL. Hemolysis and acute kidney injury also contribute to hyperbilirubinemia. Liver biochemistries including the AST, ALT and ALP levels may reach values exceeding 1000 mg/dL; however, normal to only slightly elevated values are possible. Coagulopathy, evidenced by elevated prothrombin time (PT), partial thromboplastin time (PTT), INR and hypofibrinogenemia, is typically seen. Multi-factorial acute kidney injury is commonly observed as well. To date, no cohesive list of diagnostic criteria has been proposed; we propose that multi-system organ failure with extreme hyperbilirubinemia and accompanied by altered mental status in patients with SCD should raise the clinical index of suspicion for acute intrahepatic cholestasis with an ALF phenotype^{1,2}.

Liver biopsy will typically demonstrate dilated blood sinusoids with clusters of sickled RBCs, associated with fibrosis and as intracanalicular and intraductal cholestasis^{1,3,7}. Findings of extramedullary hematopoiesis and Kupffer cell hypertrophy with intracellular engulfed sickled RBCs have also been described in the literature³. According to the degree of hypoxic injury, ballooning of hepatocytes, and in more severe cases, widespread anoxic necrosis with areas of acute and chronic inflammation have also been reported^{1,8}. Based on the described histopathologic characteristics, it is believed that this condition results from diffuse sickling in the blood sinusoids leading to widespread ischemia, hepatocyte injury and fibrosis¹. Kupffer cell hypertrophy and extramedullary hematopoiesis may also contribute to liver sinusoidal obstruction with compression of the adjacent bile ducts, contributing to cholestasis.

A recent report in the literature of acute sickle cell intrahepatic cholestasis by Lui et al described a more complex histological pattern of injury, including a combination of centrilobular fibrosis, occasional occlusion and constriction of the central veins, and sinusoidal fibrosis. This pattern more closely resembles the histological findings of chronic sinusoidal obstruction syndrome and veno-occlusive disease. This finding prompts the suggestion that intrahepatic cholestasis in SCD may result from RBC-mediated damage of small vessel endothelium, resulting in endothelial cell death and subsequent fibrosis of the small hepatic veins and sinusoids. Progression of this process would result in obstruction and distention of the sinusoids. It has been therefore hypothesized that endothelial dysfunction is the direct consequence of ischemic RBC-mediated injury in the small outflow veins and sinusoids³.

In patients with SCD and intra-hepatic cholestasis, cause of death is typically related to multi-system organ failure. Therapy is aimed at aggressive supportive measures, including exchange transfusions to replace HbS and correct anemia. Coagulopathy is usually treated with blood product and factor transfusions. Temporary renal replacement therapy may be required for acute kidney injury; renal function should correct with improvement of liver function¹. If supportive measures fail, LT remains the only viable therapeutic option. Outcomes for patients with intrahepatic cholestasis undergoing LT are summarized in Table 2. Recurrence of this disease process has been reported after LT; the role of hydroxyurea to prevent sickle cell intrahepatic cholestasis is uncertain^{9,10}.

In patients with SCD, an acute presentation of acute-on-chronic liver failure with an ALF phenotype has been reported in patients with underlying chronic liver disease related to chronic viral hepatitis and/or iron overload³. Vaso-occlusive events may also precipitate acute-on-chronic liver failure in patients with advanced chronic liver disease. Patients are at elevated risk of hepatic decompensation despite exchange transfusion given their low hepatic synthetic reserve; LT should accordingly be considered as a viable rescue therapy in selected patients.⁶

Two case series describing LT for SCD patients are present in the literature. The first series described 6 patients with 1-, 5- and 10-year survival rates of 83.3%, 44.4% and 44.4% respectively⁶. The second series described 3 pediatric patients, followed for a mean of 4.3 years, with a reported survival rate of 66%⁹.

The risk of vaso-occlusive crisis is increased peri-operatively, and crises may involve the transplanted liver. It has been recommended to initiate exchange transfusion before surgery with an HbS target of < 20-30% and for the HbS level to be maintained between 8 and 10 g/dL post-operatively in the long term^{6,9}.

Iron overload is a risk factor for progression of hepatic fibrosis related to chronic HCV infection among transplanted liver organs. Hemosiderosis should be managed by minimizing simple blood transfusions as able, by considering exchange blood transfusion as an alternative, and with iron chelators as indicated. Total body iron stores should be monitored serologically on a regular basis. Liver biopsy remains the gold standard for determination of hepatic iron concentration, however; magnetic resonance imaging in combination with serum ferritin level has been proposed as a non-invasive alternative¹². However, serum ferritin levels may vary over time in the setting of infectious or inflammatory processes, vaso-occlusive crises and liver dysfunction¹³. Chelation therapy is indicated in adults after receiving 20-30 blood units, in

patients with a serum ferritin >3000 ng/mL with a hepatic iron index of > 7-9 mg/g dry weight 14.

The evaluation of abnormal liver biochemistries after LT may be challenging in patients with SCD; it can be challenging to non-invasively differentiate acute and/or chronic rejection and infectious processes from the normal hepatic pathophysiology of SCD. As part of normal SCD physiology, Kupffer cells will continue to engulf sickled RBCs, which can lead to congestion of the liver allograft and mild elevation of aminotransferases and bilirubin levels¹⁵. Furthermore, low grade fever and leukocytosis are commonly seen in patients with SCD during vaso-occlusive crises¹⁶. Liver biopsy remains the gold standard for evaluation of possible rejection following LT¹⁷.

In conclusion, we present a rare case of acute sickle intrahepatic cholestasis managed with successful LT. This case represents the first report of an HCV NAT positive allograft being transplanted into an HCV negative SCD patient, and is the 23rd reported case of LT in SCD patients overall. Unfortunately, LT will not reverse the underlying pathophysiology of SCD; diligent post-transplant hematologic and immunosuppressive management care is needed in these cases. As our understanding of SCH evolves, paralleling technical advances in LT, post-LT management should be aimed at improving quality of life and optimizing survival.”

“5. Tables 1 & 2 were not properly presented. The tables should not be ambiguous and should be self-explanatory. I suggest the authors redo both tables, with the title of table 1 placed on top not below the table”

Reply: Thank you for this feedback. We have edited Tables 1 and 2 and hope to present more precisely the summarized data

Table 1: Summary of unique manifestations of sickle cell hepatopathy

<i>SCD manifestation</i>	<i>Pathophysiology of the disease</i>	<i>Histopathology</i>	<i>Clinical presentation</i>	<i>Amino-transferases</i>	<i>ALP</i>	<i>Bilirubin</i>	<i>Management</i>
Acute sickle cell hepatic crises	Sickled RBCs obstruct liver sinusoids causing ischemic infarction	- Presence of sickle cell aggregates in the liver sinusoids - Kupffer cell hypertrophy and centrilobular necrosis	Fever, abdominal pain, jaundice and tender hepatomegaly	Elevated up to 3 fold the upper limit of normal followed by rapid resolution	Normal to slightly elevated	Conjugated hyperbilirubinemia up to 15 mg/dL, usually normalizes within 2 weeks	Supportive; hydration, oxygenation, pain control and blood exchange as needed
Acute hepatic sequestration	Kupffer cell erythrophagocytosis traps sickled RBCs resulting in blood pooling within liver sinusoids	- Presence of dilated blood-filled liver sinusoids	Sudden severe RUQ pain and rapidly worsening anemia with appropriate reticulocytotic; severe cases can present with shock and hepatomegaly	Normal	Elevated; up to 650 U/L	Conjugated hyperbilirubinemia up to 24 mg/dL	Cautious blood transfusion or exchange transfusion; excessive transfusion can result in rapid rise of Hb during resolution phase precipitating stroke and heart failure
Acute intrahepatic cholestasis	Diffuse sickling in liver sinusoids leading to widespread ischemia as well as Kupffer cell hypertrophy and extramedullary hematopoiesis which contribute to cholestasis	- Presence of massively dilated blood sinusoids with clusters of sickled RBCs - Presence of intracanalicular and intraductal cholestasis - Ballooning of hepatocytes, necrosis, inflammation	Fever, RUQ pain, acute liver failure and multi-system organ failure	Elevated; typically > 1000 U/L	Normal or elevated up to >1000 U/L	Conjugated hyperbilirubinemia up to > 30 mg/dL	Supportive with exchange transfusion and LT
Sickle cell cholangiopathy	Incomplete occlusion of the peribiliary vascular plexus results in hypoxia and dilatation of the bile ducts; recurrent insults can result in ischemic stricture	- Presence of ischemic necrosis and fibrosis of the bile ducts	Jaundice and biliary stone complications, imaging can reveal non-obstructive bile duct dilatation and/or obstructive biliary strictures	Normal or elevated	Elevated	Elevated	ERCP stenting and balloon dilatation , LT

SCD; Sickle Cell Disease, AST; Aspartate aminotransferase, ALT; alanine aminotransferase, ALP; Alkaline Phosphatase, RBC; Red Blood Cell, RUQ; Right Upper Quadrant, Hb; Hemoglobin, LT; Liver Transplant, ERCP; Endoscopic Retrograde Cholangiopancreatography

Table 2: Reports of patients with intrahepatic sickle cell cholestasis who underwent liver transplantation

Author	Year	Number of cases	Age of the patient	Outcomes
Emre [15]	2000	1	6	First transplant was complicated by graft failure from veno-occlusive disease, required re-LT. Second transplant was complicated by graft failure from hepatic artery thrombosis, required re-LT. The patient died 6 months after third LT from sepsis.
Ross [18]	2002	1	49	The patient died 22 months after LT due to pulmonary embolism.
Gilli [19]	2002	1	22	The patient was alive 3 months after LT.
Baichi [7]	2005	1	27	Post-LT course was complicated by sepsis, multiorgan failure, perihepatic hematoma and hemorrhagic ascites; the patient died 35 days after LT.
Mekeel [9]	2007	2	8,17	Patients were followed up over a mean period of 4.2 years. Patient 1 was alive at end of follow-up with mild recurrent HCV. Patient 2 had recurrent sickle cell hepatopathy post-transplant and died of cerebral complications 6 years following LT.
Hurtova [6]	2011	5	32-47	Patient 1 died of recurrent HCV-induced decompensated cirrhosis and sepsis 11 years after LT. Patient 2 had recurrent HCV with moderate fibrosis; died of ischemic cholangitis and sepsis after 4 years after LT. Patient 3 had recurrent HCV infection. He was alive 8 years after LT. Patient 4's post-operative course was complicated by posterior leukoencephalopathy; the patient died from sepsis 16 months after LT. Patient 5 developed biliary strictures requiring stenting. The patient was alive 42 months after LT.
Blinder [20]	2013	1	37	Immediate post-LT course was complicated with seizure and respiratory failure. The patient had no post-operative SCD-related complications in the 12 months after transplant and was maintained on hydroxyurea without need for exchange transfusion.
Lui [3]	2018	1	29	The patient was alive 7 months after LT with no reported complications.

LT; liver transplant, HCV; hepatitis C virus

“Minor concerns 1. The authors should be consistent with the use of terminology. For instance, the terms ‘acute kidney injury’ and ‘acute renal failure’ were used interchangeably. Acute kidney injury is the more current terminology. 2. Few syntax errors should be corrected. 3. No subheading indicating ‘References’ was seen”

Reply: Thank you for bringing this to our attention. We have made significant edits to the manuscript addressing this concern and include these revisions below:

Page 4 Lines 61-62: “Laboratory evaluation was notable for hyperbilirubinemia, leukocytosis, anemia, thrombocytopenia, acute kidney injury and elevated INR.”

Page 7 Lines 132-134: “The patient was diagnosed with acute liver failure secondary to acute sickle cell intrahepatic cholestasis based on presence of encephalopathy, coagulopathy, acute kidney injury and hyperbilirubinemia.”

Page 7 Line 120-121: “He was diagnosed with an acute kidney injury with a serum creatinine of 3.48 mg/dL (baseline creatinine 0.6-0.7 mg/dL).”

Page 8 Lines 127-129: “The patient was diagnosed with acute-on-chronic liver failure with multi-system organ failure secondary to acute sickle cell intrahepatic cholestasis based on the presence of new-onset acute liver injury, encephalopathy, coagulopathy, and acute kidney injury.”

Pages 10 Lines 180-183: “Hemolysis and acute kidney injury also contribute to hyperbilirubinemia. Liver biochemistries including the AST, ALT and ALP levels may reach values exceeding 1000 mg/dL; however, normal to only slightly elevated values are possible. Coagulopathy, evidenced by elevated PTT and INR and hypofibrinogenemia, is typically seen. Multi-factorial acute kidney injury is commonly observed as well.”

Page 11 Lines 210-211: “ Temporary renal replacement therapy may be required for acute kidney injury; renal function should correct with improvement of liver function¹.”

Page 13 Line 265: World Journal of hepatology format was used in Endnote X9 program, PubMed and DOI hyperlinks were added.

References:

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