



## Reversible Cerebral Vasoconstriction Syndrome After Heart Transplantation: A Case Report

Y. Kumai<sup>a</sup>, O. Seguchi<sup>a,\*</sup>, T. Sato<sup>b</sup>, K. Wada<sup>c</sup>, M. Shiozawa<sup>d</sup>, C. Yokota<sup>d</sup>, K. Kuroda<sup>a</sup>, S. Nakajima<sup>a</sup>, T. Sato<sup>a</sup>, M. Yanase<sup>a</sup>, Y. Matsumoto<sup>e</sup>, S. Fukushima<sup>e</sup>, T. Fujita<sup>e</sup>, J. Kobayashi<sup>e</sup>, and N. Fukushima<sup>a</sup>

<sup>a</sup>Department of Transplantation, National Cerebral and Cardiovascular Center, Osaka, Japan; <sup>b</sup>Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan; <sup>c</sup>Department of Pharmacy, National Cerebral and Cardiovascular Center, Osaka, Japan; <sup>d</sup>Department of Stroke and Cerebrovascular Diseases, National Cerebral and Cardiovascular Center, Osaka, Japan; and

<sup>e</sup>Department of Cardiovascular Surgery, National Cerebral and Cardiovascular Center, Osaka, Japan

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### ABSTRACT

**Background.** Reversible cerebral vasoconstriction syndrome (RCVS) is a transient cerebrovascular disorder putatively caused by some immunosuppressive agents.

**Case Report.** We recently encountered a 47-year-old female patient diagnosed with dilated cardiomyopathy who developed RCVS after heart transplantation. A triple-drug regimen consisting of tacrolimus, mycophenolate mofetil, and a corticosteroid was started after surgery. On postoperative day (POD) 11, the patient developed a severe headache, although computed tomography of the head demonstrated no signs of hemorrhage or infarction. At first, both a painkiller and migraine drugs were regularly administered to the patient. On POD 21, however, she developed an unbearable headache with a visual field defect and mild hemiparesis of the right hand. Magnetic resonance imaging (MRI) of the brain revealed a cerebral infarction in the left occipital lobe with diffuse vasoconstriction of both the middle and posterior cerebral arteries. A diagnosis of RCVS was made and tacrolimus, a drug suspected to cause RCVS, was discontinued. In its place, two doses of basiliximab followed by everolimus, both of which are alternatives for tacrolimus, were given. The corticosteroid dose was also increased. Furthermore, to release vasoconstriction, both verapamil and diltiazem were administered. On POD 27, cerebrovascular constrictions were shown to be relieved on brain MRI and the patient's neurological symptoms subsequently almost completely diminished.

**Conclusion.** RCVS should always be considered as a cause of headache in heart transplant recipients because tacrolimus, an immunosuppressive agent, may trigger RCVS. This will allow rapid intervention that is essential for avoiding irreversible neurological deficits.

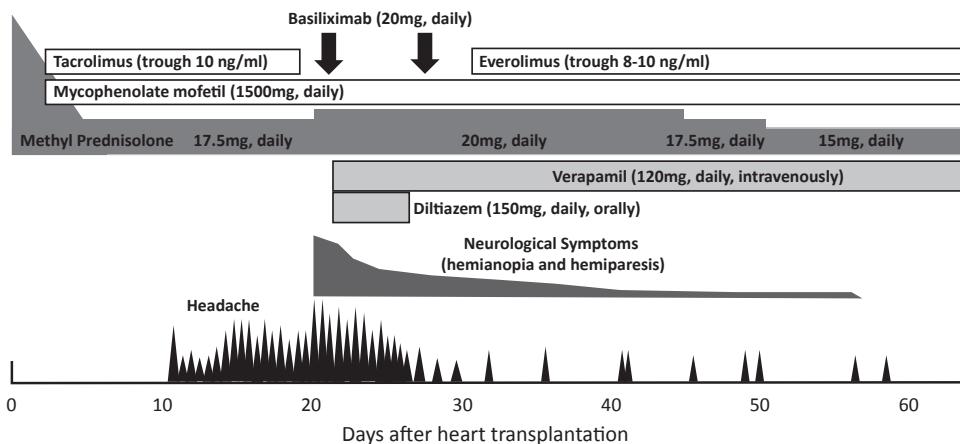
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**R**EVERSIBLE cerebral vasoconstriction syndrome (RCVS) is a transient cerebrovascular disorder that is characterized by severe headaches with or without other acute neurological symptoms [1–3]. Although it mainly occurs spontaneously, various drugs including immunosuppressive agents are a putative cause for this syndrome. RCVS is physiologically hallmark by reversible vasoconstriction of the cerebrovascular arteries, leading to abrupt development of a severe headache that peaks within

seconds and is named the “thunderclap headache” [4]. Because ischemic and hemorrhagic stroke with neurological deficits can subsequently occur, rapid and accurate

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\*Address correspondence to Osamu Seguchi, MD, PhD, Department of Transplantation, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. E-mail: [oseguchi@ncvc.go.jp](mailto:oseguchi@ncvc.go.jp)



**Fig 1.** Clinical course after heart transplantation. Severity of headache and neurological disorders were demonstrated following the patient's complaint.

diagnosis with proper intervention is essential to avoid unfavorable neurological sequelae.

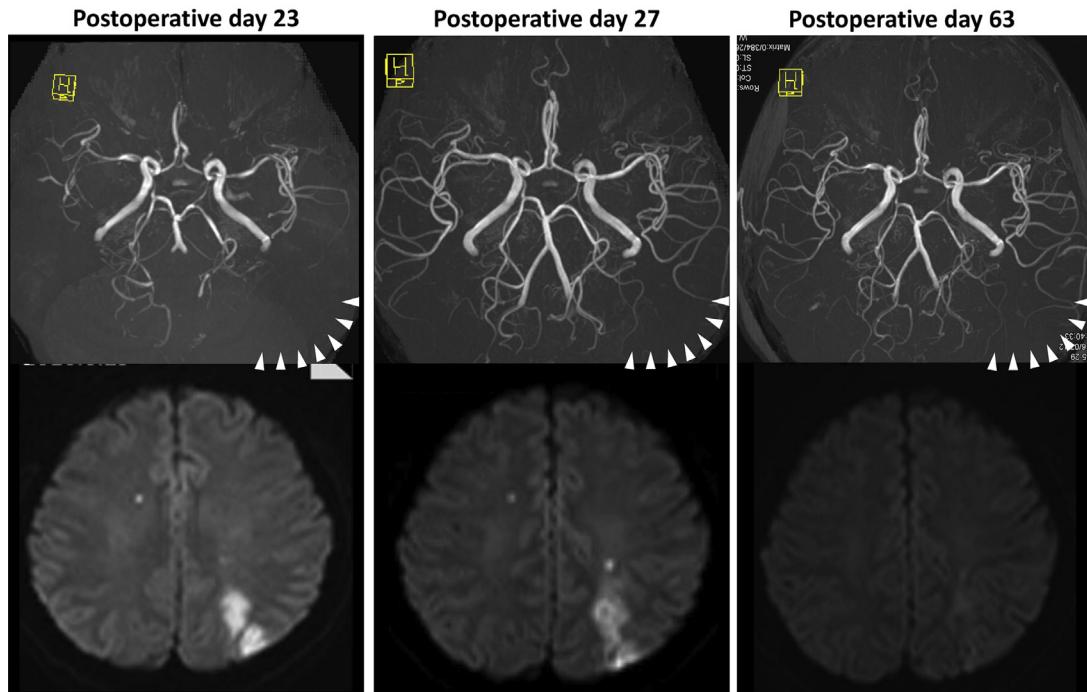
We recently encountered a heart transplant recipient who had been diagnosed with RCVS before developing a cerebral infarction with transient neurological deficits.

#### CASE REPORT

A 47-year-old female who had been suffering from heart failure since the age of 41 presented to our institution with a diagnosis of dilated

cardiomyopathy. After multiple episodes of hospitalization due to heart failure, she became dependent on inotropic infusions and was listed as a candidate for heart transplantation. Soon after being listed as a transplant candidate, the patient underwent implantation of a left ventricular assist device (LVAD) as a bridge to transplantation. The patient's postoperative course was mostly uneventful and she received a heart transplant 3 years after LVAD implantation.

Following transplantation surgery, a triple-drug regimen consisting of tacrolimus, mycophenolate mofetil (1500 mg twice daily), and a corticosteroid was started, with trough levels of tacrolimus maintained at 10 ng/mL during the early post-transplantation phase (Fig 1). On



**Fig 2.** Serial MRA images (top row) and MRI images (bottom row) of the head. An early cerebral infarction in the left occipital lobe with diffuse vasoconstriction of both the left middle and posterior cerebral arteries was found in MRI and MRA of the brain.

postoperative day (POD) 11, the patient developed a severe headache without any other neurological findings. Computed tomography (CT) of the head demonstrated no signs of cerebral hemorrhage or infarction. Because she had habitual migraine attacks prior to heart transplantation, both a painkiller and migraine drugs were regularly administered. Even after administration of these drugs, the patient experienced intermittent headaches, although they were mostly under control with prescription drugs.

On POD 21, however, the patient developed an unbearable headache with right hemianopsia and mild hemiparesis of the right hand. Despite no specific findings on brain CT images, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) of the brain revealed an early cerebral infarction in the left occipital lobe with diffuse vasoconstriction of both the left middle and posterior cerebral arteries (Fig 2). There were no findings for posterior reversible encephalopathy syndrome (PRES). A diagnosis of RCVS and secondary cerebral infarction was therefore made and tacrolimus, a drug suspected to cause RCVS, was discontinued and replaced with basiliximab (20 mg daily on POD 22 and 26). The patient's current methylprednisolone dose of 17.5 mg daily was also increased to 20 mg daily. For releasing cerebrovascular vasoconstriction, verapamil was administered orally (120 mg daily) in addition to amlodipine. Furthermore, because the patient's headaches intermittently persisted, diltiazem was intravenously administered from POD 23 to 27.

On POD 27, cerebrovascular constrictions were shown to be relieved on brain MRI and MRA (Fig 2). On POD 32, everolimus was initiated because surgical wound healing was almost accomplished, and titrated to trough levels of 8–10 ng/mL. The patient's subsequent clinical course was mostly satisfactory apart from allograft rejection (International Society for Heart and Lung Transplantation grade 2R) without graft dysfunction, which required pulse steroid therapy with methylprednisolone (1000 mg once daily for 3 days) at 4.5 months after heart transplantation. The patient's neurological symptoms of right hemianopsia and mild right hemiparesis also gradually improved and finally almost completely disappeared.

## DISCUSSION

RCVS is a group of syndromes characterized by severe headaches and the transient narrowing of cerebral arteries and has been reported to occur mainly in middle-aged women [5]. Originally, RCVS had been identified using diverse nomenclature, such as Call-Fleming syndrome, benign angiopathy of the central nervous system, and migraine angitis, and had been diagnosed and treated in various clinical settings [6]. The etiology of RCVS is similarly diverse, with various pathophysiological conditions, such as pregnancy, hypertension, malignancies such as hormonal abnormality, and exposure to various drugs and blood products, considered to be triggers for this syndrome.

Tacrolimus, an immunosuppressive agent, has also been linked with various neurological complications such as headache, which is one of the most frequently reported adverse events following tacrolimus administration and whose mitigation has been correlated with a reduction in the dose of this drug [7]. Tacrolimus has also been linked with the development of RCVS, which may be associated with these adverse neurological events in the early phase of tacrolimus use in clinical settings.

Because tacrolimus is mainly used after organ transplantation, transplant recipients are especially at risk of RCVS. In the field of

heart transplantation, there has been one case report to our knowledge that was published by Korean clinicians. In this report, a 50-year-old man developed PRES on POD 4, followed by RCVS on POD 13, and transiently became comatose from multiple infarctions due to RCVS [8]. In our case, the patient did not develop PRES and first noted a headache on POD 11. At that time, the patient did not undergo MRI and, because there were no brain CT findings, only a painkiller and migraine drugs were prescribed. However, it is clear from our case that MRI should be performed in all heart transplant recipients who are given tacrolimus and subsequently display neurological signs such as headache. This is because they are particularly vulnerable to both PRES and RCVS and any delay in treatment could result in various transient and/or persistent neurological symptoms.

With respect to the treatment of the present patient, tacrolimus was discontinued as soon as RCVS was diagnosed, and the dose of methylprednisolone was increased. Because everolimus, an alternative immunosuppressive agent for tacrolimus, has been reported to delay wound healing, it was only administered after the surgical wound had completely healed [9,10]. To cover the immunosuppression treatment gap between tacrolimus discontinuation and everolimus administration, two doses of basiliximab were given. This drug was chosen because it has been reported to be a useful choice for heart transplant recipients who require an interval between treatment with tacrolimus and everolimus in the early post-transplantation phase [11]. For releasing cerebrovascular vasoconstriction, nimodipine, a calcium-channel blockade with a relatively selective vasodilatory effect on cerebral arteries, has been reported to be effective for RCVS. Because nimodipine is not available in our country, however, verapamil and diltiazem were instead orally and intravenously administered, respectively [12]. Intra-arterial administration of calcium channel blockades and/or intravenous administration of epoprostenol should also be considered if vasoconstriction is refractory to conventional treatments using oral and intravenous calcium channel blockades [13,14]. However, this did not occur in our study.

In conclusion, RCVS should always be considered as a cause of headache in heart transplant recipients. This is because tacrolimus may trigger RCVS, and both accurate diagnosis and rapid intervention are essential for avoiding irreversible neurological deficits.

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