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Isolated Liver Transplantation: A Worthy Choice for Atypical Hemolytic Syndrome in Resource-Restricted Settings

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INTRODUCTION

Atypical hemolytic syndrome (HUS) is a disease characterized by hemolytic anemia, thrombocytopenia, and renal failure. If untreated, this disease leads to end-stage renal disease. Renal transplantation in this setting is not generally advocated, as recurrence rates are very high.[S1] It can, however, be done in patients with genetic mutations that have been shown to have low rates of recurrence, such as membrane cofactor protein mutation.[1] For many years, plasma exchange has been the therapy of choice in atypical HUS. British Transplantation Society guidelines issued in 2009 recommended an initial daily plasma exchange (50–70 ml/kg) with further titration of frequency according to clinical response.[2] For many patients, lifelong plasma exchange is a problem, as vascular access may be difficult, and patients may not tolerate the process of plasma exchange. A near cure for atypical HUS became a reality with the introduction of eculizumab, a C5 blocker. As the drug must be taken lifelong, the deterrent for most patients is the financial burden. The first evidence that liver transplantation could prevent recurrence of atypical HUS due to factors synthesized in the liver was reported in 2002. A child with atypical HUS who was unable to continue plasmapheresis because of unavailability of vascular access underwent a combined liver-kidney transplantation. Although the child succumbed to other causes, there was no indication of disease activity during 3 years of follow-up.[3] Thus, liver transplantation was proposed to be curative in patients with atypical HUS associated with defects in factors H and I. Unfortunately, operative complications in the initial patients were high and graft loss a major concern possibly due to complement dysregulation. This treatment modality was hence not widely used.[4] Establishment of consensus guidelines in 2009,[1] with emphasis on perioperative management, surmounted this difficulty with subsequent successful liver transplantations for atypical HUS. We report here, a successful management after liver transplantation in a patient with atypical HUS.

CASE PRESENTATION

A 27-year-old woman, who had an uneventful full term of pregnancy, underwent lower segment cesarean delivery, as she had antepartum hemorrhage. After discharge from the hospital on the eighth postpartum day, she had altered sensorium and loose watery stools sans dysentery. Subsequently, she developed oliguria and anasarca. At her local hospital, she was found to have anemia. Her hemoglobin level, which was 12 g/dl after cesarean delivery had dropped to 4.3 g/dl. Blood platelet count was 150,000/mm^3 and serum creatinine level was 11.2 mg/dl. Serum lactate dehydrogenase level was 5331 U/L. Microscopy of the peripheral smear revealed evidence of micro angiopathic hemolytic anemia. Haptoglobin level was low. Stool culture was negative for *Shigella* and *Escherichia coli*. She was transfused with packed red blood cells and given hemodialysis support. Due to a strong clinical suspicion of atypical HUS, a blood sample was sent for complement factor H antibody detection and she was started on therapeutic plasma exchange. She required alternate-day plasma exchange and hemodialysis with fluid removal as well as packed red blood cell transfusions. Despite aggressive ultrafiltration, she had recurrent pulmonary edema and 1 episode of

cardiopulmonary arrest requiring mechanical ventilation. Cardiac evaluation, which included echocardiography indicated fair left ventricular function at that time. She continued to have recurrent pulmonary edema. A repeat echocardiography done after intensive dialysis sessions showed evidence of severe left ventricular systolic and diastolic dysfunction, and she was started on digoxin and hydralazine. Following this, left ventricular ejection fraction improved to 40%. Due to severe cardiovascular complications while on dialysis and plasma exchange, she was started on eculizumab. Weekly doses of eculizumab, 900 mg each, were given for 3 weeks. She rapidly improved and was discharged in a stable state without need for dialysis, with a good urinary output and a serum creatinine level of approximately 3 mg/dl. Genetic analysis revealed mutation in complement factor H variant. Test for antibody to complement factor H was negative. One month after the last dose of eculizumab, she was readmitted with acute pancreatitis, possibly due to recurrence of the primary disease.

With a subsequent fourth dose of eculizumab, all her symptoms subsided. However, she had disease flare as evidenced by rising creatinine and schistocyte count and thus required eculizumab every month. As she was not able to afford this treatment, she was planned for liver transplantation as an alternative cost-effective treatment.

She underwent liver transplantation with her husband as an unrelated donor. Induction of immunosuppression was given with methylprednisolone. The last dose of 900 mg eculizumab was given 9 days before surgery. Surgery was complicated by failed ductal anastomosis; cholangiogram failed to demonstrate post-sectoral duct. Hepato jejunostomy was hence done. She was transfused plasma during the procedure following the consensus group protocol. Renal biopsy done during the liver transplantation revealed thrombotic microangiopathy with 10% interstitial fibrosis and tubular atrophy. One prophylactic plasma exchange was done on the second postoperative day. She, however, had oliguria and fluid overload for which she required hemodialysis and fluid removal. She was started on maintenance immunosuppression with steroids, tacrolimus, and mycophenolate mofetil. There were repeated instances of derangement of liver enzymes in the immediate postoperative period. Repeated liver biopsies did not show any evidence of rejection. Serology for cytomegalovirus was negative. She had 1 episode of generalized tonic clonic seizures with clinical and imaging features suggestive of posterior reversible encephalopathy syndrome, due to worsening blood pressure control. With strict blood

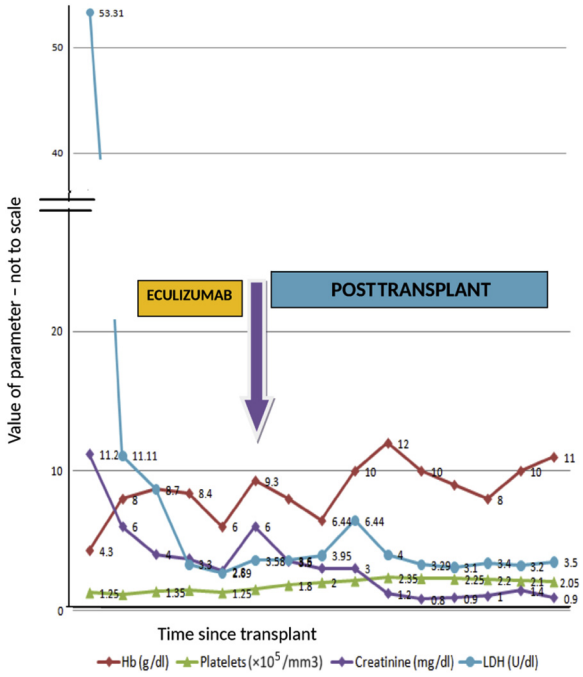

Figure 1. The hematological and biochemical parameters before and after liver transplantation (not to scale). Hb, hemoglobin; LDH, lactate dehydrogenase.

pressure control and optimization of volume status with diuretics, she became asymptomatic and was discharged with a serum creatinine level of 1.4 mg/dl. The laboratory results before and after liver transplantation are shown in Figure 1.

CLINICAL FOLLOW-UP

The young woman has been on follow-up for the past 9 months. She had 1 episode of allograft rejection 3 months after liver transplantation and was successfully managed with steroids. One week after this episode, she had 1 episode of *E coli* sepsis during which serum creatinine level transiently increased to 1.5 mg/dl and later came down to 0.9 mg/dl. Eight months after liver transplantation, she had biliary sepsis with multidrug-resistant *Klebsiella*. She had another episode of rejection as well. At the ninth month of follow-up, hemoglobin level, renal function, and platelet count were normal. She has not required any further treatment with eculizumab. The costs for various modalities of treatment that she underwent are given in Table 1.

CONCLUSION

We present our observation on a young woman with atypical HUS who underwent a successful liver transplantation. We suggest that liver transplantation is an attractive option for treatment of atypical HUS in patients who cannot afford long-term treatment with complement factor 5 inhibitors, and also in resource-limited conditions. Eculizumab, now

Table 1. The costs incurred by the patient for various modalities of treatment during the course of her illness

Procedure/drug administered	Approximate cost incurred in US $
Plasmapheresis: 15 sessions	1780 in 2 months
Eculizumab: 7 doses	79,600
Liver transplantation	28,430
Immunosuppressants on follow-up	450/month
Cost of maintenance eculizumab if had not been transplanted	11,400/month
Cost of maintenance plasmapheresis if not transplanted	1780/month

Table 2. Teaching points

1. Eculizumab is the first-line treatment available at present for patients with atypical HUS; the cost of the drug and its availability are major limitations for its use especially in resource-restricted settings.
2. Liver transplantation is an alternative treatment modality in patients with atypical HUS and is an option in countries in which eculizumab is not available or is too expensive for use.
3. Liver transplantation is safe and effective, although with variable perioperative morbidity, when done with concurrent eculizumab administration during the pretransplant period.
4. Performing liver transplantation before permanent renal injury obviates the need for a combined liver-kidney transplant; liver transplantation alone can have favorable outcomes in patients with atypical HUS.

considered to be the first-line treatment, seems to be a wonder drug for atypical HUS; however, it is an expensive drug and is not so easy to procure in many countries. There is only 1 report of use of eculizumab from India.[5] There is no data as to when the drug can be stopped or whether the dosing interval can be prolonged. As per international consensus guidelines, stopping eculizumab may be considered in children with anti–complement factor H antibody, once a titer of anti–complement factor H antibody less than 1000 AU/ml has been achieved.[6] Those with genetic mutations may, however, require lifelong eculizumab, which effectively suppresses manifestation of the disease. In contrast to blocking complement action, liver transplantation results in a near complete cure by preventing production of the abnormal complement fraction and synthesis of deficient factors produced in the liver. In theory, this is a more definitive procedure, although it is associated with the risks of morbidity and mortality. In centers with expertise in liver transplantation, the risks would be minimal and the cost of treatment definitely more affordable than that for eculizumab.

Liver transplantation for atypical HUS was suggested nearly 2 decades ago, but the early desperate attempts were unsuccessful.[S2,S3] The earlier attempts had a high rate of fatal outcomes, possibly due to uncontrolled and persistent complement activation immediately post liver transplantation.[7] These attempts, however, indicated that liver transplantation can possibly cure the disease and further transplantations demonstrated favorable outcomes.[8,S4–S6] In 2009, a study group prescribed guidelines for the perioperative care of these patients.[1] They emphasized on large volumes of plasma exchange before transplantation and plasma supplementation during transplantation. The rationale for this approach was to obtain near normal levels of functional factor H until the graft begins normal function as well as to remove defunct factor H. Following the guidelines of the 2009 study group, several successful liver transplantations have been done in many centers for patients with atypical HUS. Saland *et al.* reported a favorable outcome of 16 surviving grafts in a follow-up of 20 patients who underwent liver transplantations. Most deaths in their patients were related to vascular failure rather than because of disease recurrence.[8] In our patient, plasma exchange was not done immediately before transplantation, as eculizumab had been administered previously.

There is debate over whether to do a combined liver-kidney transplantation or a liver transplantation alone. In our patient, because renal biopsy revealed only 10% interstitial fibrosis and tubular atrophy, the prognosis of renal function was predicted to be good, a decision validated by subsequent events. Previous studies also have found renal function to be stable following isolated liver transplantation. On follow-up, our patient was found to have a serum creatinine level of 1 mg/dl and a normal urine output. Thus, liver transplantation before the development of end-stage renal disease may obviate the need for a renal transplantation.

Eculizumab is not always effective; there are reports of resistance to eculizumab when used for other indications. This resistance may due to C5 polymorphism.[9] The efficacy may also vary with time and with lifelong use of eculizumab.[6] Liver transplantation on the other hand is definitive, cost-effective, and a 1-time intervention. It could be of relevance not only in resource-restricted countries such as India where eculizumab is unavailable and is too expensive for use, but also in rich countries because resources are not enough to cover treatment costs for all patients with the disease.

Thus, liver transplantation is effective and provides near complete cure for complement-mediated atypical HUS and should be considered in patients with vascular complications who are unable to continue plasma exchange and in those who are unable to afford treatment with the complement 5 blocker eculizumab. The teaching points of this case are presented in Table 2.

DISCLOSURE

All the authors declared no competing interests

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SUPPLEMENTARY MATERIAL

Supplementary References.

Supplementary material is linked to the online version of the paper at www.kireports.org.

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