Reversible Posterior Leukoencephalopathy Syndrome (RPLS) in a Heart Transplant Recipient Treated by Substitution of Cyclosporine A with Tacrolimus

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Abstract
Reversible posterior leukoencephalopathy syndrome (RPLS) is one of the important adverse events following organ transplantation, associated with calcineurin inhibitors (CNIs). We describe a case of a 54-year-old woman, who was diagnosed with RPLS within weeks after transplantation. Considering the risk of causing fatal rejection by discontinuation of CNIs, the immunosuppressive regimen of the patient was switched from a cyclosporine A-based regimen to a tacrolimus-based regimen. The patient recovered rapidly from RPLS following the switch to tacrolimus. This case demonstrated that not only discontinuation but also a substitution of CNIs would be a valid treatment option for RPLS in transplant recipients.

Key words: heart transplant, immunosuppression, complications, reversible posterior leukoencephalopathy syndrome, calcineurin inhibitors

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Introduction
Calcineurin inhibitors (CNIs) such as cyclosporine A (CSA) and tacrolimus (Tac) are essential immunosuppressive agents administered after organ transplantation. Severe CNI-associated neurotoxic adverse events are considered to be rare, but can sometimes result in fatal complications (1, 2). Neurotoxicity of CNIs has been reported in liver and kidney transplant recipients, especially those who have further complications of co-existing hypertension, renal insufficiency, or insufficient recovery of hepatic function after liver transplant (3, 4). One side effect of CNI treatment can be the occurrence of reversible posterior leukoencephalopathy syndrome (RPLS), which is now being increasingly reported due to widespread use of magnetic resonance imaging (MRI) (4-8). In patients with RPLS, MRI of the brain shows edema in the cortex and subcortical white matter of the posterior brain regions. The abnormal findings of brain MRI are generally reversible by discontinuation of CNIs (4, 7-10). The clinical management of RPLS has therefore been focused on discontinuation of CNIs or on dose reduction strategies (3, 7, 10).

However, in the early phases after transplantation, discontinuation of CNIs creates a tremendous risk of rejection, resulting in graft loss. Acute rejection is the major cause of morbidity and mortality in the first 3 to 6 months after heart transplantation. If not treated early, episodes of acute rejection lead to more severe and recurrent episodes of rejection (11).

In this paper, we describe a case of a heart transplant recipient who developed RPLS at the initial phase after transplantation under a CSA-based immunosuppression regimen. The patient was successfully treated by switching her CNI

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A 54-year-old woman with end-stage heart failure due to dilated cardiomyopathy underwent heart transplantation at our institution. Her initial immunosuppressive therapy included CSA, mycophenolate mofetil (MMF), and a steroid. The CSA initial target trough levels were 350-450 ng/mL. Acute rejection was monitored by endomyocardial biopsies, cytoimmunological examination such as a panel reactive antibody, ECG, and echocardiography. Her perioperative course was quite uneventful, with systolic blood pressure ranging from 90 to 130 mmHg, diastolic blood pressure ranging from 60 to 75 mmHg, and a reasonable water balance for heart transplant surgery such as a daily urinary output ranging from 2,000 to 3,000 mL.

On the seventh day after heart transplantation, she developed transient disturbance of consciousness. Brain computed tomography (CT) scan was performed, but revealed no remarkable findings. We diagnosed this episode as a transient ischemic attack, and adjusted the anticoagulant therapy on the patient.

Two weeks after transplantation, she started to complain of visual disturbance, numbness and continuous pains of the distal parts of limbs, headache, and speaking difficulties. Brain CT scan was performed again, which revealed low-density lesions in the bilateral occipital lobes (Fig. 1). On the day following her second CT scan, she developed convulsions. Her blood pressure was 144/92 mmHg at that time, serum magnesium level was 0.44 mmol/L, total-cholesterol level was 242 mg/dL, BUN level was 28 mg/dL, and creatinine level was 0.85 mg/dL. The CSA trough levels were 350-450 ng/mL during the entire observation period. Emergent brain magnetic resonance imaging (MRI) revealed high signal intensities in the bilateral basal ganglia and occipital lobes by the fluid-attenuated inversion recovery (FLAIR) images (Fig. 2). The patient was suspected of having developed RPLS as a consequence of CSA administration.

According to previous reports, discontinuation or marked reduction of CNIs is essential for the treatment of transplant recipients with RPLS (3, 7, 10). However, discontinuation of CNIs could have exposed this patient to a high risk of fatal rejection since she was in the initial phase after transplantation. Therefore, she was treated by substituting the immunosuppressive treatment from a CSA-based to a Tac-based regimen, under careful observation. Neurological disorders including visual disturbance, numbness and continuous pains of the distal parts of limbs, headache, speaking difficulties and tremors were dramatically improved after switching CSA to Tac, and all of these neurological disorders were resolved completely within 2 weeks after the switch. The brain MRI obtained on the seventh day after switching CSA to Tac revealed that normalization of the abnormal findings shown in the first MRI was almost complete (Fig. 3). She was discharged without a neurological deficit. No rejection...
episodes or neurological aftereffects have been detected through her clinical course.

The clinical course of the present case is shown in Fig. 4.

**Discussion**

We have reported the successful treatment of a heart transplant recipient with RPLS by switching her immunosuppressive treatment from a CSA-based to a Tac-based regimen. To the best of our knowledge, this is the first case report to describe the successful treatment of RPLS by substitution of CNIs, from CSA to Tac.

An image feature of RPLS is reversible posterior predominant white and gray matter lesions on brain MRI (4-8). FLAIR images of MRI in particular can detect a subtle subcortical lesion and a cortical lesion in RPLS and are valuable for diagnosis of this disease. RPLS after organ transplantation is now being increasingly reported due to the widespread use of MRI (4-8, 10). The clinical syndrome of RPLS typically involves headache, encephalopathy, visual symptoms, and seizures (8). Mak et al described an algorithm for diagnosing RPLS, and they explained that when the patients developed characteristic RPLS symptoms following recent immunosuppressive use, with urgent brain MRI revealing characteristic RPLS, then the patient could be diagnosed with RPLS (12). We believe that the patient sufficiently met the diagnostic criteria for RPLS.

The specific mechanism by which CNIs cause this adverse condition is still unclear. Previous reports have indicated that CSA has a cytotoxic effect on the vascular endothelium, leading to brain-capillary leakage, and acute blood brain barrier disruption, which may trigger vasogenic edema (1, 8). Regarding Tac-associated RPLS, the Tac itself and Tac-FK binding protein complex might play an important role in this mechanism. Owing to the lipophilic properties of the FK-binding protein-Tac compound, the high lipid content of the white matter could be a preferential bridging site (13). Singh et al reported that CNI-associated RPLS in the presence of a therapeutic drug level occurred more frequently in patients treated with CSA compared with those treated with Tac (14).

According to previous reports, discontinuation or marked reduction of CNIs was essential for the treatment of transplant recipients with RPLS (3, 7, 10). Dzudie et al reported 2 cases of heart transplant recipients with CSA-associated RPLS, one of which recovered from RPLS only after discontinuation of CSA (15). However, considering the risk of causing fatal rejection by discontinuation of CNIs, we decided to treat our patient by switching the immunosuppressive regimen from a CSA-based to a Tac-based regimen under careful observation. In addition, our decision of switching to Tac was made by reference to the report by Singh et al (14) describing low frequency of Tac-related RPLS with therapeutic trough level. The patient recovered rapidly from RPLS by the switching to Tac.

The mechanism underlying CNI-induced RPLS and the reasons for the fewer neurotoxic effects of Tac are still unclear. However, this case demonstrated that not only discontinuation of CNIs but also a substitution of CNIs would be a valid option for treatment of RPLS in transplant recipients.

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