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TACROLIMUS ASSOCIATED POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME: A CASE REPORT

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ABSTRACT
Posterior reversible encephalopathy syndrome (PRES) is a rare clinic-radiological entity that presents with headache, generalized seizures, nausea, visual disturbances, altered mental status, focal deficits and coma. Tacrolimus is an immunosuppressive drug mainly used to lower the risk of transplant rejection in individuals who are post solid organ or hematopoietic transplantation. It acts via competitive inhibition of calcineurin that inhibits transcription of Interleukin-2 (IL-2) by T-helper lymphocytes and inhibits their proliferation. Although PRES is a suspected complication of tacrolimus therapy, the literature regarding management of this complication in the setting of immunosuppression is rare. In the present case study the authors would like to highlight the importance of early recognition, high index of suspicion, importance of symptomatic management with cessation of tacrolimus therapy.

KEYWORDS: Posterior reversible encephalopathy syndrome(PRES), Tacrolimus, Solid organ transplantation.

Key message: Tacrolimus induced Posterior Reversible Encephalopathy Syndrome is a known complication and is notorious for heterogeneous presentation and clinical course. High index of suspicion is warranted to accurately diagnose and manage such cases to prevent disastrous complications.

INTRODUCTION
The use of Calcineurin inhibitors has led to major advances in the field of transplantation with excellent short term outcomes. Tacrolimus is the new age calcineurin inhibitor that has revolutionized post operative outcomes in transplant recipient patients owing to greater potency as compared to cyclosporine. However, neurotoxicity is amongst major side effects and PRES is the most severe form. The reported incidence of tacrolimus induced PRES is 1.6%[1] while incidence in kidney transplant subgroup patients was reported to be around 0.39% in a study. The literature in this regard consists of a handful of case reports and a therapeutic consensus on its management is yet to be reached. Through this case report the authors would like to elucidate the importance of early clinical suspicion and prompt cessation of the drug.

CASE REPORT
A 31-year-old hypertensive patient (on beta-blocker) was brought to the Emergency department with complaints of recurrent vomiting and headache. She had a history of renal transplant two months back and was on triple immunosuppressive regimen (tacrolimus, prednisolone and mycophenolate mofetil). Her neurological examination was normal and vitals were within normal limits. MRI showed bilateral symmetrical areas of altered T2 & FLAIR (fluid-attenuated inversion recovery) signal intensity with restricted diffusion in the periventricular and subcortical white matter regions involving internal capsule, and basal ganglia bilaterally. A diagnosis of PRES, secondary to tacrolimus therapy was made. Tacrolimus was stopped and serum levels of tacrolimus were sent that was normal (3.69 ng/ml). Patient was managed conservatively with anti-hypertensives and analgesics. On day 4 of admission she had two episodes of generalized tonic clonic seizure (GTCS) followed by loss of consciousness. She was

intubated, shifted to ICU and was started on antiepileptics (Lorazepam and fos phenytoin). Patient was intubated and was put on mechanical ventilator for airway protection. Meanwhile patient was managed with Anti-hypertensives and other conservative management. Her neurological condition improved gradually over next two days and she was extubated after 48 hours (Day 6). Repeat MRI at 4 weeks was reported to be normal. She was put on Sirolimus regimen and followed up for a period of six months. She had a complete recovery from this event. No additional seizures or new neurological findings occurred during this time.

DISCUSSION

PRES is characterized by an acute or subacute encephalopathy with headache, vomiting, focal neurological deficits, altered mental status, visual impairment and seizures.[2,3] Hypertension is seen in 70-80% cases which can be mild, moderate or severe.[4] The severity of visual symptoms may vary from blurred vision, homonymous hemianopsia to cortical blindness.[5] Severity of cortical symptoms may range from confusion , agitation to coma.[5] It can less commonly present with brainstem deficits. Although it is known to resolve clinically after a mean duration of 5.3 days,[2] delay in recognition, poor control of hypertension and persistent seizure activity may result in permanent sequelae in the form of infarcts.[6]

Multiple causes of PRES have been reported in literature including autoimmune conditions like thrombotic thrombocytopenic purpura, systemic lupus erythematosus, drugs like chemptherapy agents, immunosuppressants hypertension, pregnancy, sepsis and renal failure.

Calcineurin inhibitors are thought to cause cerebral auto-dysregulation and vasogenic edema owing to strong vasoconstrictor action on cerebral vasculature that ultimately leads to signs and symptoms of PRES.[7] The reported incidence of PRES in solid organ transplant recipients varies from 0.5-5%[7] in which 1.6% was reported to be caused by tacrolimus.[1]

So although PRES has been a well reported complication of tacrolimus therapy, the reported literature shows a non uniform presentation with respect to age of the patients, time of onset since initiation of tacrolimus therapy, serum levels of tacrolimus, time taken for clinical resolution and presence of comorbidities like hypertension.[1,4,7,8]

In the present case study, the patient developed symptoms within 2 months of initiation of tacrolimus therapy. Reported cases have shown that it may present within a few days to a few months.[4,7,8,9] Clinical diagnosis was confirmed based on MRI findings. Development and progression of symptoms was not related to therapeutic levels of the drug. A similar scenario was reported by Apuri et al[8] in their study where onset of clinical symptoms was noticed after cessation of tacrolimus therapy. Hence sub-therapeutic drug levels cannot rule out the possibility of clinical progression. Also the patient in this study did not have hypertension at the time of presentation. Hence it can be inferred that hypertension might not be present in patients on immunosuppression. This finding was in concordance with the findings of Staykov et al.[10]

Tacrolimus induced PRES is a fairly known complication of tacrolimus therapy, the heterogenous nature of presentation and progression poses a diagnostic dilemma. A high index of suspicion is crucial. However larger studies are warranted for standardization of therapeutic management.

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