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TACROLIMUS-ASSOCIATED POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME IN ALLOGENIC HEMATOPOIETIC STEM CELL TRANSPLANT

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ABSTRACT:

Bckground: Tacrolimus is an immunosuppressive drug used to lower the risk of transplant rejection in individuals after solid organ or hematopoietic transplantation. Cases of posterior reversible encephalopathy syndrome (PRES) as a complication of tacrolimus therapy are infrequently documented. The pathogenesis of this phenomenon is not well understood. Here, we report a case of an 18-year-old female with a history of acute myeloid leukemia that developed PRES after undergoing an allogeneic stem cell transplant and subsequent immunosuppressive therapy with tacrolimus.

Keywords: Posterior Reversible Encephalopathy Syndrome, PRES, Tacrolimus, Stem Cell Transplant, Graft Versus Host Disease

INTRODUCTION: Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder with a wide variety of clinical presentations and unique radiological findings mainly reflective of vasogenic edema. It most commonly involves bilateral parieto-occipital regions of the brain[1]. PRES presents clinically with acute neurological findings consisting of encephalopathy, seizures, visual disturbances, headache, focal neurological deficits and status epilepticus[1]. Tacrolimus is a calcineurin inhibitor that works by inhibiting T-lymphocyte activation and suppresses cellular immunity [2]. Tacrolimus is often utilized for the prevention of Graft Versus Host Disease (GVHD) in patients who have received stem cell transplant (SCT) for hematogenous disorders and malignancies. PRES associated with Tacrolimus secondary to allogeneic stem cell transplant is a relatively rare complication documented in both pediatric and adult patients [3-7]. The exact incidence of PRES due to tacrolimus therapy is unknown. Hammerstrom et al. reported an incidence of 1.1% in their retrospective chart review study on tacrolimus-associated PRES in hematopoietic allogeneic SCT, whereas Wong et al. reported an incidence of 1.6% [6,7]. We report the first case of tacrolimus-associated PRES in an allogeneic hematopoietic stem cell transplant patient from Pakistan.

Case Description

An 18-year-old female with a history of acute myeloid leukemia (AML) refractory to chemotherapy underwent an allogeneic hematopoietic SCT that occurred in December, 2018. She was on cyclophosphamide for immunosuppression. Her post-transplantation course was complicated by hemorrhagic cystitis, reactivation of cytomegalovirus (CMV) infection and mild GVHD. CMV infection was diagnosed using a Polymerase Chain Reaction (PCR) which yielded the CMV quantity of 3600 IU/ml. Patient also presented with a urinary tract infection which the urine culture and sensitivity showed to be due to an enterococcus species. Valacyclovir and ciprofloxacin were added for her on-going infections and her immunosuppressive therapy was switched to Tacrolimus 1.5mg once daily. On the third day of Tacrolimus treatment, she developed two episodes of generalized tonic-clonic seizures which were one hour apart, lasted for 15 - 20 seconds and were self-aborted. These episodes were followed by postictal confusion, visual hallucinations and altered behavior

compromising of agitation and irritability.

On examination, she had a blood pressure of 110/70 mm Hg, a heart rate of 102 per minute, a temperature of 370C, and a respiratory rate of 18 breaths per minute. She was drowsy but oriented to place and person only. She obeyed single-step commands and had fluent speech. Motor and sensory examinations were normal. Neck was supple.

Baseline laboratory investigations were within normal limits. Magnetic resonance imaging (MRI) of the brain with gadolinium contrast revealed diffuse subcortical hyperintense signals in bilateral cerebral hemispheres in T2/FLAIR sequences without evidence of diffusion restriction, susceptibility signal or contrast enhancement (Figure 1). These findings were consistent with PRES. Her electroencephalogram (EEG) showed diffuse theta and delta slowing as well as intermittent generalized delta bursts.She was given levetiracetam. Tacrolimus level was 19 ng/mL (normal range: 5-20 ng/ml). Tacrolimus was removed from the patient's medication regimen and she was given immunosuppresent cellcept(Mycophenolate mofetil). A 6 week follow-up visit and neuro-imaging showed complete resolution of PRES both clinically and on MRI with contrast.

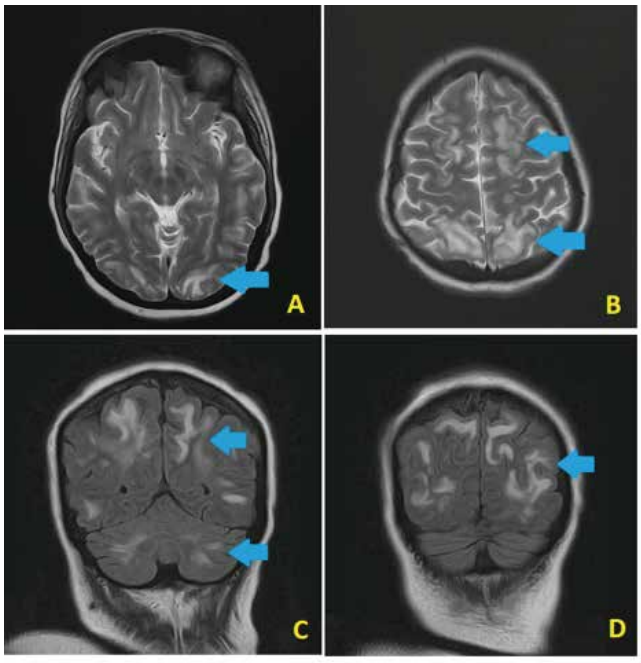

Figure 1: MRI Brain showing diffuse subcortical hyperintense signals in bilateral cerebral hemispheres in T2/FLAIR sequences and T2 hyperintense signals in bilateral cerebellar hemispheres without evidence of diffusion restriction, susceptibility signal or enhancement, as shown by the blue arrows.

A repeat MRI of the brain on follow-up visit (six weeks after discharge) showed complete resolution of PRES (Figure 2) along with significant clinical improvement of her neurological symptoms. She did not experience recurrence of seizures or altered mental status.

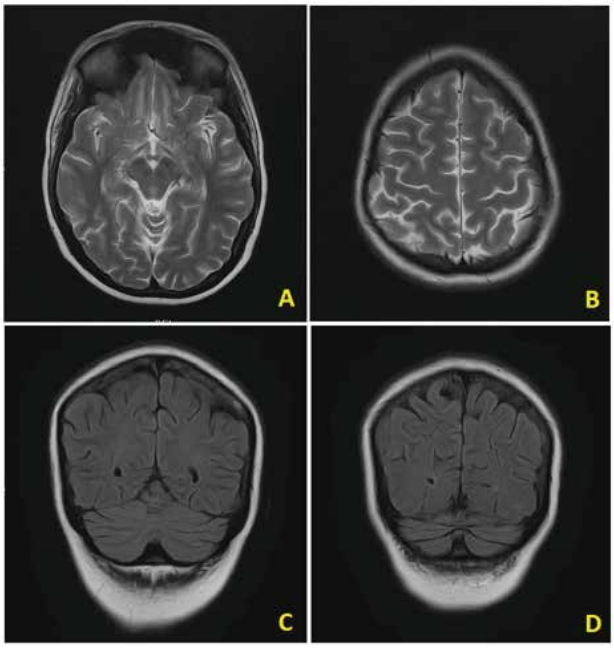

Figure 2: Follow-up MRI Brain showing resolution of diffuse hyperintense signals in bilateral cerebral hemispheres in T2/FLAIR sequences shown in figure 1.

Discussion:

PRES as a complication of immunosuppressive tacrolimus therapy after hematopoietic allogeneic SCT is relatively rare with a few documented cases in the literature (Table 1). The pathogenesis of PRES includes failure of the cerebrovascular auto-regulatory function, endothelial dysfunction and breakdown of the blood-brain barrier (BBB) all of which lead to extravasation of brain plasma resulting in interstitial edema [1]. Hypertension is often associated with PRES (an average rise of 25% from baseline blood pressure). The sympathetic nervous system aids in regulating when it is challenged by hypertension, however, the posterior parts of the brain are deficient in sympathetic innervation, rendering these regions more susceptible to vasogenic edema [3]. Similarly, endothelial injury leading to PRES is linked with inflammatory conditions and cytotoxic effects of certain drugs. (1)
Tacrolimus is used as an immunosuppressive therapy and prophylaxis for GVHD after a hematopoietic SCT [2]. Tacrolimus is known to cause hypertension which is

strongly linked to PRES. However, our patient was normotensive throughout her hospital course. Hypertension is not always present in PRES patients on immunosuppressive therapy [4, 7]. 15-20% of patients with PRES are found to be normotensive [3]. GVHD itself may also be precipitating this condition via endothelial vascular cell damage [6], including small and medium vessel diseases 6,8]. Generalized tonic-clonic seizures, associated with bilateral occipital sharp waves, may be seen on EEG. Alternatively, PRES in our patient could also be related to cyclophosphamide treatment which she received prior to the Tacrolimus therapy. Cases of cyclophosphamide-associated PRES have also been reported in literature [9]. Furthermore, it is also worth addressing that sepsis and infection have also been previously associated with PRES since the underlying cytokine-mediated mechanisms that are observed in sepsis share many similarities with those associated with PRES – resulting in increased vascular permeability of the brain vessels and interstitial extravasation of plasma [9, 10]. Our patient had ongoing infections at presentation as well which could've compounded to development of PRES.

Treatment of this condition depends on withdrawal of tacrolimus and supportive management. A significant resolution of PRES is seen in all cases. However, Hammerstrom et al. found no difference between three groups that were either made to stop tacrolimus entirely, temporarily stopped tacrolimus for 12 days or made to switch to another immunosuppressant [6].As the patient was given antiepileptic for seizures initially now after resolution of symptoms both clinically and radiologically it has planned to do eeg and considered antiepileptics tapering. Although PRES is a mild and reversible condition, occasionally with inadequate management the condition proves to be irreversible and can proceed to coma or death [3, 9]. The mortality rate associated with PRES is 3-6% [3].

Conclusion

Tacrolimus-associated PRES in hematopoietic stem cell transplant patients is an uncommon but serious complication that requires efficient and timely management. PRES should be considered as a possible cause of any neurological symptoms arising in a patient receiving tacrolimus, even with controlled blood pressure and normal serum Tacrolimus levels. Other contributing factors could include GVHD and infections associated with an immunosuppressed state. For the resolution of PRES, tacrolimus should be immediately withheld and supportive treatments should be provided for other precipitating factors.

Article	Patient	Duration between Tacrolimus therapy and onset of PRES	Clinical Features	T2-weighted/FLAIR MRI findings	Management and Outcome
Hossain et al. (2015) [3]	20, male	30 days	2 episodes of generalized tonic-clonic seizures and altered mental status.	Hyperintense signals in bilateral focal regions of subcortical white matter involving the left inferior frontal, temporal and right parietal lobe. No diffusion abnormalities.	Tacrolimus was discontinued and the patient was started on Mycophenolate mofetil. No further episodes of seizures. Patient discharged.
Apuri et al. (2014) [4]	36, female	16 days	Altered mental status, staring into space with right gaze preference.	Hyperintense signals in the cortex of the infero-posterior, posterior temporal and occipital lobes with absence of diffusion abnormality	Tacrolimus was discontinued and Sirolimus was started in its place. 1-year follow-up: complete resolution of symptoms. MRI scans were clear. No further episodes of seizures or altered mental status. Patient discharged.
Apuri et al. (2014) [4]	51, female	25 days	Severe headache and confusion.	Hyperintense signals in the left and right cerebellar hemispheres. No restricted diffusion.	Tacrolimus was discontinued and the patient was started on Mycophenolate mofetil. Within 24 hours, patient was normotensive and neurological symptoms started to improve. Patient discharged with complete resolution of neurological findings.
Apuri et al. (2014) [4]	Female Age: N/A	4 days	Visual disturbances (flashing lights and inability to distinguish between colors), headache and ataxia.	Hyperintense signals bilaterally involving the occipital lobes and portions of the temporal lobes. No diffusion restriction.	Tacrolimus was discontinued and patient was started on Mycophenolate mofetil and then later cyclosporine. Patient was re-admitted with recurrent PRES and altered mental status (now attributed to cyclosporine). Patient continued to deteriorate and expired.
Hodnett et al. (2008)	18, female	14 days	Seizures, altered mental status	Hyperintense signals seen bilaterally and	Tacrolimus was discontinued and Mycophenolate mofetil
[5]			and headache.	symmetrically involving the cerebellar hemispheres. Hyperintense signals asymmetrically involving the subcortical white matter. No diffusion abnormalities.	was started. Patient was normotensive again and no further seizures were observed.

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Author's contribution:
Hina Imtiaz; concept, data collection, data analysis, manuscript writing, manuscript review
Maryam Jamil Syed; data collection, data analysis, manuscript writing, manuscript review
Durreshahwar Kanwar; data analysis, manuscript writing, manuscript review
Bushra Taimuri; data analysis, manuscript writing, manuscript review
Sajid Hameed; data collection, data analysis, manuscript writing, manuscript review