Case Reports

Posterior Reversible Encephalopathy Syndrome

after Heart Transplantation: Diagnosis and Immunosuppressive Therapy

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Posterior reversible encephalopathy syndrome, an infrequent neurotoxicity associated with the use of tacrolimus, was first described in 1996, as a reversible syndrome manifested by headache, altered mental function, seizures, and visual disturbances. We describe the case of a 37-year-old woman who developed neurologic symptoms consistent with encephalopathy after treatment with tacrolimus, which was prescribed to maintain immunosuppression after orthotopic heart transplantation.

This report also discusses the imaging methods used in the diagnosis of posterior reversible encephalopathy and highlights the difficulty of maintaining immunosuppression and managing medication-related adverse effects, while taking into account the risk of acute rejection after transplantation. ***(Tex Heart Inst J 2017;44(3):205-8)***

Key words: *Brain diseases/diagnostic imaging; drug therapy, combination; graft rejection/heart transplantation/adverse effects; immunosuppressive agents/therapeutic use; nervous system diseases/chemically induced; tacrolimus/adverse effects/therapeutic use; treatment outcome*

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Posterior reversible encephalopathy syndrome (PRES) is an infrequent neurologic sequela occurring in response to tacrolimus therapy. One of our recent cases is a prime example of the difficulties faced by physicians when they attempt to balance immunosuppression and drug toxicities. We highlight the most relevant features of our case, in an attempt to bring greater understanding of the pathophysiology of PRES. Further, we discuss the methods typically used to diagnose PRES, and we attempt to consolidate previous knowledge within the scope of PRES in a patient who was receiving immunosuppression after orthotopic heart transplantation.

Case Report

A 37-year-old woman with a medical history of type 2 diabetes mellitus and hypothyroidism presented with generalized tonic-clonic seizures 16 days after orthotopic heart transplantation. Her home medications included 6 mg of tacrolimus, 1,500 mg of mycophenolate mofetil, and 20 mg of prednisone, each taken orally twice daily; trimethoprim/sulfamethoxazole; and valganciclovir. She had had 3 seizures that involved tongue-biting and stool incontinence. Initially, she was treated with diazepam, intravenous phenytoin, and intravenous ceftriaxone for suspected meningitis, a frequent sequela in an immunocompromised patient. On admission, the patient was somnolent but rousable and reported a throbbing temporal headache. Her blood pressure was 130/77 mmHg, and her pulse was 110 beats/min. No focal deficits were present upon neurologic examination. Laboratory data included a white blood cell count of 16.4×10^9 cells/L, a potassium level of 5.4 mmol/L, a magnesium level of 1.77 mmol/L, a blood urea nitrogen level of 47 mg/dL, and a creatinine level of 1.25 mg/dL with an anion gap of 23 mmol/L. Her tacrolimus levels at the time of admission were 8.4 ng/mL. Her previous tacrolimus levels had been 9.7 to 13.9 μg/mL, which, in a normotensive patient without a tremor, made toxicity less likely. Her examination included a lumbar puncture that was negative for any infectious process, an electroencephalogram that showed no evidence of seizure activity, and a computed tomogram of the head that showed no intracranial bleeding. A brain magnetic resonance image (MRI) was ordered, and the findings suggested PRES (Fig. 1A).

On the basis of these findings, we discontinued tacrolimus and replaced it with 2 mg/d of oral sirolimus. A repeat MRI showed resolution of the patient's high signal intensities (Fig. 1B). The mycophenolate mofetil was continued at 1,500 mg and the prednisone was slightly reduced to 15 mg, twice a day. The patient was discharged

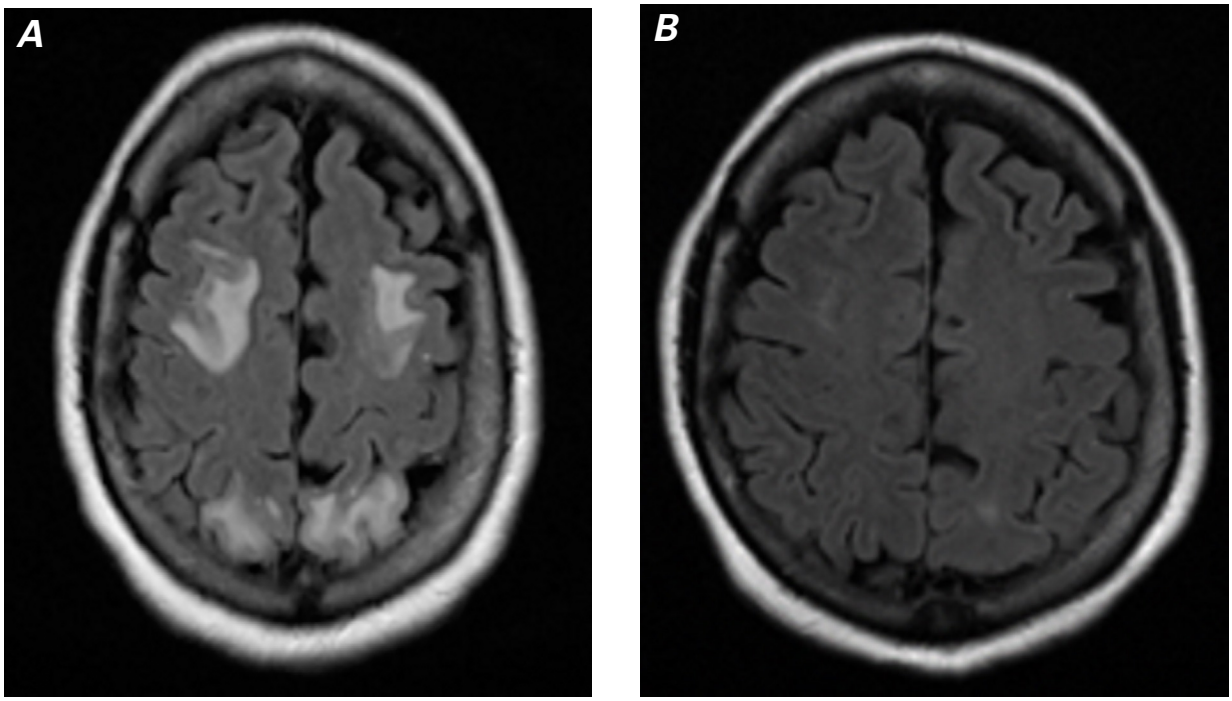

Fig. 1 *Magnetic resonance images.* ***A****) Upon the patient's presentation with seizures, multiple areas of high signal intensity within the cortex of the bilateral frontal and parietal lobes were seen, along with subtle signs of abnormality in the temporal and occipital cortices.* ***B****) Previous findings resolved after discontinuation of tacrolimus therapy, which correlated with the resolution of symptoms.*

from the hospital in stable condition. However, one week later, she presented with signs of exacerbated acute congestive heart failure, which possibly indicated acute cellular rejection. Moreover, she manifested severely elevated right-sided filling pressures and a compromised cardiac index. Upon her readmission, we initiated intravenous milrinone and dobutamine infusions, and an endomyocardial biopsy confirmed International Society for Heart & Lung Transplantation grade 3R rejection. The patient was treated with intravenous antithymocyte globulin and plasmapheresis, and sirolimus was changed to cyclosporine. Although the administration of cyclosporine was associated with a risk of recurrence of PRES,[1] prompt antirejection treatment for the transplanted heart was a priority. After a week of therapy, the patient returned to baseline functioning, and her repeat biopsy results showed resolution of rejection.

Discussion

The calcineurin inhibitors (CNIs) tacrolimus and cyclosporine have revolutionized the care of heart-transplant patients by reducing the episodes of acute and chronic rejection.[2,3] The well-known adverse effects of tacrolimus include nephrotoxicity,[4] hypertension,[5] neurotoxicity,[6-10] and glucose intolerance.[11,12]

Posterior reversible encephalopathy syndrome was first reported in 1996 by Hinchey and colleagues,[13] who described a reversible syndrome associated with headache, altered mental function, seizures, and visual disturbances. This small-vessel microangiopathy of the cerebral vasculature occurs in 0.5% to 5% of solid-organ transplant recipients. It is most often associated with CNIs—because of their vasoconstrictive effects and direct injury to the vascular endothelium,[14] which can cause capillary leakage through disruption of the blood-brain barrier, thereby leading to vasogenic edema (Fig. 2).

There are 2 main theories regarding the pathogenesis of PRES:

Hypertension-hyperperfusion theory. Severe hypertension, which cannot be controlled by the autoregulatory mechanism, injures the capillary beds, leading to blood-brain barrier damage and to subsequent vasogenic edema.[6,15]

Vasoconstriction-hypoperfusion theory. Evolving hypertension causes autoregulatory vasoconstriction, which eventually leads to decreased perfusion and ischemia. The vasogenic edema is secondary to the ischemia.[15]

The literature suggests that MRI is superior to computed tomography for the diagnosis of PRES[16] and that early diagnosis is crucial to preventing sequelae, which include cerebral ischemia, cerebral hemorrhage, cerebral herniation, and status epilepticus.[17] Furthermore, prompt correction of PRES is crucial to decrease the risk of microvascular damage and cerebral vascular dysregulation. In case studies, PRES has been shown to improve either by decreasing the dose of the offending drug or by removing the drug altogether. Although

changing to another CNI remains an option, in some cases the development of neurologic symptoms might not have been directly related to the dose; rather, it might have been an idiosyncratic effect secondary to the properties of vasoconstriction associated with the CNI. As a result, we elected to halt CNI (sirolimus) therapy and switch to a mechanistic target of rapamycin inhibitor (cyclosporine). The treatment of PRES is case-specific, and patients might also need blood-pressure control, dialysis, or other interventions. In most cases, withdrawal of the offending agent leads to complete resolution of symptoms and to reversal of the abnormalities seen on MRI.

In a study of 136 patients with PRES, 3 main radiologic patterns and variations were reported[16,18,19]:

Holohemispheric watershed pattern (in 23%) (Fig. 3A). Confluent vasogenic edema extends through the frontal, parietal, and occipital lobes in a linear pattern. However, involvement of the temporal lobes is less marked.

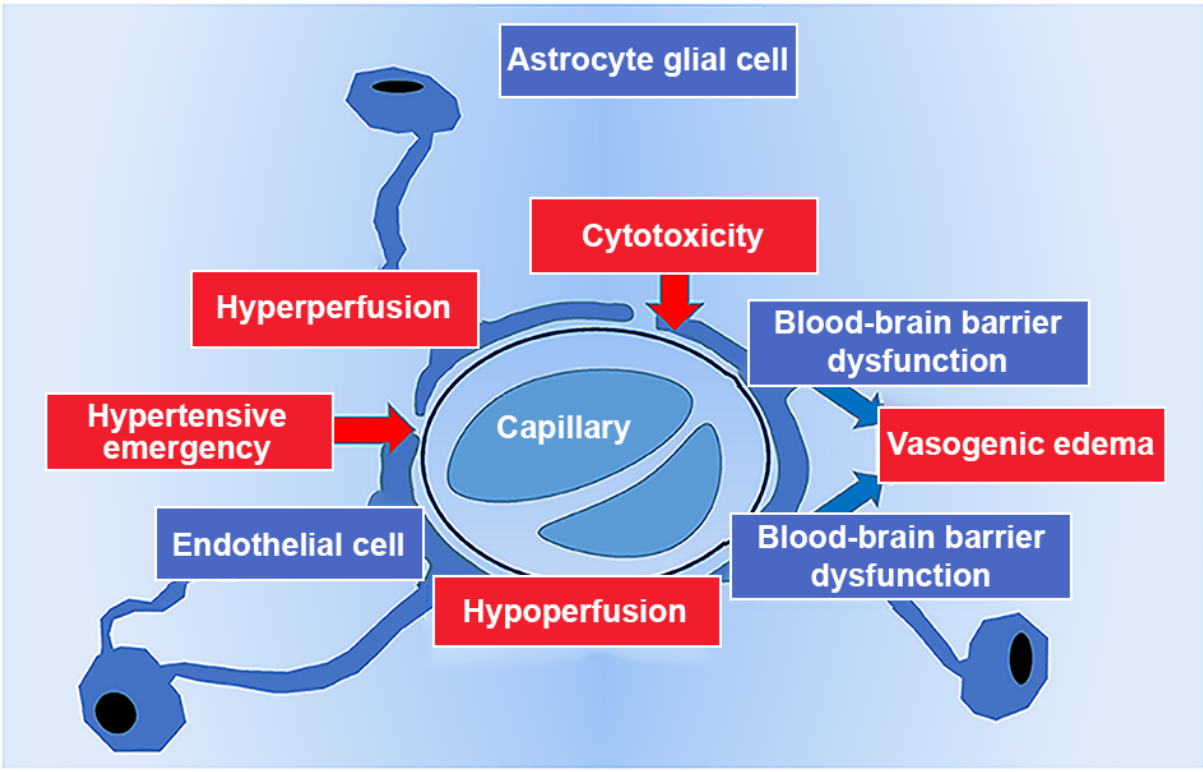

Fig. 2 *Drawing shows the pathophysiology of endothelium damage contributing to the development of posterior reversible encephalopathy syndrome.*

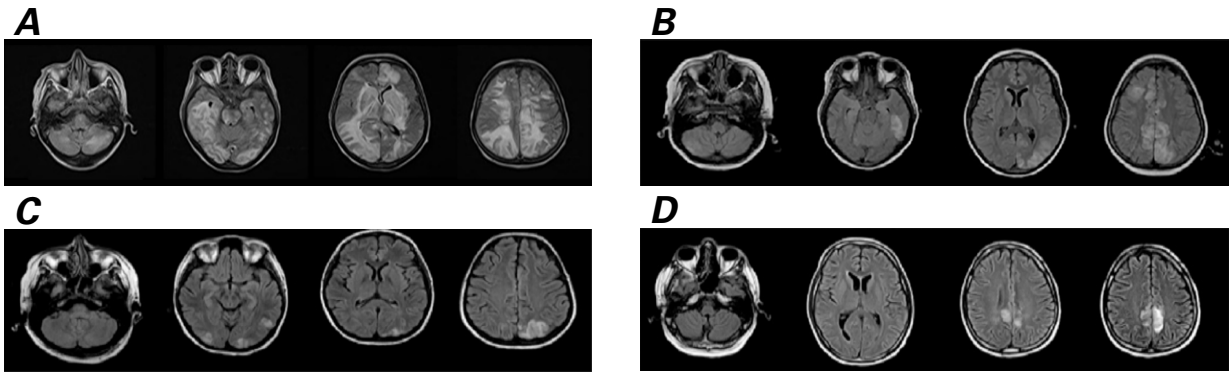

Fig. 3 *Diffusion-weighted magnetic resonance images in patients with posterior reversible encephalopathy syndrome show findings consistent with vasogenic edema:* ***A****) holohemispheric watershed pattern;* ***B****) superior frontal sulcus pattern;* ***C****) dominant parietal-occipital pattern; and* ***D****) partial or asymmetric expression of the primary patterns.*

(Reprinted with permission from Arzanian MT, et al.[19])

Superior frontal sulcus pattern (in 27%) (Fig. 3B). Focal or patchy edema predominates in the frontal lobes along the superior frontal sulci. The parietal and occipital lobes are variably involved.

Dominant parietal-occipital pattern (in 22%) (Fig. 3C). In this pattern, previously thought to be typical of PRES, the posterior parts of the parietal and occipital lobes are predominantly involved, and there is variable involvement of the temporal lobe. Edema varies from mild to extensive.

Partial or asymmetric expression of the primary patterns (in 28%) (Fig. 3D). This pattern exhibits incomplete expression of the primary patterns. In the partial form, bilateral absence of edema in either the parietal or the occipital lobes is described, and the frontal lobes are often involved. The asymmetric form shows unilateral absence of edema in either a parietal or an occipital lobe. The partial and asymmetric expressions display both a lack of involvement of either the parietal or occipital lobes and an asymmetric abnormality.

Our patient had undergone 2 MRIs: the first upon presentation with generalized seizures, and the second 2 weeks after discontinuation of tacrolimus. The initial MRI results suggested PRES, and the subsequent MRI showed no intracranial abnormality.

Our patient's neurologic symptoms resolved upon discontinuation of the offending medication. However, she subsequently had severe allograft rejection after withdrawal of tacrolimus, which necessitated therapy with antithymocyte globulin and plasmapheresis. Switching from one CNI to the other is usually attempted under controlled settings to prevent the risk of graft rejection. Re-challenging patients with the same CNI that caused PRES is usually not advised; changing drug classes altogether is safer.

We think that PRES should be considered in a post-heart-transplant patient who is receiving a CNI and is displaying hypertension and central neurologic alterations. Our case illustrates the complexity of managing and maintaining immunosuppression after heart transplantation.

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