Posterior reversible encephalopathy syndrome in a renal allograft recipient: A complication of immunosuppression?

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ABSTRACT

Posterior reversible encephalopathy syndrome (PRES) is an uncommon post-renal transplant complication. We report a 16-year-old boy who had an acute cellular rejection immediate post-transplant and was given intravenous methylprednisolone along with an increase in tacrolimus dose. He was diagnosed to have PRES based on clinical and radiological features within 6 h of intensified immunosuppression. This is an unusual case report of successfully managing PRES with continuation of the intensified immunosuppression as warranted by the clinical situation, along with aggressive blood pressure control. After 6 weeks, magnetic resonance imaging showed complete resolution of lesions. He has good graft function and no residual neurological deficits while on small doses of three antihypertensives, 12 months after transplantation.

Key words: Kidney transplant recipient, posterior reversible leukoencephalopathy syndrome, pulse methylprednisolone, renal allograft recipient, tacrolimus

Introduction

Posterior reversible encephalopathy syndrome (PRES) was first described as a distinct clinico-radiological entity by Hinchey *et al.* in 1996.[1] Most common causes reported in literature are secondary to hypertensive crisis or immunosuppression. Calcineurin inhibitors (cyclosporine and tacrolimus), high-dose steroid therapy, intravenous immunoglobulin, and sirolimus have been implicated. The overall incidence of PRES was 0.49% amongst 4,222 solid organ transplant recipients from 1998 to 2006 in the USA.[2] Typical magnetic resonance imaging (MRI) features are bilateral symmetrical brain edema in the cortical and subcortical regions of the parietal and occipital lobes. Treatment strategy is temporary or permanent withdrawal of immunosuppression along with good control of blood pressure.[3] However, immunosuppression withdrawal can be detrimental and in fact, it may need to be intensified as highlighted in our case, due to concomitant acute rejection of the allograft.

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Case Report

A 16 year-old male with end-stage renal disease of unknown cause had a living-related renal allograft surgery. He was given induction with basiliximab 20 mg on days 0 and 4. Tacrolimus and mycophenolic acid (MPA) were started pre-transplant (day - 3) and prednisolone was added from day 0 of transplant. Serum creatinine was low at 1.1 mg/dl on day 4. On day 6, there was acute graft dysfunction with serum creatinine 1.6 mg/dl. The tacrolimus trough level was 2.5 ng/ml. Renal Doppler showed good perfusion of the graft and no evidence of renal artery stenosis. Renal biopsy was deferred because of uncontrolled blood pressure and intravenous (IV) methylprednisolone 1 g was empirically given on day 7 for probable acute cellular rejection, after stabilizing systolic blood pressure to 140 mmHg, along with an increase in tacrolimus dose to 3 mg twice daily (0.23 mg/kg/day). Six hours later, he had sudden acceleration of systolic blood pressure to 220 mmHg with three episodes of generalized tonic clonic seizures. He was given IV diazepam and a loading dose of phenytoin. In intensive care unit (ICU), he was sedated with midazolam and

propofol infusions and required upto two parenteral and four oral short acting antihypertensive drugs in the next 48 h under close monitoring. Maintenance antiepileptic was initially clobazam followed by levetiracetam. MRI showed bilateral multifocal subcortical hyperintensities in T2-weighted imaging, with no diffusion restriction, in keeping with a diagnosis of PRES [Figures 1-3]. He further received IV methylprednisolone 500 mg each for the next 2 days. On day 9, he was discharged from the ICU with five oral antihypertensive drugs including minoxidil and antiepileptic levetiracetam. Serum creatinine had reached a nadir of 1.2 mg/dl on day 8 but increased to 1.6 mg/dl within a week. He had transient proteinuria of 342 mg in 24 h collection. Renal biopsy showed moderate to severe tubulitis with transplant glomerulitis, no hypertensive changes, and a negative C4d stain. He was treated as steroid-resistant acute cellular rejection with seven doses of antithymocyte globulin (2.5 mg/kg/day) and serum creatinine normalized to 1.1 mg/dl. The tacrolimus trough was at 3.2 ng/ml and the dose was further increased. MPA area under the curve was adequate at 53.8 mg.h/L. MRI brain repeated 6 weeks later showed resolution of all abnormalities [Figure 4]. At 12 months after transplantation, he is doing well and has good graft function on three antihypertensive drugs.

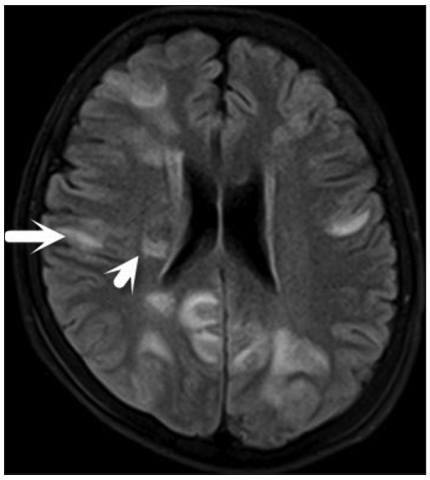

Figure 1: Fluid-attenuated inversion recovery magnetic resonance image of the brain shows bilateral multifocal subcortical hyperintensities in the parietal lobe (long white arrow) with relative sparing of the left frontal lobe and also involvement of the deep white matter of the right internal capsule (short white arrow) and ganglionic region

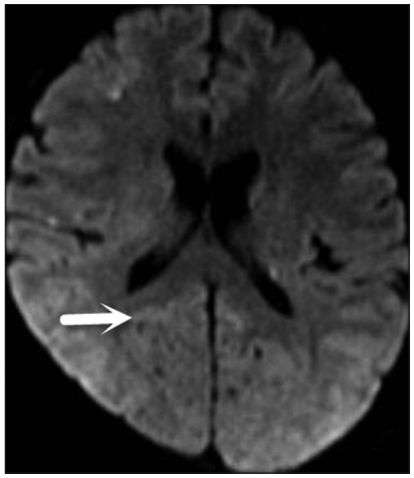

Figure 2: Corresponding diffusion-weighted magnetic resonance image demonstrates lesions that are partially confluent and iso intense signals with no diffusion restriction (white arrow)

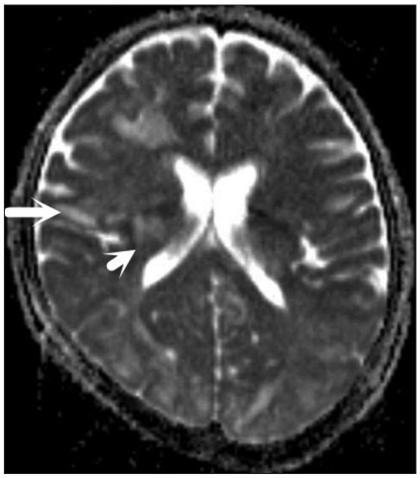

Figure 3: Those areas with increased signal intensities in fluid-attenuated inversion recovery [Figure 1] also have increased apparent diffusion coefficient values signifying vasogenic edema (long and short white arrows)

Discussion

PRES was first described by Hinchey *et al.*[1] in 1996 as a clinico-radiological entity, characterized by typical neurological deficits, distinctive MRI features, and usually a benign clinical course. Most cases in literature have occurred after hematopoietic or liver transplants.[4-7] Fifty cases of calcineurin inhibitor associated PRES in transplant recipients reported in the literature were reviewed by Singh *et al.* with only eight among renal transplant recipients.[8] Besenski *et al.*[9] looked at 77 consecutive renal transplant patients who presented with neurological symptoms and found MRI findings of PRES in 5%. These occurred most commonly within the first three months post-transplant, usually following immunosuppression given in the intravenous bolus form.[5] Severe hypertension post-solid organ transplantation can also cause PRES.[10]

Contributing factors that led to PRES in our patient are the young age, higher doses of corticosteroids, tacrolimus, and a prolonged period of uremia prior to transplant. In the article by Wong *et al.*, most patients with PRES had serum tacrolimus level in the therapeutic range and unlike our case, tacrolimus was restarted after a brief period of withdrawal.[4] Other studies have shown that

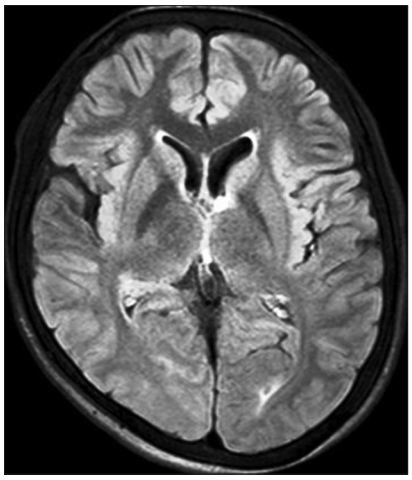

Figure 4: Magnetic resonance imaging brain shows that the previously noted bilateral multifocal non-enhancing, subcortical and deep white matter hyperintensities in the fluid-attenuated inversion recovery magnetic resonance image [Figure 1] have completely resolved

there is no correlation with neurotoxicity and the trough levels of tacrolimus.[5,11] A few case reports have shown high CSF tacrolimus levels, when corresponding serum levels have been within therapeutic limits.[4] Research of Yanagimachi *et al.,*[12] and Yamauchi *et al.,*[13] showed that polymorphisms in CYP3A5, ABCB1, and MDR1 genes were linked to calcineurin-associated neurotoxicity.

Continuation of immunosuppression entails maintaining a balance between prevention of rejection and aggravation of neurotoxicity. In a setting of PRES with no suspected rejection and low-risk transplant, reduction or even temporary interruption of tacrolimus may be beneficial in neurological recovery. Though it is well recognized that blood levels of immunosuppressants do not correlate with the presence of PRES, it still remains the only practical aid for guiding physicians.[2] If the neurological recovery is delayed even after reduction, then temporary stoppage of calcineurin inhibitors may be necessary. Pharmacogenomic studies may help in identifying susceptible patients, once widely available as a diagnostic test. Our case exemplifies a rare scenario where rejection and PRES co-existed. Immunosuppression was intensified after informed consent was obtained from the family. This management requires therapeutic drug monitoring, dedicated ICU team, and neurologist supervision. A complete neurological recovery without cessation of tacrolimus has also been reported in two pediatric renal transplants by Parvex *et al.*[14] It is likely that our patient had a genetic polymorphism, though not formally tested, as he required high doses of tacrolimus (0.35 mg/kg/day) to achieve the desired trough concentration in the serum. Our report is the first to demonstrate that intensified immunosuppression, if clinically warranted can still be continued with close monitoring and control of blood pressures.

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