

Case Report

Posterior Reversible Encephalopathy Syndrome Following Orthotopic Liver Transplantation for Sickle Hepatopathy

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Abstract

Posterior reversible encephalopathy syndrome (PRES) occurs with increased frequency in solid organ transplant recipients and sickle cell disease patients. Sickle hepatopathy patients who require liver transplantation may be at markedly increased risk for developing PRES in the post-operative setting. Here, we describe two such cases and carefully consider causative factors.

Keywords: Posterior Reversible Encephalopathy Syndrome; Orthotopic Liver Transplant; Sickle Cell Disease

1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a rare neurologic disorder that presents with headaches, altered mental status, visual disturbances, and seizures [1]. The pathogenesis of PRES is controversial, but likely involves defects in cerebral autoregulation of blood pressure with or without associated endothelial cell dysfunction [2]. While PRES is so infrequent that its incidence is not reported in the general population, the incidence of PRES following solid organ transplantation is estimated between 0.4 and 5% [3, 4]. This association is likely related to the propensity of calcineurin inhibitor-based immunosuppression to augment hypertension, exert cytotoxic effects on

the endothelium, and cause mitochondrial dysfunction and cellular injury leading to the breakdown of the blood-brain barrier [5-7]. Likewise, PRES occurs with frequencies approaching 10% in patients with sickle cell disease (SCD) [8]. The detailed pathogenesis of PRES in SCD is also highly disputed; however, alterations in endothelial cell function caused by the accumulation of sickled cells undoubtedly contribute [9].

Sickle hepatopathy is an exceedingly rare indication for liver transplantation. Patients transplanted for sickle hepatopathy and subsequently treated with calcineurin inhibitors (CNI) have two potent risk factors for PRES. Here, we describe PRES occurring post-transplant in two such patients and explore the relationships between hypertension, sickle fraction, CNI trough, and PRES onset.

2. Case Reports

2.1 Case 1

A 54-year-old male with a past medical history of SCD and cryptogenic cirrhosis presented for liver transplantation with a Model of End Stage Liver Disease (MELD) score of 38. His sickle fraction immediately prior to surgery was 42%. The patient underwent orthotopic liver transplantation without operative complications. Intra-operative transfusion was sufficient to achieve complete exchange transfusion. Pathology from the explanted native liver was remarkable for cirrhosis with sinusoidal plugging by sickled cells and increased iron deposition (Figure 1a, 1b). Immunosuppressant medications given included a rapid methylprednisolone taper, basiliximab, and mycophenolate. Tacrolimus was started on post-operative day one.

On post-operative day five, the patient developed two episodes of witnessed seizure activity. The first episode consisted of two minutes of bilateral upper and lower extremity tonic-clonic movements and facial grimacing. The seizure stopped without treatment and was followed by a postictal period of confusion without focal neurologic deficits. A second tonic-clonic seizure occurred two hours later that lasted one minute and also resolved without treatment. Of note, the patient was hypertensive at the times of these seizures with systolic blood pressure as high as 177 mmHg (Figure 3a). Hypertension was treated, levetiracetam was given, and head computed tomography (CT) did not reveal acute intracranial pathology. Magnetic resonance imaging (MRI) was significant for bilateral hyperintensities involving the parietal lobes, the superior frontal lobes, and temporal-parieto-occipital watershed regions consistent with a diagnosis of PRES (Figure 2). Tacrolimus was discontinued. Phlebotomy was performed to reduce any contribution from hyperviscosity. At the time of these seizures, the tacrolimus level was 5.7 ng/mL and the sickle fraction was 9.9% (Figure 3a).

The patient's subsequent inpatient course was unremarkable. He was discharged to a skilled nursing facility on post-operative day 13 and transitioned to home shortly thereafter. At the time of discharge, transaminases had normalized and total bilirubin was down-trending. Discharge medications included everolimus, mycophenolate, prednisone, and levetiracetam. Three months after the transplant, everolimus was discontinued and tacrolimus was restarted under

close observation and strict blood pressure control. No further seizure activity has occurred. Regrettably, a liver biopsy performed four months after transplant demonstrated recurrent sinusoidal distention and sickle cell clumping (Figure 1c, 1d) suggestive of recurring sickle hepatopathy. Ongoing management of the patient's SCD continues, and overall he is doing well as he approaches his first transplant anniversary.

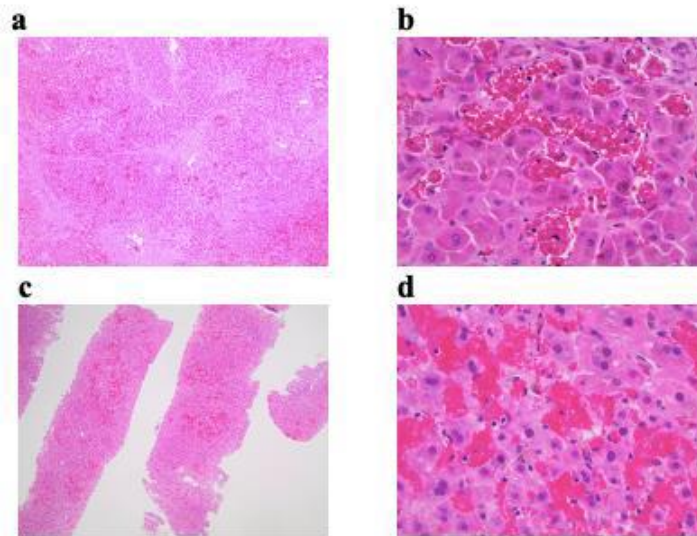


Figure 1: Hemotoxylin and Eosin (H&E) stains of explanted (a, b) and 3.5 months post-transplant (c, d) liver for the patient described in Case 1. (a) Low power (40x) showing cirrhotic nodules and congested sinusoids (b) High power (400x) showing plugging of sinusoids by clumps of sickled cells, consistent with sickle cell hepatopathy (c) Low power (40x) showing sinusoidal congestion (d) High power (400x) showing diffuse sinusoidal distention by clumps of sickled cells.

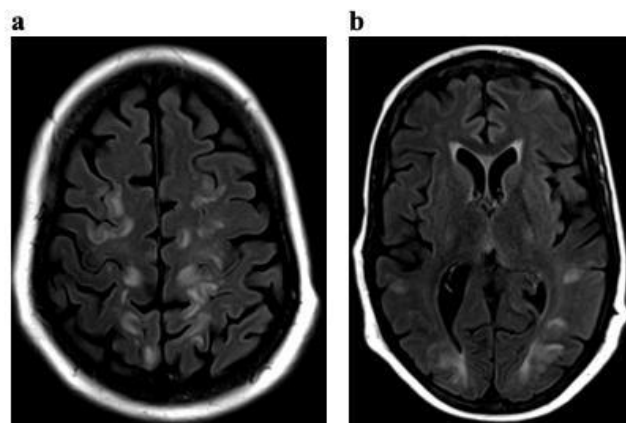


Figure 2: MRI images demonstrating (a) frontoparietal paracentral cortical and (b) subcortical hyperintensity consistent with PRES for the patient presented in Case 1.

2.2 Case 2

A 29-year-old male with a past medical history of SCD and cirrhosis secondary to severe sickle hepatopathy presented for liver transplantation with a MELD score of 48. The patient underwent orthotopic liver transplantation and required return to the operating room on post-operative day one to control bleeding. Following this re-operative laparotomy, he was quickly weaned off vasopressors and transferred out of the intensive care unit. Immunosuppression included a rapid steroid taper and mycophenolate.

On post-operative day three, tacrolimus was started. Just hours after the first tacrolimus dose, the patient developed new hypertension with systolic blood pressure as high as 168 mmHg (Figure 3b). The following day he experienced a witnessed generalized tonic-clonic seizure. Lorazepam, lacosamide, and levetiracetam were administered, and a head CT was negative for acute intracranial hemorrhage. MRI revealed extensive abnormal cortical/subcortical signal throughout the bilateral cerebral hemispheres with leptomeningeal enhancement suggestive of severe PRES. Tacrolimus was stopped, cyclosporine was substituted, and hypertension was treated. At the time of the seizure event, the sickle fraction was 6.6% and the tacrolimus level was 2.6 ng/mL (Figure 3b).

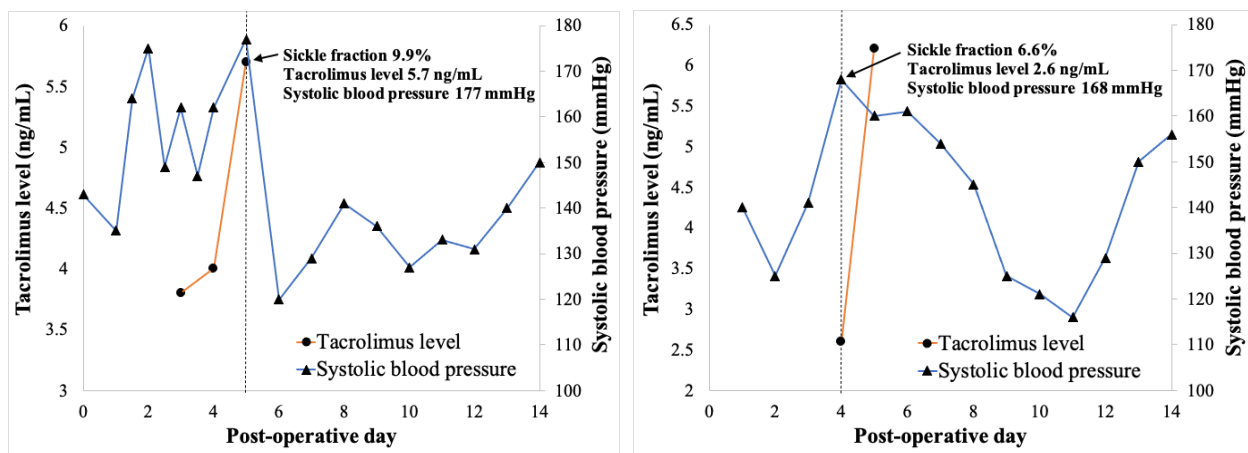


Figure 3: Systolic blood pressures and tacrolimus levels following transplant in Case 1 (a) and Case 2 (b). The dashed line represents the day of seizure onset. Tacrolimus was stopped at seizure onset, though further troughs were recorded in Case 2.

Although medically stable following this event, the patient began to manifest notable behavioral changes including refusal to take his medications, aggressive and inappropriate sexual behaviors, trichotillomania, and handling of his feces. A brain MRI was obtained on post-operative day 17, which demonstrated a new focal 3.6×3.0 cm left frontal intraparenchymal hemorrhage with trace adjacent extra-axial hemorrhage. He was transferred to the neurocritical care unit and cyclosporine was stopped. An electroencephalogram (EEG) demonstrated status epilepticus which was broken with topiramate and fosphenytoin.

On post-operative day 18, the patient was started on rapamycin. Behavior improved, although serum transaminases and gamma-glutamyl transferase levels rose. A liver biopsy was performed on post-operative day 32 that demonstrated moderate acute cellular rejection for which a steroid pulse was given. Tacrolimus was restarted the following day with close neuro-monitoring and no further seizure activity occurred. The patient was discharged from the hospital on post-operative day 44 with appropriate liver function and normalized cognition and behavior. Throughout this hospitalization, the sickle fraction never exceeded 16.5%.

Since the transplant, the patient was re-admitted twice for acute chest syndrome treated with exchange transfusion and twice for elevated liver function tests in the setting of medication non-compliance. During these admissions, biopsies demonstrated moderate to severe acute cellular rejection and prominent sinusoidal dilation and congestion with sickled red blood cells, consistent with recurrent sickle cell hepatopathy. He was eventually discharged to home hospice and died of recurrent hepatopathy and allograft failure 2.5 years after his transplant.

3. Discussion

PRES is an acute neurologic disorder characterized by subcortical vasogenic brain edema. Conditions such as renal failure, hypertension, autoimmune disease, immunosuppression with CNIs, and sickle cell disease predispose to developing PRES. Following orthotopic liver transplantation, PRES must be considered in the differential for any SCD patient with acute neurologic changes after stroke has been ruled out [9-11]. Symptoms of PRES are generally non-specific and include headaches, visual disturbances, seizures, and focal neurologic abnormalities. Diagnosis is made with MRI which classically shows vasogenic edema in the bilateral parieto-occipital regions. Most cases of PRES are reversible, but some cases progress to status epilepticus, intracranial hemorrhage, and death. Treatment aims to reverse the precipitating cause, including blood pressure control, changing or stopping immunosuppression, and anti-epileptic medications as needed [1, 2].

The liver transplant recipients described here had both SCD and CNI exposure as risk factors for PRES. In both cases, PRES occurred 4-5 days post-transplant and during periods of uncontrolled hypertension. It is worth noting that liver transplant recipients on-track in their recovery typically begin to mobilize third-spaced fluid during these post-operative days resulting in moderate hypertension. In both patients, PRES occurred shortly after initiation of CNIs, although drug levels were not supra-therapeutic in either case. At the time of neurologic symptom onset, the sickle fraction in each case was well within the recommended range, likely due to intra-operative blood loss and resulting transfusions. In the first case, everolimus was immediately substituted for tacrolimus. PRES resolved and immunosuppression was sufficient to prevent rejection. In the second, younger patient, there was a reluctance to stop CNIs altogether due to a heightened risk of acute rejection. However, cyclosporine was poorly tolerated and neurocognitive side effects led to medication non-compliance and early acute rejection. Levetiracetam was continued long-term in both patients, and in this setting, tacrolimus was successfully reintroduced without recurrent PRES. These cases highlight the challenges posed by liver transplantation in this patient population, as PRES can

occur even when the sickle fraction is well-controlled and CNI trough levels are low. Potential strategies to mitigate the risk of post-transplant PRES in sickle cell patients include meticulous control of post-operative blood pressure, initiation of prophylactic levetiracetam at the time of transplant, and delay of CNI initiation for as long as possible. Furthermore, in addition to the risks of PRES posed in SCD patients, these cases also illustrate that recurrent sickle hepatopathy is a significant threat to long-term allograft survival.

A recent comprehensive review identified only twenty-eight total liver transplant cases for sickle hepatopathy in the entire Scientific Registry for Transplant Recipients (SRTR) database [12], and one of two patients described in detail in this series experienced PRES. The largest published single-center experience with liver transplantation for sickle hepatopathy, from the Henri Mondor University Hospital in France, describes PRES in three of twenty-one total patients [13]. Within a six patient series by Hurtova and colleagues, four patients experienced neurologic complications of some type including one definitively diagnosed case of PRES [14]. Because there is no reporting system that comprehensively captures neurologic complications following liver transplantation, we suspect the actual incidence of PRES and other neurologic complications may be much higher than reported in SCD patients. Control of hypertension and maintaining a high index of suspicion are essential for prompt detection, treatment, and to avoid devastating neurologic complications.

References

1. Fugate JE, Claassen DO, Cloft HJ, et al. Posterior reversible encephalopathy syndrome: associated clinical and radiologic findings. *Mayo Clin Proc*;85 (2010): 427-432.
2. Fischer M, Schmutzhard E. Posterior reversible encephalopathy syndrome. *J Neurol* 264 (2017): 1608-1616.
3. Bartynski W, Tan H, Boardman J, et al. Posterior Reversible Encephalopathy Syndrome after Solid Organ Transplantation. *Am J Neuroradiol* 29 (2008): 924-930.
4. Barbas A, Rege A, Castleberry A, et al. Posterior reversible encephalopathy syndrome independently associated with tacrolimus and sirolimus after multivisceral transplantation. *Am J Transpl* 13 (2013): 808-810.
5. Hoorn EJ, Walsh SB, McCormick JA, et al. Pathogenesis of calcineurin inhibitor-induced hypertension. *J Nephrol* 25 (2014): 269-275.
6. Wu O, Marescaux C, Wolff V, et al. Tacrolimus-Associated Posterior Reversible Encephalopathy Syndrome after Solid Organ Transplantation. *Eur Neurol* 64 (2010): 169-177.
7. Kou R, Greif D, Michel T. Dephosphorylation of endothelial nitric-oxide synthase by vascular endothelial growth factor. Implications for the vascular responses to cyclosporin. *J Biol Chem* (2002); 277.
8. Khademian Z, Speller-Brown B, Nouriaie S-M, et al. Reversible posterior leuko-encephalopathy in children with sickle cell disease. *Pediatr Blood Cancer* 52 (2009): 373-375.

9. Solh Z, Taccone MS, Marin S, et al. Neurological PRESentations in Sickle Cell Patients Are Not Always Stroke: A Review of Posterior Reversible Encephalopathy Syndrome in Sickle Cell Disease. *Pediatr Blood Cancer* 50 (2016): 1018-10 25.
10. Sullivan K, Kissoon N, Gauger C. Nitric oxide metabolism and the acute chest syndrome of sickle cell anemia. *Pediatr Crit Care Med* 9 (2008): 159-168.
11. Wahl S, Quirolo K. Current issues in blood transfusion for sickle cell disease. *Curr Opin Pediatr* 21 (2009): 15-21.
12. Hogan R, Kim M, Lee Y, et al. Liver Transplantation in Patients with Sickle Cell Disease in the United States. *J Surg Res* 255 (2020): 23-32.
13. Levesque E, Lim C, Feray C, et a.l. Liver transplantation in patients with sickle cell disease: possible but challenging—a cohort study. *Transplant Intl* 33 (2020): 1220-1229.
14. Hurtova M, Bachir D, Lee K. Transplantation for liver failure in patients with sickle cell disease: challenging but feasible. *Liver Transplantation* 17 (2011): 381-392.

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