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Posterior Reversible Encephalopathy Syndrome After Orthotopic Heart Transplantation: A Case Report

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Conflict of interest: None declared

Patient: Female, 32
Final Diagnosis: Posterior reversible encephalopathy syndrome
Symptoms: Seizures
Medication: Tacrolimus
Clinical Procedure: —
Specialty: Cardiology

Objective: Rare disease

Background: Calcineurin inhibitor-induced posterior reversible encephalopathy syndrome (PRES) is well described in liver and kidney transplant patients, but there is a paucity of data in heart transplant patients. PRES syndrome in the setting of heart transplantation can occur as early as 5 days following transplantation.

Case Report: A 32-year-old woman who had recently undergone orthotopic heart transplantation developed headaches, visual disturbances, and generalized tonic clonic seizures 5 days after initiating anti-rejection therapy (tacrolimus, mycophenolate, and prednisone). No focal neurological deficits were noted on physical exam. Multifocal subcortical fluid attenuation inversion recovery (FLAIR) hyperintensity signals and areas of diffusion restriction with postcontrast enhancement, diagnostic of PRES, were found on MRI brain. Her symptoms resolved 2 days after tacrolimus was switched to cyclosporine. A follow-up MRI after 6 weeks demonstrated complete resolution of areas of flair hyperintensity signal. She was sent home on a short course of seizure prophylaxis, which was discontinued after the resolution of radiological findings. She had no further episodes of seizures for 6 months following discontinuation of her anti-epileptic regimen.

Conclusions: Tacrolimus-induced PRES can occur as early as 5 days after orthotopic heart transplantation. Early recognition of symptoms and management can prevent permanent neurological sequelae.

MeSH Keywords: Heart Transplantation • Immunosuppression • Seizures • Tacrolimus

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/903403>



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Background

Calcineurin inhibitors revolutionized management of patients who underwent solid organ transplantation by effectively reducing acute rejection episodes and improving survival [1]. Neurotoxicity with these medications ranges from a mild tremor, acute confusional state, to status epilepticus or even major speech and motor abnormalities. Posterior reversible encephalopathy is one such neuroradiological phenomenon diagnosed by an MRI. Without prompt recognition and management, it can lead to progression of vasogenic edema to cytotoxic edema, resulting in permanent neurological deficits. This phenomenon is well studied in liver, kidney, and hematopoietic stem cell transplant patients, but very little data exist in the current literature about its incidence in post-heart transplant patients [1–3]. Here, we discuss the clinical course of one such case that was successfully identified and managed appropriately.

Case Report

A 32-year-old woman with a history of end-stage non-ischemic cardiomyopathy on chronic home milrinone therapy and chronic migraines was admitted to the hospital for cardiogenic shock. An intra-aortic balloon pump was placed as a bridge to orthotopic heart transplantation owing to persistent hypotension despite dual-ionotropic support. She experienced intermittent bouts of her typical migraine headaches consisting of a prodrome of kaleidoscope-like visual disturbances. Her symptoms were generally well controlled with sumatriptan when administered at the advent of her prodrome. However, given the patient's underlying cardiac complications, intravenous Divalproex sodium was instituted as abortive therapy (continued oral Divalproex sodium for migraine prophylaxis) with successful resolution. After a suitable donor heart was obtained, she underwent orthotopic heart transplantation. Her anti-rejection (immunosuppressive) therapy consisted of mycophenolate mofetil, Prednisone, and tacrolimus. Five days following initiation of tacrolimus, she reported a severe headache that was without prodromal symptoms and was resistant to abortive migraine therapy. A few hours later, she had an episode of generalized tonic clonic seizures, which resolved spontaneously after 1 minute. While an emergent CT head was being performed, she suffered another episode of generalized tonic clonic seizure. This time, seizures subsided following administration of intravenous Ativan. No evidence of bleeding or infarct was noted on the CT head. Vital signs were unremarkable except for a significantly elevated systolic blood pressure of 180/90 mmHg. A comprehensive neurological exam was performed and was noted to be unremarkable without any focal neurologic deficits. Complete blood count and complete metabolic panel were within normal limits. Serum tacrolimus level

and magnesium levels were 2.8 ng/ml and 1.5 mg/dl, respectively. She received a loading dose of Divalproex sodium intravenously for seizure prophylaxis and an anti-epileptic regimen was instituted. An electroencephalogram (EEG) demonstrated mild-to-moderate generalized slowing without clear epileptiform discharges. An MRI showed areas of subcortical FLAIR hyperintensity in the bilateral frontal, parietal, and occipital lobes, as well as the cerebellum, consistent with PRES (Figure 1). After the patient regained baseline mentation, she described transient visual disturbances (with patches of green in her visual fields). Considering MRI findings and the recent use of tacrolimus, PRES was our leading hypothesis. Therefore, tacrolimus was switched to cyclosporine. Hypertension was addressed with intravenous hydralazine with a systolic blood pressure goal of less than 140 mmHg, and magnesium was supplemented. Over the course of 3 days, her headache and visual disturbances gradually resolved. A follow-up MRI after 6 weeks demonstrated resolution of previous FLAIR signal abnormalities, with no abnormal post-contrast enhancement, corroborating the diagnosis of PRES. No further episodes of seizures were reported after the discontinuation of her anti-epileptic regimen following radiological resolution.

Discussion

Hinchey and colleagues were the first to describe posterior reversible encephalopathy syndrome (PRES) in 1996 in 15 patients, most of whom were on immunosuppressive therapy [4]. PRES is a clinico-neuroradiological syndrome that commonly manifests as seizures (77.5%), encephalopathy (62%), headache (29.6%), visual disturbances (22.5%), or focal neurological symptoms (22.5%). A wide range of neurological symptoms are reported with PRES, from mild transient reversible neurological symptoms to severe and debilitating, occasionally resulting in permanent neurologic sequelae. A literature review by Song and colleagues discovered that 89.3% of patients with CNI-associated PRES had a full recovery and an additional 10.7% recovered with neurological sequelae [3]. Patients with notable hemorrhagic lesion on imaging recovered with neurological sequelae. The patho-physiological mechanism underlying PRES is not fully understood. Postulated hypotheses include medication-induced endothelial damage and hypo- or hyperperfusion due to disruption of cerebral autoregulation precipitated by uncontrolled hypertension. Regardless of the underlying mechanism, transient vasogenic edema occurs, which can be detected on MRI. Delayed diagnosis can offset cytotoxic edema and result in permanent neurological sequelae. Frequently implicated triggers are eclampsia, hypertensive emergency, or exposure to immunosuppressive therapy (as reported in our case), as well as numerous other uncommon causes. Commonly implicated immunosuppressant medications are calcineurin inhibitors (e.g., cyclosporine and tacrolimus).

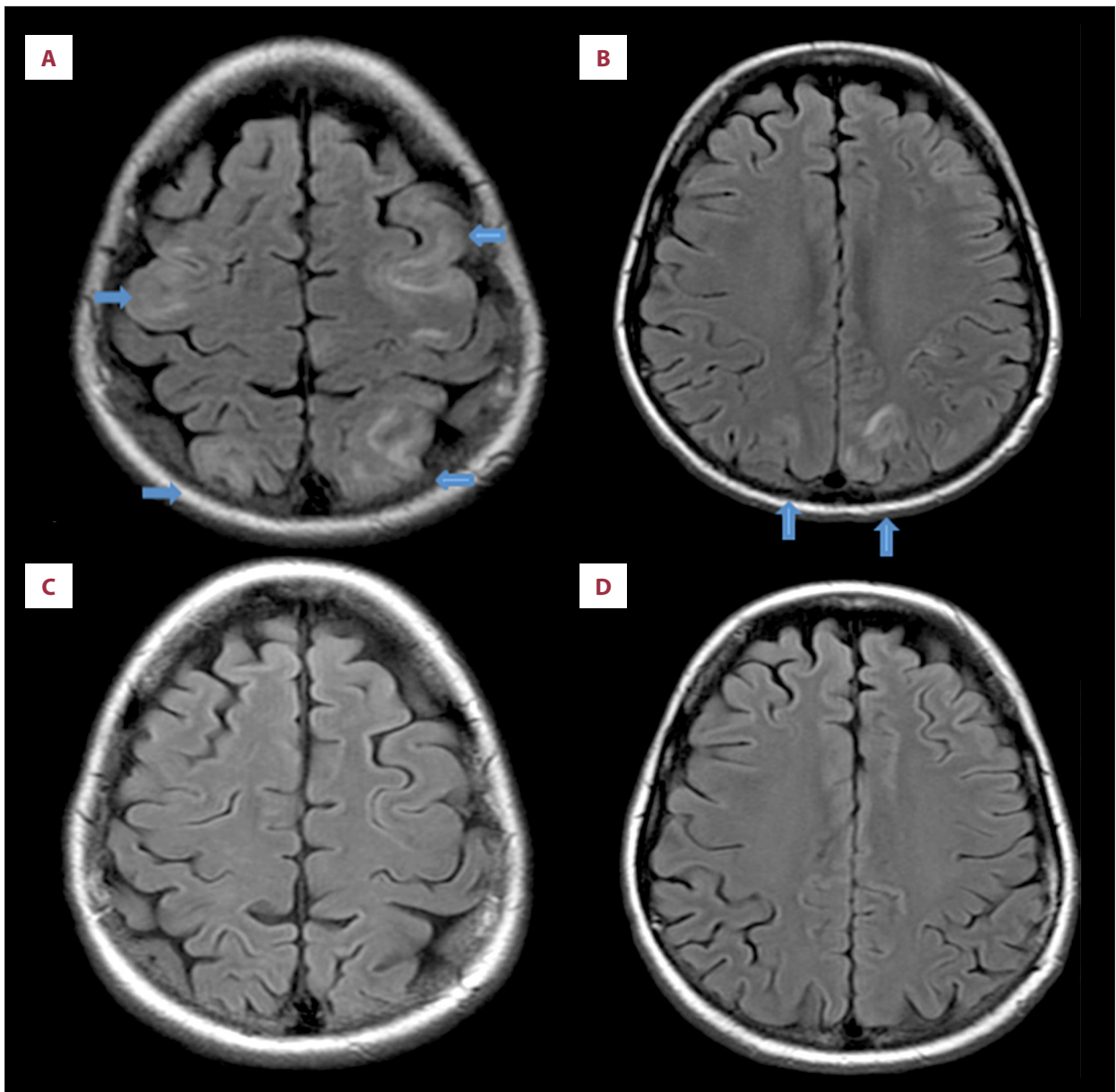


Figure 1. (A, B) Represent initial MRI brain findings (immediate post-seizure imaging): Areas of subcortical FLAIR hyperintensity in the bilateral parietal and occipital lobes (arrows) consistent with posterior reversible encephalopathy syndrome. (C, D) Represent follow-up MRI brain findings (6 weeks after switching tacrolimus to cyclosporine): Resolution of the previous FLAIR hyperintensity signal abnormality.

Growing numbers of organ transplantations and use of calcineurin inhibitors inadvertently resulted in an escalating incidence of their neurotoxic adverse effects. According to a recent case report, sirolimus has joined this group of implicated medications, although at a much lower frequency [5].

PRES is extensively described in the literature in patients who underwent solid organ and hematopoietic stem cell transplantation. Bartynski et al., studying 4222 patients who underwent solid organ transplantation (SOT) and on immunosuppressive

therapy (especially with calcineurin inhibitors), reported that in kidney and liver transplant patients the incidence of PRES was around 0.49% and 0.84%, respectively [2]. The mean time of onset of the toxicity (following transplantation or initiation of immunosuppressant therapy) also varied between different SOT subtypes. When immunosuppressive therapy is the causative factor, dose reduction, switching medication, or discontinuation of the medication were all reasonably successful strategies. Tacrolimus-related PRES was noted to be unrelated to the drug levels. Therapeutic drug monitoring is recommended to

prevent tacrolimus toxicity but PRES is known to occur even at normal therapeutic drug levels. Clinical recovery was noted to occur within a few days, while radiological recovery took days to weeks. Hypertension, elevated serum creatinine or CKD/Dialysis, solid organ or hematopoietic stem cell transplantation, hypomagnesemia, pregnancy, and sepsis are among the co-morbid conditions associated with PRES. Management of hypertension and hypomagnesemia are noted to be important in the recovery of these patients.

PRES is a neuro-radiological phenomenon characterized by bilateral and symmetric vasogenic edema involving subcortical white matter. It is diagnosed by a FLAIR hyperintensity signal, which has the ability to detect even subtle PRES lesions, noted on T-2 weighted images, typically involving the parieto-occipital areas (posterior circulation) on MRI. Supplemental diffusion-weighted imaging (D-WI) and apparent diffusion coefficient (ADC) mapping helps differentiate reversible vasogenic edema (represented by iso-/hyperintense D-WI and hyperintense ADC correlating with areas of FLAIR hyperintensity) from irreversible cytotoxic edema (hypointense ADC) [6]. Complete reversibility of all these changes on subsequent imaging is a unique characteristic of PRES and is often diagnostic (Figure 1). Rarely, hemorrhages and micro-ischemic infarcts are the residual findings noted on MRI. These changes are associated with residual neurological deficits.

References:

1. Song T, Rao Z, Tan Q et al: Calcineurin inhibitors associated posterior reversible encephalopathy syndrome in solid organ transplantation: Report of 2 cases and literature review. *Medicine (Baltimore)*, 2016; 95: e3173
2. Bartynski WS, Tan HP, Boardman JF et al: Posterior reversible encephalopathy syndrome after solid organ transplantation. *Am J Neuroradiol*, 2008; 29: 924–30
3. Wu Q, Marescaux C, Wolff V et al: Tacrolimus-associated posterior reversible encephalopathy syndrome after solid organ transplantation. *Eur Neurol*, 2010; 64: 169–77
4. Barbas AS, Rege AS, Castleberry AW et al: Posterior reversible encephalopathy syndrome independently associated with tacrolimus and sirolimus after multivisceral transplantation. *Am J Transplant*, 2013; 13: 808–10
5. Hinchey J, Chaves C, Appignani B et al: A reversible posterior leukoencephalopathy syndrome. *N Engl J Med*, 1996; 334: 494–500
6. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA: Clinical spectrum of reversible posterior leukoencephalopathy syndrome. *Arch Neurol*, 2008; 65: 20–10

Atypical PRES denotes involvement of areas of the brain other than posterior circulation. Involvement of frontal and fronto-parietal lobes, thalami, internal capsule, isolated brainstem, cerebellum, cortical grey matter, unilateral lesions, foci of permanent injury, and hemorrhage into lesions demonstrable on MRI constitute atypical neuro-imaging findings. Since atypical PRES is more common, the term PRES is essentially considered a misnomer.

Conclusions

Drug-induced PRES can occur in solid-organ transplant patients as early as the first week of initiation of immunosuppressant therapy. Early diagnosis followed by discontinuation of the causative agent, dose reduction, or switching immunosuppressant regimen can result in complete resolution of symptoms. This can also be demonstrated by the resolution of radiological findings on follow-up MRI.

Conflicts of interest

No conflicts of interest to declare.