CASE REPORT

Reversible tacrolimus associated with posterior encephalopathy in a patient after a lung transplantation

Sánchez Salazar S[1*], Zuluaga Jaramillo L[2], Ramírez Gutiérrez R[2], Chavarría Martínez U[3], Wong Jaén M[4]

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The Posterior Reversible Leukoencephalopathy Syndrome (PRES), secondary to immunosuppressive calcineurin inhibiting drugs, is a frequent neurological complication in post-transplanted patients. Presentation is variable, that said, PRES should always be ruled out and treatment started, out prior to an onset of an acute neurological manifestation. We present the case of a 67-year-old man with pulmonary fibrosis who underwent right lung transplantation, under immunosuppressive treatment with tacrolimus, mofetil micophenolate, and prednisone. During his stay post-transplant, he presented acute neurological symptoms, and systemic arterial hypertension; his tacrolimus levels were taken and resulted within normal range. Then, imaging studies were performed showing alterations in cerebral Magnetic Resonance Imaging (MRI), although discarding thrombotic or cardioembolic vascular events. The dose of tacrolimus was suspended corrected, to which then the patient showed clinical improvement in the days after. A second MRI was taken, showing improvement of previously seen alterations.

Keywords: Immunosuppressants; neurotoxicity; neurological complications; transplantation of organs; posterior reversible encephalopathy syndrome

ABBREVIATIONS

PRES: Reversible Posterior Leukoencephalopathy Syndrome; CT: Tomography; MRI: Magnetic Resonance; CNS: Central Nervous System; FLAIR: Recovery of Attenuated Fluid Inversion; mTOR: Mammalian Rapamycin Target Inhibitors.

INTRODUCTION

Neurotoxicity, is a common complication in organ transplantation. It can occur as a reversible Posterior Leukoencephalopathy Syndrome (PRES), often associated with immunosuppressive drugs [1]. The main drugs involved in such response are calcineurin inhibitors. Dosage or toxic levels of the medication are independent for the development of PRES. Prior exposure to the drug does not appear to be protective; studies show development of PRES several months after patient exposure to the drug at therapeutic levels. The clinical symptoms of PRES evolve rapidly from hours to days; in addition, the presence of arterial hypertension is very frequent [2]. The clinical manifestations vary, with seizures being the most common presentation. Headache, impaired alertness, and visual disturbances are also frequent.

Neuroimaging is essential for diagnosis, alterations can often be visualized in brain Tomography (CT); however, MRI has a better sensitivity and specificity than CT. In PRES, both the CT scan and the MRI show edema of the white substance that is more prominent in the posterior hemispheres.

In the MRI, characteristic findings include focal or confluent areas with a greater signal in the T2 sequence, and in the attenuated Fluid Inversion Recovery Sequence (FLAIR), with an improved sensitivity, it helps detect peripheral lesions and vasogenic edema. Characteristic lesions of PRES are usually visualized as hyper intense signals in T2/FLAIR sequences [3].

It is suggested to repeat imaging studiest post-teatment; in which lesions are expected to improve or disappear within days to weeks, which suggests edema instead of infarction¬ such changes should be suspected in patients with hypertension, immunosuppressive therapy, and acute neurological manifestations. Immediate recognition and proper treatment improve prognosis significantly.

CASE STUDY

A 67-year-old man with hypertension, with a 2 year history of idiopathic pulmonary fibrosis, in treatment with Nintedanib 150 mg every 12 hours. He underwent a right lung transplant with 2 mg of tacrolimus and 1 g of mofetil micophenolate administered prior to the procedure without complications.

Immunosuppressive treatment was continued with tacrolimus, mofetil micophenolate, and prednisone. On the eighth postoperative day, he presented sudden deterioration of consciousness with a Glasgow Score of 3 points, deviation of sight to the right, anisocoria, and left hemiparesis [4]. His vital signs at the time were: blood pressure 170/110, heart rate 125 beats per minute, T 36°C, respiratory rate 22 breaths per minute, and hypoxemia of 85%. Labs workup was: Hemoglobin at 16 g/dl, Leukocytosis of 21.04 K/ul at the expense of 14.73 K/UL neutrophils, Platelets at 133 K/ul, Hyperglycemia 153 mg/dl, and Tacrolimus levels 14.5. Orotracheal intubation and cranial tomography were performed without evidence of hemorrhage. Subsequently and under suspicion of an ischemic brain event, cerebral panangiography was performed (Figure 1).

[1]*Department of Pharmacy, University of Monterrey, Monterrey, Nuevo León, Mexico*

[2]*Department of Internal Medicine, University of Monterrey, Monterrey, Nuevo León, Mexico*

[3]*Department of Pulmonology, University of Monterrey, Monterrey, Nuevo León, Mexico*

[4]*Department of Surgery, University of Monterrey, Monterrey, Nuevo León, Mexico*

Correspondence: Sánchez Salazar S, Department of Pharmacy, University of Monterrey, Monterrey, Nuevo León, Mexico, E-mail: dr.sergio.saul.sanchez@gmail.com

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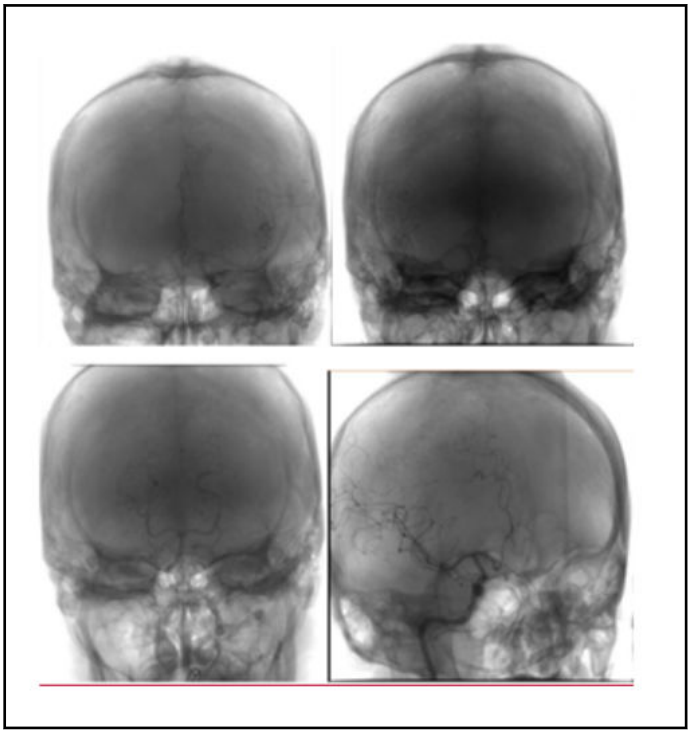

Figure 1: Cerebral Panangiography: Reporting permeable vasculature.

Transthoracic echocardiography was also requested, ruling out a cardioembolic situation [5,6]. During the next 12 hours to the event, the patient presented myoclonic movements in the upper and lower right limb. In suspicion of seizures, an electroencephalogram was performed, which reported abnormally due to a severe generalized dysfunction predominantly towards the right hemisphere, where epileptiform activity was observed. On suspicion of (PRES) secondary to tacrolimus (Figure 2), an MRI was requested.

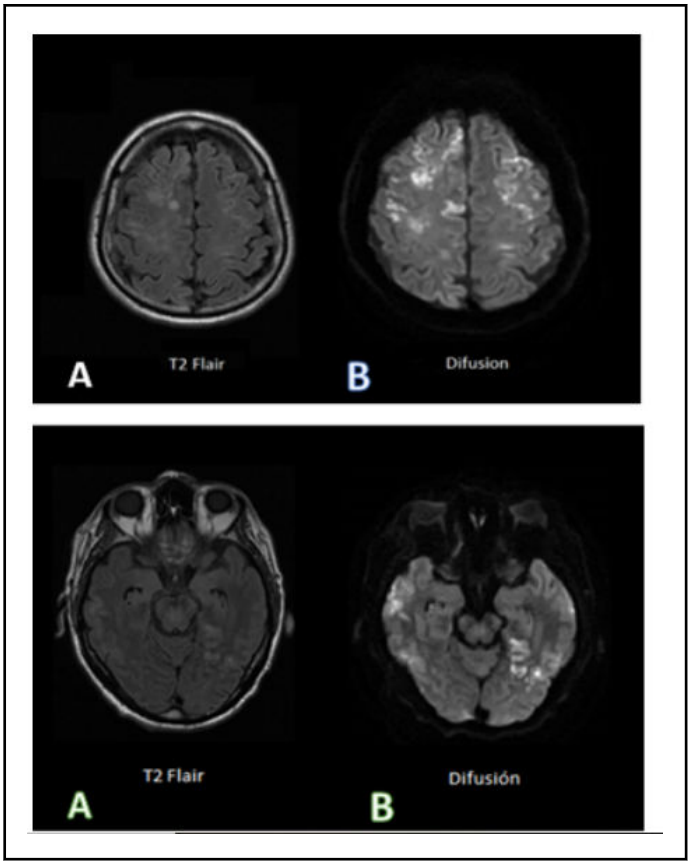

Figure 2: Initial Simple Brain Resonance in coronal sections, where multiple hyper intense areas located on the frontal and temporal parietal regions are observed bilaterally-which show diffusion restriction and hyper intensity in flair sequences

Due to the ruling out acute brain events, and the lesions described in the resonance, despite the normal levels of tacrolimus, the diagnosis of PRES was integrated. Therefore, suspension of the administration of the drug was indicated [7]. 72 hours later the patient showed clinical improvement, demonstrated by him being oriented in his three social spheres, and mobilizing his four extremities. MRI was performed one month after the episode, which showed correlation with an improve med clinic (Figure 3) [8,9].

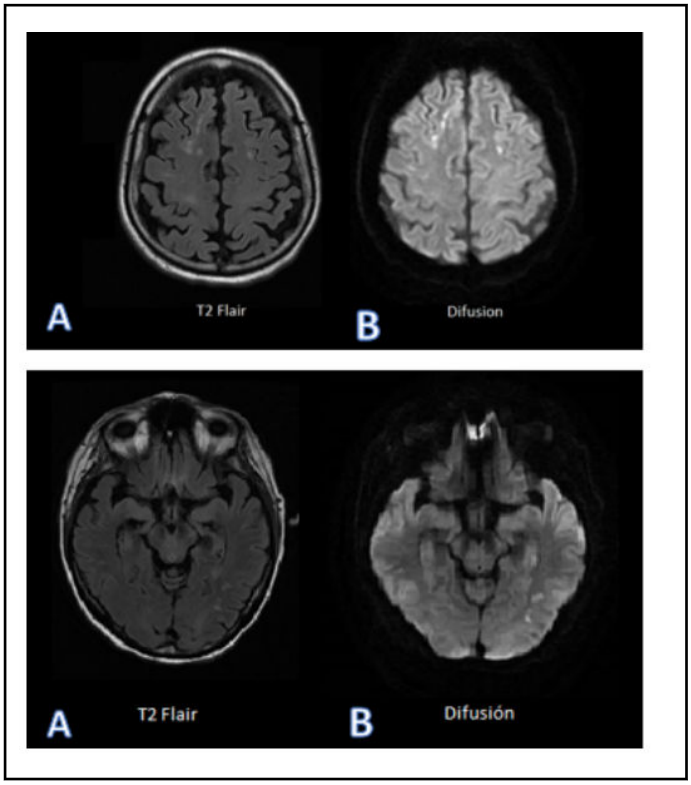

Figure 3: Control brain resonance, showing improvement in the areas of supra and infratentorial restriction when compared with previous study, at the periventricular level in the cerebellar hemispheres and on the frontal and parietal region, mainly to the right side and lower degree to the left.

DISCUSSION

Among the complications in transplant patients, we'd like to highlight neurological ones. In this case of tacrolimus neurotoxicity, an inhibitor of calcineurin, it can be associated with development of PRES [10]. PRES associated with calcineurin inhibitors should always be suspected in a patient with acute neurological abnormalities after transplantation, since their prognosis is favorable when early diagnosis is made, and treatment is initiated correctly.

CONCLUSION

It is of great importance to recognize PRES since the large percentage of cases improve with appropriate management measures. Most case reports on PRES associated with immunosuppression by calcineurin inhibitors in post-transplant patients have been reported in cardiac and renal transplantation. Two reported cases of young male post-kidney transplants, both in tacrolimus therapy; one presented headache, visual disturbance, and seizures at 15 days post-transplant, and the other patient, two months following transplant presented a similar clinic. Both presented convulsive crisis, which supports that they are the most frequent form of neurological manifestation. It is worth mentioning, most of these patients present the complications at the beginning of the therapy; however, this can also

develop even when a patient carries a chronic therapy with immune suppressants. In the case of our patient with normal blood levels of tacrolimus, the initial and most relevant differential diagnosis was an ischemic or hemorrhagic cerebrovascular event. At the time of performing the CT there was no evidence of hemorrhage; therefore a cerebral panangio graphy was performed, reporting permeable vasculature and ruling out ischemic event. An MRI was then performed, showing multiple areas of diffuse restriction, reason why tacrolimus was suspended resulting in both clinical and radiological improvement. Performing another imaging study in addition to MRI is indicated when there is suspicion of a vascular event or diagnostic doubt as in the case of this patient.

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