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Case Report

Neurological fallout of mycophenolate: A PRES case

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Abstract

Posterior reversible encephalopathy syndrome (PRES) is a rare, neurological disorder characterized by visual disturbances, altered mental status, seizures, and radiographic evidence of 'cacogenic' cerebral edema. It is most often associated with hypertensive crises, renal failure, and immunosuppressive therapies, especially Calcineurin Inhibitors. PRES is a treatable condition with favorable prognosis, if recognized early. It typically presents with headache, seizures, confusion, and visual disturbances like blurred vision or cortical blindness. Symptoms develop rapidly and are often reversible with early treatment. We report a rare case of Mycophenolate Mofetil - induced PRES in a 43-year-old male patient following allogeneic stem cell transplantation for very severe aplastic anemia.

Keywords: PRES, Mycophenolate Mofetil, Aplastic Anemia, Allogeneic Stem Cell Transplantation, Neurotoxicity, Immunosuppression.

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1. Introduction

Posterior reversible encephalopathy syndrome (PRES) is a sporadic neurological disorder that causes brain swelling and a variety of neurological symptoms such as headache, altered mental status, seizures, and visual disturbances. It's often triggered by endothelial dysfunction, which can be caused by severe hypertension, autoimmune disorders, or certain drugs.[1] It is commonly associated with hypertensive encephalopathy, eclampsia, and immunosuppressive drugs—particularly Calcineurin Inhibitors like Cyclosporine and Tacrolimus. However, other agents such as Mycophenolate Mofetil (MMF), though rarely, have also been implicated. Early recognition and prompt withdrawal of the offending agent is crucial to prevent permanent neurological damage.

2. Case Presentation

Here we present the case of a 43-year-old male with a known diagnosis of severe Aplastic Anemia, diagnosed 8 months back (was managed on T Cyclosporine 50mg OD, T.Danazol 200 mg BD and T.Eltrombopag 50 mg OD) for which he underwent an allogeneic hematopoietic stem cell transplantation (HSCT) as definitive treatment. Following the transplant, he was maintained on immunosuppressive therapy comprising Mycophenolate Mofetil (MMF) 500 mg twice daily and Methylprednisolone 4 mg once daily on alternative days, for graft-versus - host disease (GvHD) prophylaxis. The post-transplant period was uneventful, with no significant complications. Routine follow-up investigations, including an XY chimerism analysis performed on the consecutive days, demonstrated 100% donor chimerism (transplant patient may have a mix of their own cells and donor cells with different sex chromosomes

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XX or XY), confirming successful engraftment of the donor stem cells.

However, in the weeks following transplantation, the patient began experiencing progressive blurring of vision, generalized fatigue, painful oral ulcerations, and peeling of the skin. On clinical examination, patient was found to be hemodynamically stable and afebrile. Neurological examination did not reveal any focal deficits or signs of meningeal irritation. However, ophthalmological evaluation noted a significant reduction in visual acuity in both eyes, although there was no evidence of papilledema, retinal hemorrhage, or elevated intraocular pressure. Given the recent transplant history and the emergence of visual symptoms with systemic signs, a neurological workup was warranted. An MRI of the brain with an orbit protocol was conducted, which revealed symmetrical hyperintensities on T2-weighted and FLAIR (Fluid Attenuated Inversion Recovery-a darkish appearance of CSF fluid making it easy to visualize CSF fluid) sequences in the bilateral occipital deep white matter and bilateral peri Rolandic subcortical white matter. These imaging findings were consistent with vasogenic edema, characteristic of Posterior Reversible Encephalopathy Syndrome (PRES). Also, some nonspecific T2/FLAIR hyperintensities were noted in the right frontal deep white matter and left thalamus. (**Figure 1**, **Figure 2**)

During his previous admission, the patient was started on Tacrolimus and developed micro thrombotic angiopathy and hence, the drug was withdrawn. In the absence of Calcineurin Inhibitors, a search for alternative potential causes of PRES was undertaken. Mycophenolate Mofetil (MMF), although less frequently associated with PRES, was identified as a possible contributing agent and was promptly discontinued. The patient had no prior history of neurological illness like hypertension, or renal dysfunction, which are commonly implicated as risk factors for neurological complications following transplantation. The patient was managed symptomatically and continued on Methylprednisolone alone for GvHD prophylaxis, along with additional supportive care. Following the cessation of MMF, the patient demonstrated significant clinical improvement. His visual symptoms gradually resolved, and his overall neurological status stabilized. Repeat ophthalmological evaluations confirmed improvement in visual acuity, and subsequent imaging showed partial reversal of the MRI findings consistent with PRES.

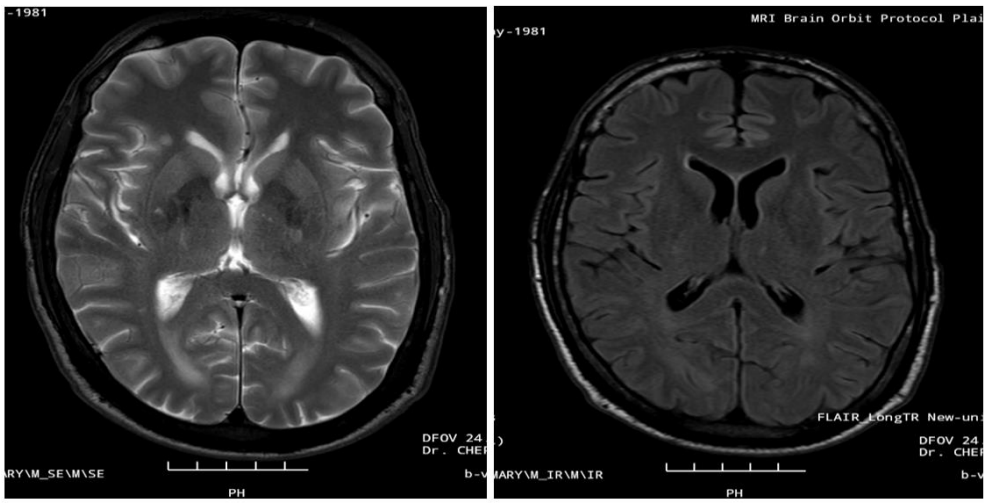

Figure 1: MRI Images showing FLAIR

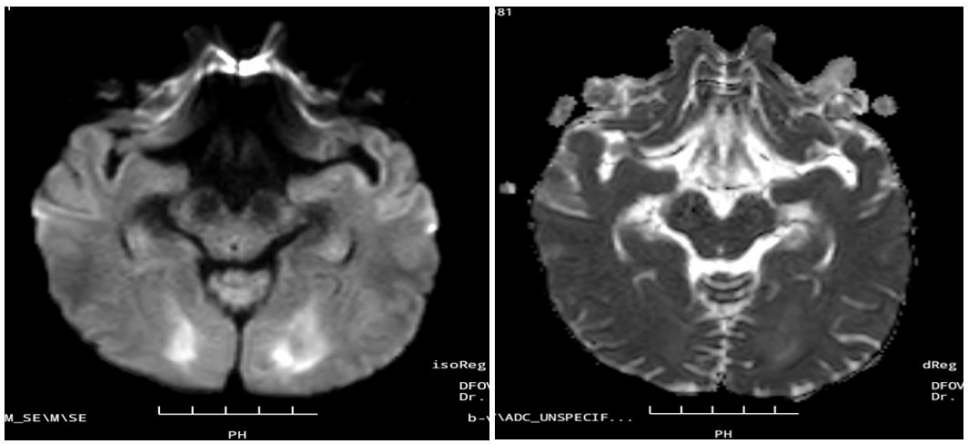

Figure 2: Brain MRI showing bright spots in both temporal lobes

3. Discussion

Posterior Reversible Encephalopathy Syndrome (PRES) is a condition that affects the brain and often shows up as headaches, seizures, confusion, or vision problems. It is usually caused by high blood pressure, kidney issues, or the use of certain immunosuppressive drugs such as Tacrolimus or Cyclosporine.[2,3] In patients who have had a bone marrow transplant, PRES is an important condition to recognize early since if left untreated it may lead to seizures, visual problem, cognitive impairment and may also lead to death.[4]

Mycophenolate Mofetil (MMF) is an immunosuppressive prodrug that is converted into its active form, mycophenolic acid (MPA). MPA selectively and reversibly inhibits the enzyme inosine monophosphate dehydrogenase (IMPDH), which is essential for de novo synthesis of guanine nucleotides. Since T and B lymphocytes rely heavily on this pathway for proliferation, MMF effectively suppresses both cell-mediated and humoral immune responses. This makes MMF particularly useful for preventing graft rejection and treating autoimmune diseases.[5,6]

MMF's strong immunosuppressive effect can increase infection risk, which may trigger systemic inflammation and damage to blood vessel linings—factors that contribute to PRES. This condition involves disruption of the blood–brain barrier and fluid buildup in the brain.[3] MMF is often combined with neurotoxic drugs like tacrolimus or cyclosporine, which can amplify the risk of PRES in patients. It also leads to worsening kidney function, indirectly leading to high blood pressure, another known cause of PRES.[7,8] PRES mainly affects the brain's posterior regions, including the visual cortex. This can result in blurred vision, field loss, or even temporary blindness. These symptoms are typically reversible with prompt diagnosis and treatment, such as adjusting medications and managing blood pressure.[2]

Here the patient has no prior history of any comorbid conditions or any long-standing lifestyle diseases. Generally, Calcineurin Inhibitors, Immunosuppressive drugs such as Tacrolimus (859 cases) or Cyclosporine (656 cases) have been implicated in causation of PRES in many patients.[3] Tacrolimus had already been stopped due to another complication (microangiopathy), and the timeline made it unlikely to be the cause. Since the only active immunosuppressive drug was MMF, and his symptoms started while he was taking it, MMF was suspected as the possible trigger. Though MMF is not commonly associated with PRES, there are a few reports (265 reports as per VigiAccess) of it causing similar problems.[5-8] After stopping MMF, the patient began to recover quickly—his vision improved, and a follow-up MRI showed that the brain changes had started to reverse. Other possible causes were considered, such as brain infections or central nervous system involvement from GvHD. However, the patient did not have fever, neurological deficits, or other signs of infection. CNS GvHD is also very rare and typically presents differently.[3] Stroke was also ruled out because the MRI findings were symmetrical and did not show restricted blood flow.[2]

The adverse drug reaction was comprehensively evaluated using standardized pharmacovigilance tools. The causality of the reaction was assessed as "Probable" according to the Naranjo Algorithm, supported by a temporal relationship between drug exposure and symptom onset, as well as clinical improvement following drug withdrawal. In terms of ADR type, it was classified as "Type B" (Bizarre) based on the Rawlins and Thompson classification, as the reaction was idiosyncratic, unpredictable and non-dose related. The severity was graded as "Level 3" (Moderate) using the Modified Hartwig and Siegel scale, reflecting that the suspected drug, Mycophenolate Mofetil, was discontinued without the need for additional therapeutic intervention or hospitalization. According to the World Health Organization (WHO) criteria, the reaction was categorized as "Other Medically Important Condition", given the involvement of reversible neurological changes and the need for urgent clinical evaluation. The outcome of the ADR was documented as "Recovering", as the patient showed progressive clinical and radiological improvement following the discontinuation of Mycophenolate Mofetil. Finally, preventability, assessed via the Schumock and Thornton scale, was determined as "Not Preventable", since the drug was prescribed appropriately, monitoring was adequate, and the patient did not have identifiable risk factors for developing Posterior Reversible Encephalopathy Syndrome (PRES).

PRES when left undiagnosed and untreated, can lead to irreversible brain damage, seizures, stroke, or death. Early detection is crucial as timely treatment can reverse the condition in a majority of cases.[2,3] This case highlights that PRES should be considered as a possibility in post-transplant patients presenting with neurological symptoms—even in the absence of classic risk factors—and that MMF, though uncommon, can be a potential cause. Early recognition and withdrawal of the offending agent are key to recovery. Supportive care for PRES includes controlling blood pressure, managing seizures, and stopping the offending agent. Monitoring fluid balance and neurological status is also essential to prevent permanent neurological sequelae.[3]

4. Conclusion

This case underscores the need for heightened clinical vigilance for PRES in patients on MMF, particularly in the post-transplant setting. Neurological symptoms such as blurred vision or altered mental status in these patients warrant immediate investigation. MRI brain imaging and timely withdrawal of the suspected agent are essential for favorable outcomes. This case highlights the importance of clinicians and healthcare professionals considering PRES as a differential diagnosis in post-transplant patients presenting

with visual and neurological symptoms, even in the absence of commonly implicated risk factors such as hypertension or calcineurin inhibitor use. Furthermore, it underscores the need for caution and patient education regarding atypical drug-induced etiologies such as MMF, which, although rare, can lead to significant and reversible neurotoxicity when promptly identified and managed.

5. Abbreviations

PRES: Posterior Reversible Encephalopathy Syndrome; MMF: Mycophenolate Mofetil; HSCT: Hematopoietic Stem Cell Transplantation; GvHD: Graft-versus-Host Disease.

6. Author Contributions

Jenny Susan Varghis: Data collection, literature review, manuscript drafting, final approval of the version to be published. **Sara Kurien Kodiattu:** Study design, critical revision of manuscript, final approval. **Bobby Abraham:** Clinical supervision, interpretation of data, manuscript review. **Aakash Chozakade:** Clinical case review, data interpretation, manuscript review. **Chepsy C. Philip:** Data analysis, manuscript editing, approval of final draft. **Jacob Jesurun R. S**.: Overall study supervision, conceptualization, critical revision, and final approval.

7. Conflict of Interest

There is no conflict of interest

8. Acknowledgment

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