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Int J Case Rep Images 2022;13:101297Z01TI2022.
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Tacrolimus-associated posterior reversible encephalopathy syndrome after kidney transplantation

Takamasa Ishiuchi, Masatoshi Takagaki, Hajime Nakamura, Shayne Morris, Takayuki Sakaki, Haruhiko Kishima

ABSTRACT

Calcineurin inhibitors are essential immunosuppressive agents for kidney transplant patients. Posterior reversible leukoencephalopathy syndrome is a rare complication of treatment with calcineurin inhibitors. Herein, we report three cases of tacrolimus-associated posterior reversible leukoencephalopathy syndrome after kidney transplantation and their unique clinical courses. Patients in Cases 1 and 2 presented with headache and visual field disturbance on the fourth day after transplantation. Both patients were successfully treated with antihypertensive therapy and a change in medications from tacrolimus to cyclosporine and everolimus. Case 3 was a kidney transplant patient at 12 years post-transplant who developed fever and conjugate eye deviation to the right. The patient was initially treated with antihypertensive medication and a reduction in tacrolimus dose, but she experienced prolonged disturbance of consciousness, which eventually improved. These cases highlight the importance of considering the possibility of posterior reversible leukoencephalopathy syndrome in kidney transplant recipients taking calcineurin inhibitors who present with acute neurological dysfunction. They also demonstrate the need to perform appropriate imaging to confirm the diagnosis and initiate treatment, even if a significant amount of time has passed since transplantation. The introduction of an mTOR inhibitor may be practical when changing or discontinuing calcineurin inhibitors.

Keywords: Calcineurin inhibitors, Kidney transplantation, PRES, Tacrolimus

How to cite this article

Ishiuchi T, Takagaki M, Nakamura H, Morris S, Sakaki T, Kishima H. Tacrolimus-associated posterior reversible encephalopathy syndrome after kidney transplantation. Int J Case Rep Images 2022;13:101297Z01TI2022.

Article ID: 101297Z01TI2022

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doi: 10.5348/101297Z01TI2022CS

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Received: 17 January 2020
Accepted: 25 March 2022
Published: 15 April 2022

INTRODUCTION

Posterior reversible encephalopathy syndrome (PRES) is an encephalopathy that presents with various neurological symptoms, such as headache and impairment of consciousness [1]. It is associated with hypertensive encephalopathy, eclampsia, and treatment with immunosuppressive drugs, especially calcineurin inhibitors (CNIs). Posterior reversible encephalopathy syndrome is a severe disease that can lead to fatal outcomes due to cerebral edema and cerebral hemorrhage. In recent years, CNIs have been increasingly used as primary immunosuppressive agents in post-transplant patients. However, the treatment for PRES in post-transplant patients has not yet been established. Therefore, there are no standard guidelines for the

reduction or discontinuation of CNIs. We report three cases of post-kidney transplant patients who developed PRES while using tacrolimus (TAC), one of the CNIs, and discuss the diagnosis, treatment, and prognosis. This study design was approved by the ethics review board of our hospital, and the need for informed consent was waived.

CASE SERIES

Case 1

A 41-year-old woman had end-stage renal failure due to chronic kidney disease with diabetic nephropathy and underwent prior kidney transplantation with her husband as the donor. Her preoperative immunosuppressive medications included TAC (9 mg/day, daily) and mycophenolate mofetil (1000 mg at a time, twice a day) for four days before surgery. She received basiliximab (20 mg/day, once) and methylprednisolone (500 mg/day, for three days) on the day of surgery. She developed headache and visual field disturbance on the seventh day after taking TAC (10 mg/day, daily) for immunosuppression. Her vision became totally blind on the second day of the disease, and she had bilateral mydriasis with loss of contralateral reflexes. Head magnetic resonance imaging (MRI) showed a high-signal area on fluid-attenuated inversion recovery (FLAIR) images, mainly in the bilateral occipital lobes (Figure 1A). There was no signal change on diffusion-weighted images and no apparent stenosis or occlusion of posterior cerebral artery (PCA) on magnetic resonance angiography (MRA) (Figure 1B). The patient was diagnosed with PRES. Her blood pressure was 205/111 mmHg, and her mean arterial pressure (MAP) was 142 mmHg at diagnosis. Her TAC trough value was 10.9 ng/mL. Nicardipine was administered for hypertension to achieve an MAP of less than 120. Tacrolimus was changed to everolimus (EVL, 1.5 mg/day, daily), an mTOR inhibitor, and cyclosporine (CyA, 200 mg/day, daily). Head MRI taken nine days after diagnosis showed improvement of edema (Figure 1C). Her symptoms, including her vision, went into remission, and she was discharged 40 days after the onset of PRES. Head MRI taken five months after diagnosis showed almost no vasogenic brain edema (Figure 1D).

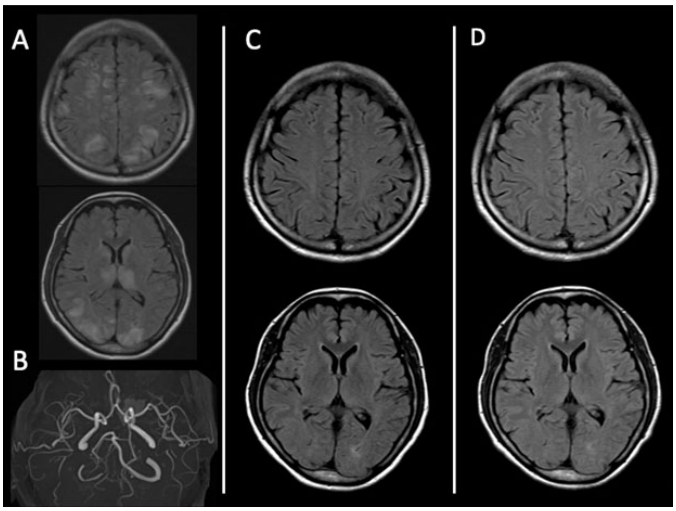

Figure 1: Head MRI findings (Case 1) (A) FLAIR at onset. (B) MRA at onset. There was no occlusion or stenosis of the vessels, including bilateral PCA. (C) FLAIR taken at nine days after onset. (D) FLAIR taken five months after onset. MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; FLAIR, fluid-attenuated inversion recovery.

Case 2

A 60-year-old woman had end-stage renal failure due to chronic kidney disease with diabetic nephropathy and underwent prior kidney transplantation with her husband as the donor. Her preoperative immunosuppressive medications included TAC (5 mg/day, daily), mycophenolate mofetil (500 mg at a time, twice a day) for 21 days before surgery and rituximab (100 mg/day, once) for 15 days and 1 day before surgery. She received basiliximab (20 mg/day, once) and prednisolone (50 mg once a day, for three days) on the day of surgery. She developed headache and visual field disturbance 32 days after taking TAC (6 mg/day, daily) for immunosuppression. Head MRI showed high-signal areas on FLAIR images, mainly in the bilateral occipital lobes, with some bleeding in the same regions on T2* (Figure 2A). There was no signal change on diffusion-weighted images and no apparent stenosis or occlusion of PCA on MRA (Figure 2B). The patient was diagnosed with PRES. The TAC trough level on admission was 9.4 ng/mL. The patient's blood pressure at diagnosis was 182/114 mmHg, and MAP was 137 mmHg. Nicardipine was administered for her hypertension. The TAC dose was reduced from 6 to 2 mg, and EVL (1.5 mg/day, daily) was started on the next day, but her left hemiparesis worsened. Head computed tomography revealed progressive edema, and an intravenous infusion of 200-mL glycerol was started every 8 h (Figure 2C). As the TAC trough value on the third day after the onset of symptoms was 23.6 ng/mL, TAC was stopped, and she was started on CyA (200 mg/day, daily) the following day. The TAC trough value decreased to 3.9 ng/mL on the seventh day. Nicardipine intravenous infusion continued, and her headache and left hemiparesis improved. Her vision was totally blind on the second day of symptom onset, but it improved to a light-sensing valve the same day. The patient's vision improved to hand motion on the 11th day of onset. On the 21st day, her visual acuity improved to the pre-onset level. Head MRI taken one month after diagnosis showed improvement of edema (Figure 2D). The patient was discharged 50 days after the onset of PRES. Two months after the onset of PRES, there was no evidence of brain edema on MRI (Figure 2E).

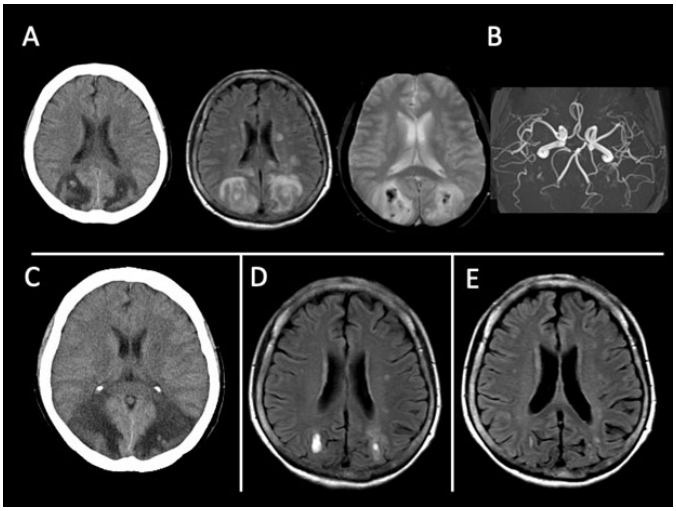

Figure 2: Head CT and MRI findings (Case 2). (A) Head CT, FLAIR, and T2* at onset. (B) MRA at onset. There was no occlusion or stenosis of the vessels, including bilateral PCA. (C) CT taken on day 2. (D) FLAIR at one month after onset. (E) FLAIR taken at three months after onset. CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; FLAIR, fluid-attenuated inversion recovery.

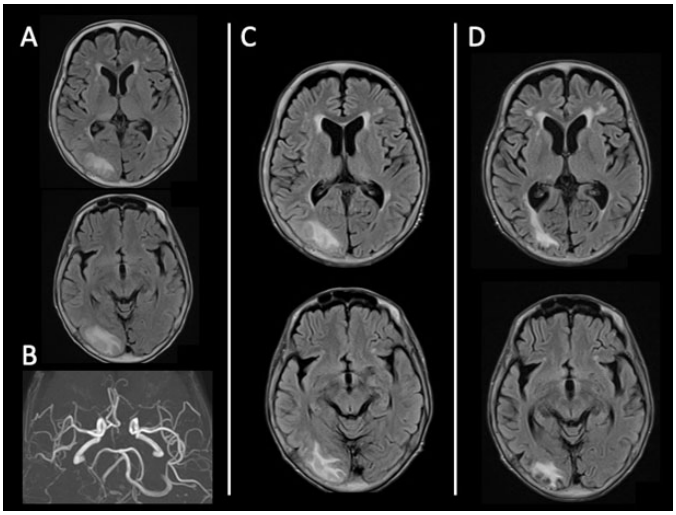

Figure 3: Head MRI (Case 3) (A) FLAIR at onset. (B) MRA at onset. There was no occlusion or stenosis of the vessels, including bilateral PCA. (C) FLAIR at seven days after onset. (D) FLAIR at five months after onset. MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; FLAIR, fluid-attenuated inversion recovery.

Case 3

A 60-year-old woman with a history of kidney transplantation due to end-stage renal failure caused by focal glomerulosclerosis 12 years ago presented to the hospital with fever, conjugate eye deviation to the right, and disturbance of consciousness. She had been taking TAC (0.5 mg at a time, twice a day) for immunosuppression. Head MRI showed vasogenic edema mainly in the right occipital lobe with a high signal on FLAIR (Figure 3A) and no apparent stenosis or occlusion of PCA on MRA (Figure 3B). Her blood pressure at diagnosis was 168/89 mmHg, MAP was 115 mmHg, and she had severe pneumonia, for which she was treated with antiepileptic drugs and antibiotics. On admission, the TAC trough level was 10.6 ng/mL. The TAC dose was changed from 1 to 0.5 mg of the extended-release formulation on the 11th day. After dose reduction, the TAC trough value decreased to 5.2 ng/mL on the 12th day and to 2.3 ng/mL on the 17th day. The dose of extended-release TAC was subsequently increased to 1 mg. The patient experienced prolonged disturbance of consciousness, which gradually improved; however, the right homonymous hemianopsia persisted. Magnetic resonance imaging of the head taken on day 9 showed worsening vasogenic edema (Figure 3C). Follow-up MRI taken four months after symptom onset showed improvement in edema (Figure 3D). During her hospitalization, she had prolonged severe diarrhea and was admitted for prolonged nutritional and fluid management. On the 80th day, she was transferred to a rehabilitation hospital. The right homonymous hemianopsia improved eight months after symptom onset. On the 105th day, she had a colonic perforation and underwent emergency laparotomy. The descending transverse colon was removed, and pathology revealed a diagnosis of diffuse large B-cell lymphoma, which led to the diagnosis of post-transplant lymphoproliferative disorder (PTLD).

DISCUSSION

We presented three cases of PRES after kidney transplantation wherein the patients were treated with TAC. Cases 1 and 2 involved PRES development several days after kidney transplantation. Nicardipine intravenous injection and switch from TAC to EVL, an mTOR inhibitor, and CyA improved the symptoms. Case 3 involved PRES development 12 years after kidney transplantation. We considered substituting other CNIs, such as CyA, but as the blood levels of TAC were unstable, we were unable to introduce other CNIs. We reduced the dosage of TAC and changed the type of drug from the regular formulation to an extended-release formulation. All patients had disease progression without rejection, and both imaging and symptoms of PRES improved. To treat PRES without rejection, it may be useful to diagnose PRES by appropriate imaging and, if necessary, to change the immunosuppressive agent to EVL, an mTOR inhibitor, or to an extended-release formulation.

Posterior reversible encephalopathy syndrome is an encephalopathy characterized by various neurological symptoms including headache, seizures, impaired consciousness, and visual abnormalities, which was first described by Hinchey et al. in 1996 [1]. It is associated with hypertensive encephalopathy, eclampsia, and immunosuppressive drugs, particularly CNIs. The use of CNIs as primary immunosuppressive agents in organ

transplant recipients has become increasingly common in recent years [2, 3]. The incidence of PRES in post-kidney transplant patients is as low as 0.34%. Owing to the rarity of reported cases and unclear pathogenesis, there are no clear treatment guidelines for PRES associated with CNIs.

Posterior reversible encephalopathy syndrome should be differentiated on imaging from ischemia/infarction (especially in the posterior circulation), demyelinating disease, infectious etiologies (meningitis, encephalitis), progressive multifocal leukoencephalopathy, vasculitis, and reversible cerebral vasoconstriction syndrome [4–6]. Acute ischemia can be differentiated from PRES because it presents with cytotoxic edema and restricted diffusion. Fugate et al. suggested the following criteria for the diagnosis of PRES: neurological symptoms of acute onset, neuroimaging abnormalities of (focal) vasogenic edema, and the reversibility of clinical and/or radiological findings [7]. All cases were clearly distinguishable from acute ischemia, as there was no occlusion or stenosis in the vessels, especially those involving the PCA region, and angiogenic edema was seen in the bilateral frontal and occipital lobes. No demyelinating disease or vasculitis was noted in either case. There were no adrenergic or serotonergic medications in all cases. Case 3 involved angiogenic edema development in the unilateral occipital lobe, which was consistent with that in the PCA region and was also associated with pneumonia; therefore, a diagnosis of PRES was not immediately made and symptomatic treatment was provided. All cases showed improvement in both symptoms and images with the change or discontinuation of CNIs.

There are three main treatment options for PRES: (1) antihypertensive therapy for patients with hypertension, (2) reduction or discontinuation of the causative drug, and (3) anticonvulsant measures. In transplant patients, dose reduction or discontinuation of CNIs may weaken immunosuppression and result in rejection. Song et al. reported treatment options for PRES in post-transplant patients on CNIs including replacement with other immunosuppressive agents, e.g., TAC to CyA (43.7%), dose reduction (22.5%), temporary discontinuation of CNI (19.7%), discontinuation of CNI (9.9%), and no intervention (4.2%). They also reported that early diagnosis and treatment yielded a better prognosis [8]. It is not yet known whether tapering or immediate discontinuation of the triggering agent is necessary, or whether dose reduction with strict control of serum concentrations within the therapeutic range is sufficient. There is no clear consensus on the frequency of TAC concentrations and the development of PRES. In our cases, the association between trough concentrations of TAC and the development of PRES was not specific.

In Cases 1 and 2, we successfully treated PRES by discontinuation of TAC and initiation of EVL and CyA. Everolimus, an mTOR inhibitor, has attracted much attention in recent years because of its unique features in reducing the frequency of viral infections and lowering the dosage of CNI. It can reduce the frequency of viral infections, such as cytomegalovirus and BK virus infections [9]. It has inhibitory effects on vascular intimal thickening and has antineoplastic effects and can reduce the dose of CNI without weakening immunosuppression [10].

In Case 3, we considered substitution with other CNIs, such as CyA. However, we could not introduce other CNIs because the blood concentration of TAC was unstable. We anticipated that even if we did introduce other CNIs, there cannot affirm that the blood levels would be stable, and there would be a high risk of rejection. Therefore, we had to resort to reducing the dosage of TAC, and TAC was changed to extended-release TAC. The extended-release TAC has less systemic fluctuation than conventional TAC agents and has a lower maximum blood concentration [11]. In this case, it took a long time for the blood TAC level to stabilize, and severe diarrhea was observed even during the adjustment of the TAC level. Although the absorption rate of TAC is usually considered low, it is reported to be enhanced in patients with diarrhea [12]. We hypothesized that a similar mechanism occurred in Case 3.

This patient was diagnosed with refractory diarrhea due to PTLD four months after the onset of PRES. Patients with PTLD may have iron-deficiency anemia, growth retardation, and gastrointestinal symptoms such as gastrointestinal bleeding, perforation, intestinal obstruction, or diarrhea in 23–56% of cases [13–15]. In addition, kidney transplant recipients often experience diarrhea due to various factors, such as side effects of immunosuppressive drugs and the alteration of the gut microbiota [16]. If a post-renal transplant patient develops PRES in the chronic phase after transplantation, as in Case 3, it may be necessary to rule out diarrhea and malignant disease in addition to medication status and compliance.

CONCLUSION

When neurological symptoms occur in a patient after kidney transplantation who is treated with TAC, PRES should be considered regardless of post-transplantation time or TAC trough values. Furthermore, switching from TAC to EVL and CyA or to extended-release TAC may safely maintain the transplanted kidney.

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Author Contributions

Takamasa Ishiuchi – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Masatoshi Takagaki – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Hajime Nakamura – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Shayne Morris – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Haruhiko Kishima – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.