Case Report

Posterior Reversible Encephalopathy Syndrome (PRES) - A reversible Tacrolimus induced neurotoxicity in a heart transplant recipient: A case report

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1. Abstract

Tacrolimus is widely used as an immunosuppressive drug following heart transplantation. Mild to severe forms of neurological symptoms are known to occur with use of Tacrolimus. Posterior Reversible Encephalopathy Syndrome (PRES) is one such manifestation that can present with multitude of neurological symptoms. We report a case of PRES in a heart transplant recipient receiving Tacrolimus.

2. Background

Tacrolimus is one of the commonly used immunosuppressive drugs in patients undergoing heart transplantation. Unfortunately, Tacrolimus is associated with renal and neural toxicity, among its other side effects of immunosuppression. One of the more uncommon presentations of neurotoxicity is posterior reversible encephalopathy syndrome (PRES). It is characterized by headache, nausea, altered mental status, focal neurological deficits, vision changes like hemianopsia, generalized seizures, paresis, or coma. There are varying reports of neurotoxicity related to Tacrolimus ranging from 7 to 32% in solid organ transplants (SOT). This report describes a case of PRES in a heart transplant recipient receiving Tacrolimus.

3. Case Presentation

Our patient was an 18-year-old boy with a history of Idiopathic Dilated Cardiomyopathy, who underwent an orthotopic heart transplant five months prior to the onset of his neurologic symptoms. His past medical history included hypothyroidism, megaloblastic anemia and CKD. During the transplant surgery he had induction therapy with Basiliximab. He started on triple immunosuppressant therapy with steroids, mycophenolate mofetil (MMF) and Tacrolimus following transplant. His Tacrolimus levels were closely monitored and dose adjusted. His post-transplant course was complicated by reactivation of pulmonary tuberculosis for which he received Anti Tuberculosis Therapy (ATT). He also started on prophylactic trimethoprim-sulfamethoxazole (TMP-SMX) for pneumocystis jiroveci pneumonia (PCP) and Valgancicyclovir for prevention of cytomegalovirus (CMV).

In the fifth month, he presented with sudden onset of headache, altered mental status manifesting as staring into space and right gaze preference followed by tonic-clonic seizure. His blood pressure was 200/100 mmHg. He was intubated and put on mechanical

ventilator in view of loss of consciousness (LOC). He started on anti-epileptic treatment; once stable he was weaned off from ventilator and extubated on the same day.

MRI Brain (Fig. 1) showed multiple ill-defined areas of non-diffusion restricting, T1 iso-hypo, T2/T2 FLAIR hyperintense signal in the bilateral cerebral hemispheres, thalami, external capsules/peri Sylvian regions and the entire brainstem and cervical spinal cord consistent with PRES (posterior reversible encephalopathy syndrome, also known as reversible posterior leukoencephalopathy syndrome (RPLS). He was diagnosed with Leukoencephalopathy (possibly Tacrolimus induced). Tacrolimus was discontinued and commenced on anti-epileptics. Viral IgM serology for CMV/EBV/HTLV was negative. He received supportive treatment and did not have further seizures. He improved with no residual neurological deficits. Repeat MRI images revealed resolution of PRES once the offending Tacrolimus was discontinued.

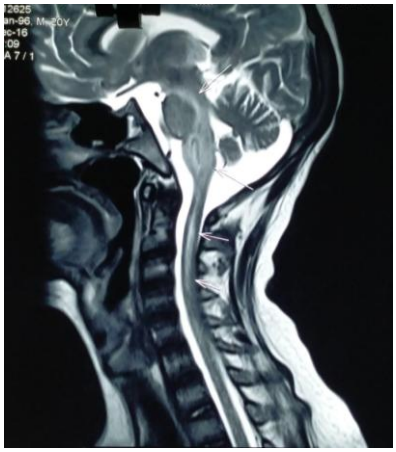

Fig. 1: Multiple ill-defined areas of T2 hyperintense signals involving thalami, external capsules/perisylvian regions, entire brainstem and cervical spinal cord.

Alternative immunosuppressant like Rapamycin or Sirolimus were discussed with Nephrologists, and on consensus, he continued with single agent (MMF) along with low dose long term oral steroids (Prednisolone 5 to 10 mg per day).

4. Discussion

Neurotoxicity secondary to Tacrolimus has been well described, particularly in solid organ transplant recipients. Both mild and major neurologic adverse effects have been reported in patients receiving Tacrolimus. Mild neurologic symptoms, including headache, paresthesias, tremors, sleep disturbances, photophobia, and dysesthesias, have been reported in 40 to 60% of patients, and major neurologic complications, such as confusion, seizures, cortical blindness, encephalopathy, and coma, occur only in 5 to 8% of patients receiving the drug. PRES, as the name suggests, is a constellation of symptoms associated with vasogenic edema, most commonly of the posterior cerebral vasculature, often affecting the parieto-occipital region. Other vascular territories can also be affected in PRES, such as the posterior portion of frontal lobe and temporal lobe. The abnormalities primarily affect white and gray matter, but the cortex can also be involved. MRI of the brain is the most sensitive diagnostic tool. Distinguishing between vasogenic edema in PRES and cytotoxic edema in the setting of cerebral ischemia can be reliably determined by diffusion weighted MR imaging.

PRES is typically a reversible phenomenon, as indicated by the name, but if not recognized early and treated appropriately, permanent brain injury may ensue.

Unfortunately, blood levels of Tacrolimus do not appear to correlate with severe neurotoxicity or PRES. Rather, side effects of Tacrolimus are thought to be related to the total amount of drug in the body. But discontinuation or change in the offending immunosuppressant can lead to clinical improvement and can be replaced with alternative agents like Rapamycin or Sirolimus to prevent recurrence. Grimbert et al reported significant levels of Tacrolimus in the CSF which suggests that this molecule can cross the blood brain barrier. Although sub therapeutic levels of immunosuppressant have been reported as causing PRES, observations of the onset of this disease at the time of declining levels seem paradoxical.

Our patient showed resolution of PRES once the offending Tacrolimus was discontinued.

5. Conclusion

Tacrolimus-associated PRES is an uncommon, but serious complication after transplantation, where higher levels of immunosuppression are required to prevent rejection. This syndrome should be promptly recognized as it is potentially reversible and generally responds to withholding or decreasing the dose of Tacrolimus in addition to controlling hypertension and seizures. Alternative immunosuppressant agents can be considered to reduce recurrence.

6. References

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