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An Unusual Presentation of Posterior Reversible Encephalopathy Syndrome Following Liver Transplantation

Akila Rajakumar, MD, FRCA,[1] Susan Paulin, MD,[1] Dinesh Devarajan, MD,[1] Dinesh Jothimani, MRCP, FRCP,[2] Shubha Subramanian, MD, DM,[3] Srinivasan Kalyanasundaram, MD,[4] and Mohamed Rela, MS, FRCS, DSc[5]

INTRODUCTION

The earliest description of posterior reversible encephalopathy syndrome (PRES) was given in 1996 by Hinchey et al[1] as a diverse group of clinical and radiological findings characterized by headache, paresis, visual disturbances, seizures, and altered consciousness, along with radiological evidence of bilateral subcortical vasogenic edema that was more apparent on the posterior cerebral hemispheres. PRES is typically described after solid organ or bone marrow transplantation with the incidence being 0.5% to 5% and is most commonly associated with tacrolimus.[2,3] The incidence of PRES following liver transplantation (LT) has been around 1%.[3] PRES is also reported in cases of hypertensive encephalopathies, such as eclampsia and haemolysis, elevated liver enzymes, and low platelet count syndrome.[4] PRES is completely reversible in majority of the instances; however, incidences of some residual neurological impairment have been reported.[5]

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[1] Department of Liver Anesthesia and Intensive Care, Institute of Liver Disease and Transplantation, Dr. Rela Institute and Medical Centre, Bharath University of Higher Education and Research, Chennai, India.

[2] Department of Hepatology, Institute of Liver Disease and Transplantation, Dr. Rela Institute and Medical Centre, Bharath University of Higher Education and Research, Chennai, India.

[3] Department of Neurology, Dr. Rela Institute and Medical Centre, Bharath University of Higher Education and Research, Chennai, India.

[4] Department of Radiology, Dr. Rela Institute and Medical Centre, Bharath University of Higher Education and Research, Chennai, India.

[5] Department of HPB Surgery and Liver Transplantation, Institute of Liver Disease and Transplantation, Dr. Rela Institute and Medical Centre, Bharath University of Higher Education and Research, Chennai, India.

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Correspondence: Akila Rajakumar, MD, FRCA, Clinical Lead, Department of Liver Anesthesia and Intensive Care, Dr. Rela Institute and Medical Centre, 7, CLC Works Rd, Chromepet, Chennai 600044, India. (drakila.rajakumar@gmail.com).

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It is important to promptly diagnose PRES, including atypical variants after LT, and initiate appropriate symptomatic treatment and management of immunosuppressive medications.

Here, we report a patient with an unusual presentation of PRES with a brief review of literature. Institutional ethical committee approval was obtained. Our patient had clinical features of PRES with atypical radiological changes after living donor LT, which has not been reported to date. Our patient showed complete recovery with modification of immunosuppressive medications and supportive management.

CASE REPORT

A 49-y-old man with a diagnosis of biopsy-proven nonalcoholic steatohepatitis–related end-stage liver disease underwent living donor LT. His preoperative decompensation included refractory ascites and 3 episodes of upper gastrointestinal bleeding. He did not have any episodes of hepatic encephalopathy. The patient had no history of alcohol or any other substance abuse and did not suffer from any comorbid medical illnesses. His model for end-stage liver disease score at transplant was 26, and his preoperative cardiopulmonary evaluation was satisfactory. His lipid profile was within normal limits. His preoperative contrast-enhanced computerized tomography abdomen showed evidence of chronic parenchymal liver disease, normal vascular anatomy, splenomegaly with portosystemic collaterals, and shunting. He had normal renal function pretransplantation.

His son came forward for donation. The patient received a right lobe graft. Right lobe without middle hepatic vein was used, and no anterior sector reconstruction was performed. The graft had a single right hepatic artery with 2 bile ducts requiring 2 anastomoses. The graft weight to recipient weight ratio was 1.02. Moderate splenomegaly was noted along with small collateral vessels in the hilum and retroperitoneum. There were no major portosystemic shunts. The portal pressure was found to be 21 mm Hg before implantation and 13 mm Hg after implantation.

The intraoperative course was straightforward. Reperfusion was uneventful, and the estimated blood loss was around 1000 mL. He was transferred to the intensive care unit for postoperative care and was extubated after 8 h of ventilation. Postoperatively, his hemodynamics were stable with no vasopressor requirement, and serum lactate levels were

consistently <2.0 mmol/L. Immunosuppression was administered as per our institutional protocol. Intraoperatively, 10 mg/kg methylprednisolone (MPS) was administered before reperfusion. MPS and tacrolimus with a target therapeutic level of 5 to 10 ng/mL were started from postoperative day (POD) 1. His blood pressure was high on the first POD, which settled with antihypertensives. Fluid management was goal directed, and there was no evidence of hypovolemia during this period. His kidney function was within normal limits. His liver function tests showed cholestasis with total bilirubin of 9.69 mg/dL, international normalized ratio of 1.6, and serum creatinine of 0.56 mg/dL on POD 5. His drain output was minimal.

On POD 5, there was a sudden onset of aphasia along with right upper and lower limb weakness, disorientation, and irritability. An immediate computerized tomography scan of the brain did not reveal any abnormality. A computerized tomography angiogram performed to rule out reversible cerebral vasoconstriction syndrome was also unremarkable. No evidence of venous sinus thrombosis was seen. Magnetic resonance imaging (MRI) brain showed diffusion restriction in bilateral frontal gyri and subcortical white matter of left parieto-occipital lobes, not conforming to any vascular territory (Figure 1). Neurologist consult was obtained. The patient was started on levetiracetam as an antiepileptic. A provisional diagnosis of tacrolimus-induced PRES was made. Tacrolimus was discontinued, and low-dose cyclosporine along with mycophenolate mofetil (MMF) was added. MPS was continued. His sensorium recovered the same day. His tacrolimus level was 6.3 ng/mL at that time. There was no evidence of any focus of sepsis, and his serum electrolytes were within normal range.

On POD 6, he developed focal seizures involving the right upper limb, which initially resolved with further addition of 2 more antiepileptics. The patient continued to have recurrent focal seizures and gradually developed altered sensorium. He was electively intubated on POD 7, and MRI brain was repeated, which showed increase in hyperintense signals on T2-weighted images and fluid-attenuated inversion recovery images in the bilateral frontoparietal lobes and interval new changes in pre- and postcentral gyri. These areas showed diffusion restriction with low apparent diffusion coefficient values along the gyral margins. On contrast administration, linear leptomeningeal enhancement was observed in the sulcal spaces of the involved cortices (Figure 2). These imaging findings were attributed to atypical manifestations of PRES. Electroencephalogram continued to show epileptiform activity; hence, further doses of cyclosporine were stopped, fosphenytoin was added, and acyclovir was started empirically. Everolimus was added in addition to MMF and MPS 40 mg once daily. In view of persistent epileptiform activity on electroencephalogram despite multiple antiepileptic drugs, lumbar puncture and cerebrospinal fluid (CSF) analyses were performed to rule out infection. Biochemical and cytological analyses of CSF were normal, and cultures were sterile. CSF meningoencephalitis panel and Gene Xpert were negative. Serum herpes simplex virus and cytomegalovirus polymerase chain reaction tests were also negative. There was gradual resolution of seizure activity, following which the patient was gradually weaned from sedation and mechanical ventilation. A liver biopsy done on day 21 for elevated liver enzymes showed bilirubinostasis and mild portal fibrosis with no evidence of rejection. Immunosuppression was continued with everolimus, prednisolone, and MMF. Aggressive neurorehabilitation was continued. His power improved gradually; he became ambulant and articulate and was discharged from the hospital on POD 46. The patient remains well 7 mo after his living donor LT. (Please see Table 1 for significant investigation reports.) Explant histopathology also confirmed the diagnosis of nonalcoholic steatohepatitis.

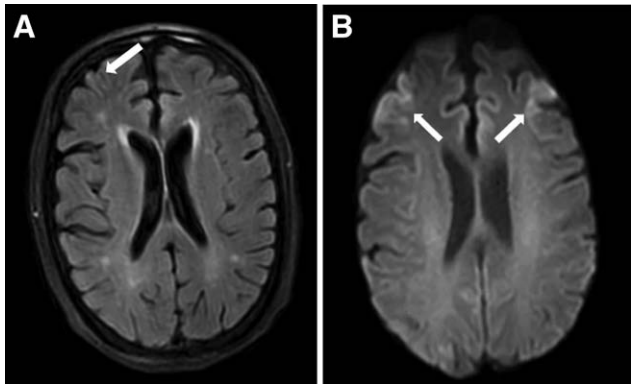

FIGURE 1. A, Axial FLAIR image shows subtle cortical hyperintense signal in the right frontal lobe (arrow). Chronic small vessel ischemic changes are noted in the bilateral white matter. Axial diffusion-weighted image (B) shows diffusion restriction in the bilateral frontal cortices and subcortical white matter of left parietal lobe (arrows). FLAIR, fluid-attenuated inversion recovery.

DISCUSSION

Calcineurin inhibitors (CNIs) have emerged as the standard of care for immunosuppression immediately after transplantation. Hypertensive episodes are also very frequent after transplantation because of the use of MPS. Both the factors have been shown to be associated with PRES. It is important to have a high index of suspicion to diagnose this condition after exclusion of other common causes because prompt identification and management have been shown to reduce morbidity and support early and complete recovery.

The typical MRI appearance of PRES includes T2-weighted and fluid-attenuated inversion recovery hyperintensities in the parieto-occipital and posterior frontal gyri and the subcortical white matter. Less commonly involved regions include the thalamus, cerebellum, basal ganglia, and brainstem.[6] The atypical imaging appearances that have been reported with PRES include diffusion restriction (15%–30% of cases), contrast enhancement (20%–30%), and hemorrhage (15%–20%) in the involved areas.[7,8] Although these findings are described as atypical, their presence in an appropriate clinical context should not impede the diagnosis of PRES. Our patient exhibited an atypical presentation, as there was diffusion restriction suggesting cytotoxic edema and leptomeningeal enhancement.

Altered sensorium along with varied neurological symptoms like paresis, other focal neurological deficits, headache, or seizures following LT can occur following ischemia, thrombosis, intracranial hemorrhage, or immune-mediated inflammation. Most of these differential diagnoses can be excluded by imaging and laboratory findings. Apart from PRES, such presentation can be seen with osmotic demyelination syndrome, posttransplantation lymphoproliferative disorders, and progressive multifocal leukoencephalopathy (PML).[9] Osmotic demyelination syndrome is because of abrupt changes in serum sodium levels, and these patients have typical features on MRI,

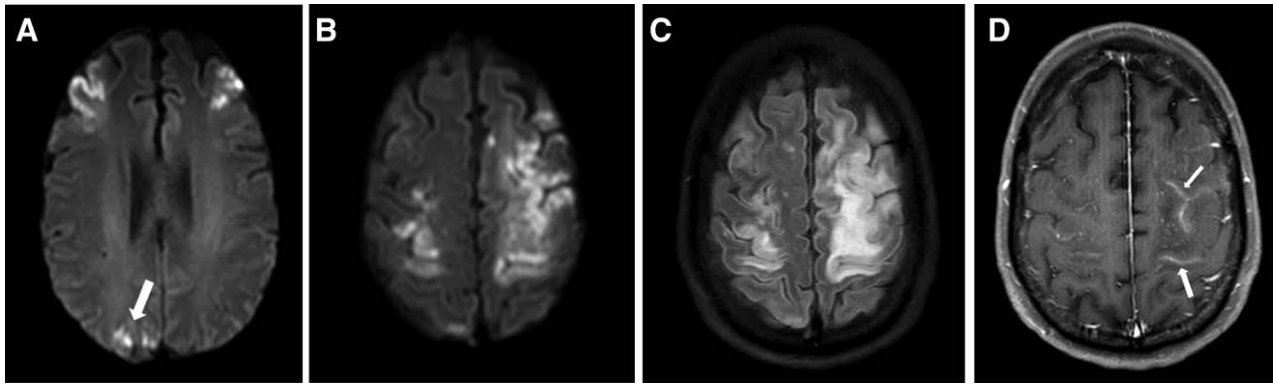

FIGURE 2. A–D, MRI performed on POD 7. Axial DW image (A) shows interval increase in extent of the signal changes in the bilateral frontal lobes and new lesion in right parietal lobe (arrow). Axial DW image (B) and FLAIR image (C) at a higher level show interval new lesions with diffusion restriction in the bilateral precentral and postcentral gyri and middle frontal gyri. Axial postcontrast T1W image (D) shows linear leptomeningeal enhancement in the bilateral frontal sulcal spaces adjoining the abnormal cortices (arrows). DW, diffusion-weighted; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; POD, postoperative day; T1W, T1-weighted.

which include hypointense lesions on T1-weighted images, hyperintense signals on fluid-attenuated inversion recovery, and T2-weighted images in pons and striatum.[10,11] Posttransplantation lymphoproliferative disorder is characterized by multiple contrast-enhancing lesions and has other tests that include Epstein Barr virus DNA, CSF cytology, and biopsy to help in diagnosis.[12,13] The imaging features of PML include multifocal white matter lesions, predominantly involving the subcortical white matter of the parietal, occipital, and frontal lobes. These lesions appear hypointense to cortex on T1-weighted images and hyperintense to cortex on T2-weighted images and show high signal on the diffusion-weighted imaging with normal-to-low signal in the apparent diffusion coefficient map. Magnetic resonance spectroscopy, detection of John Cunningham virus DNA, and brain biopsy will further help in diagnosis of PML.[14,15]

It is important to remember that in any posttransplant patient receiving CNIs, the sudden occurrence of neurological symptoms should raise the concern for PRES after careful exclusion of more common causes, which include infectious causes such as herpes virus encephalitis, PML, and cytomegalovirus meningoencephalitis. MRI needs to be performed at the earliest opportunity. Some unusual clinical presentations like optic neuropathy with monoplegia and convulsions have also been reported.[16]

The pathophysiology of PRES following LT has not been clearly understood. CNIs, because of their potent vasoconstrictor property, can result in excessive endothelin and reactive oxygen species production and vasogenic cerebral edema.[17,18] Dysfunction of cerebral autoregulation because of hypertension was also proposed to cause PRES, but normal or low blood pressure has been observed in 25% of the cases, which suggests that abrupt changes of blood pressure rather than a persistent elevation of it could play a role in pathogenesis of PRES.[17] PRES usually presents at a median of 31 d (11–68 d) posttransplant.[3] Bartynski et al[2] have reported occurrence of PRES in the immediate or early period after transplantation also because of significant bacterial infection and biopsy-positive organ rejection.

PRES has been reported with both tacrolimus and cyclosporine, and relative safety has not been studied so far.[3,19] Mammalian target of rapamycin inhibitors have also been shown to be associated with PRES.[20,21] It has also been observed that tacrolimus neurotoxicity is not dose related as seen in our patient.[16,22] There has been no literature showing association with timing of initiation of CNIs and the occurrence of PRES. The idiosyncratic neurotoxicity can be because of genetic polymorphisms in CYP3A5 that enhance susceptibility to tacrolimus-related neurotoxicity.[23,24] It is also presumed that variable pharmacogenetics can affect blood concentrations of tacrolimus and cause

TABLE 1.

Preoperative and postoperative investigations

	Preop	POD 1	POD 2	POD 3	POD 5	POD 6	POD 7	POD 8	POD 14
Bilirubin, mg/dL, total/direct	6.8/2.6	13.6/7.3	7.3/3.5	9.0/4.7	9.6/6.1	9.4/5.7	12.5/8.6	9.0/6.4	1.3/0.8
AST/ALT, U/L	32/12	118/119	80/114	53/93	29/46	43/36	67/44	42/33	76/105
INR	2.98	2.31	2.28	1.60	1.64	1.45	1.06	0.98	1.11
Creatinine, mg/dL	0.59	0.54	0.48	0.47	0.56	0.77	0.68	0.8	–
Magnesium, mg/dL	–	2.3	2.4	2.8	2.1	2.0	1.9	–	–
Ammonia, µmol/L	57	–						–	–
Tacrolimus, ng/mL				3.5	6.3			–	–
Steroid dose		MPS 16 mg	MPS 16 mg	MPS 16 mg	MPS 16 mg	P20	P20	P40	P20
Immunosuppression		Tac 1 mg BD	Tac 1 mg BD	Tac 1-0-2	Tac 2 mg BD	Cys 75 mg OD	Cys 75 mg OD + MMF 500 mg BD	MMF 500 mg BD	MMF 500 mg BD + everolimus 0.25 mg BD

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BD, twice daily; Cys, cyclosporine; INR, international normalized ratio; MMF, mycophenolate mofetil; MPS, methylprednisolone; OD, once daily; P, prednisolone; POD, postoperative day; Preop, preoperative; Tac, tacrolimus.

increased drug-related adverse effects with increasing concentrations.[25,26] In our patient, we did not find any associated issues like sepsis, rejection, or electrolyte imbalance like hyponatremia or hypomagnesemia as reported in other studies.[3] Nevertheless, therapeutic drug monitoring seems very crucial when treating patients with CNIs. Urinary magnesium excretion is increased with CNIs, causing hypomagnesemia, and this effect seems to be more pronounced with tacrolimus in comparison with cyclosporine.[27] Vasodilatory effects of magnesium sulfate can potentially help in reducing cerebral edema. Close serum magnesium level monitoring and supplementation when needed have been strongly recommended in patients on tacrolimus to limit neurotoxicity.

The incidence of rejection has been reported to be as high as 42% at 2 mo after an initial diagnosis of PRES,[3] but our patient, fortunately, did not have rejection episodes. It was also noted that these patients were on 2 immunosuppressive drugs and low tacrolimus trough levels were observed during the transitional period.[3] Therefore, changes in immunosuppression have to be done very carefully to minimize the risk of early allograft rejection. Management usually involves stopping tacrolimus and switching to cyclosporine, as has been our unit's practice and also been widely reported.[3,28] In our patient, switching over to cyclosporine caused further worsening of neurological status, necessitating stopping and switching over to everolimus. Our patient was managed successfully on everolimus, MMF, and prednisone. Heidenhain et al[29] reported a case of PRES where neurological symptoms worsened after switch to cyclosporine from tacrolimus, and subsequently after stopping CNIs completely, the patient made a complete recovery; they, therefore, recommended discontinuation of any CNIs in the event of PRES. Lunardi et al[30] have also demonstrated safe management of immunosuppression with everolimus and MMF in tacrolimus-related PRES.

It is important to understand the varied neurological presentations of PRES in posttransplant patients and to have a high index of suspicion. Prompt diagnosis, appropriate supportive therapy, and immunosuppression management can help in complete reversal of this syndrome in addition to preserving graft function. While allowing neurotoxicity to recover, it is important to avoid organ rejection. It is also imperative to address hypertensive episodes promptly in these patients.

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