Pediatric Neurology 50 (2014) 272–275

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Alternative Tacrolimus and Sirolimus Regimen Associated With Rapid Resolution of Posterior Reversible Encephalopathy Syndrome After Lung Transplantation

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ABSTRACT

BACKGROUND: Neurotoxicity is a significant complication of calcineurin inhibitor use, and posterior reversible encephalopathy syndrome has been reported. Limited data exist on the use of alternative immunosuppression regimens in the management of posterior reversible encephalopathy syndrome in transplant recipients. **METHODS:** We present the immunosuppression management strategy of a girl who underwent bilateral lung transplantation for cystic fibrosis 6 months earlier, then suddenly developed a grand mal seizure due to posterior reversible encephalopathy syndrome diagnosed by magnetic resonance imaging of the brain. In an effort to reduce her tacrolimus dose, an alternative immunosuppressant regimen combining tacrolimus and sirolimus was used. **RESULTS:** After the modification of her immunosuppressant regimen, there was rapid clinical improvement with no further seizures. Her brain findings had resolved on magnetic resonance imaging 2 months later. Over the next 6 months, allograft function remained stable and surveillance transbronchial biopsies found no allograft rejection on the combined sirolimus and tacrolimus therapy. **CONCLUSIONS:** Tacrolimus-associated neurotoxicity resolved in a lung transplant recipient with a combined tacrolimus and sirolimus regimen. This combined therapy appears to be an effective alternative for lung transplant recipients that allow them to receive the benefits of both drugs but at lower doses, which reduces the risk for adverse effects.

Keywords: lung transplantation, posterior reversible encephalopathy syndrome, sirolimus, tacrolimus

Pediatr Neurol 2014; 50: 272-275

Introduction

Maintenance immunosuppression after lung transplantation typically includes a three-drug combination with a calcineurin inhibitor, an antimetabolite, and a systemic corticosteroid.[1-3] According to the Registry of the International Society for Heart and Lung Transplantation, the most commonly used immunosuppressive regimen in both adult and pediatric patients is tacrolimus, mycophenolate, and prednisone.[2,3] Similar to cyclosporine, tacrolimus is an antiproliferative agent that binds to an immunophilin, FK-binding protein 12 (FKBP12), to exert its effect on T-cell activation and proliferation.[1] Tacrolimus is a macrolide antibiotic that binds to its cytosolic immunophilin more efficiently than cyclosporine, resulting in 10 to 100 times more potency; however, this does not translate to more therapeutic immunosuppression but allows for lower dosages.[4]

Calcineurin inhibitors have similar interactions with medications that alter the P450 system, with similar side effect profiles including opportunistic infections, dyslipidemia, electrolyte disturbances, gingival hyperplasia, hirsutism, hypertension, renal injury, and neurological sequelae.[5] However, tacrolimus is more strongly associated

Article History:
Received February 25, 2013; Accepted in final form November 12, 2013
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0887-8994/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2013.11.006

with neurological complications, including headaches, tremors, and seizures.[1] Posterior reversible encephalopathy syndrome (PRES) is an uncommon neurological condition that is associated with calcineurin inhibitor use, including tacrolimus.[6-12] There are no standard guidelines for the management of transplant recipients with PRES, especially with the actual cause of neurotoxicity being unclear and controversial. We discuss the successful management of a lung transplant recipient with PRES using an alternative strategy of a combined immunosuppression regimen with a calcineurin inhibitor and a mammalian target of rapamycin (mTOR) inhibitor.

Case description

A 17-year-old girl whohad undergone bilateral lung transplantation 6 months earlier for advanced bronchiectasis due to cystic fibrosis suddenly develop a single, short grand mal seizure. She was hospitalized 2 days earlier for intravenous ganciclovir therapy because of a cytomegalovirus infection diagnosed by an acute elevation in quantitative cytomegalovirus by polymerase chain reaction DNA levels from <20 copies/mL to >100,000 copies/mL. In addition to the cytomegalovirus infection, her posttransplantation course was complicated by hypertension and anastomotic stenosis requiring balloon dilatation. Soon after transplantation, her blood pressure was elevated with eventual control on her current therapy with sustained-release metoprolol 200 mg daily, amlodipine 10 mg daily, and enalapril 5 mg daily with her current blood pressure ranging 100-110/60-70 mm Hg. Her maintenance immunosuppressant therapy included tacrolimus 1.5 mg twice daily, azathioprine 50 mg daily, and prednisone 10 mg daily. Her tacrolimus level was 9.4 ng/mL (normal range 5-20 ng/mL) with the highest level being 12.1 ng/mL over the past 3 months.

During the seizure, intravenous lorazepam 5 mg was provided with rapid seizure resolution. Immediately after the seizure and over the next 48 hours, her blood pressure was elevated to 160/100 mm Hg on the same antihypertensive therapy. Electroencephalography (EEG) was normal with no signs of seizure activity. Magnetic resonance imaging (MRI) of the brain demonstrated multiple areas of diffusion and T2 signal abnormality in the cerebrum and cerebellum, with multifocal areas of subcortical increased T2 signal/edema, which was greater in the parasagittal posterior parietal and occipital lobes, and marked increased T2 fluid-attenuated inversion recovery signal in the body of the corpus callosum (Fig A).

With no seizure activity on EEG and chronic seizures not being a common feature of PRES, we elected not to treat with antiepileptic therapy. Because of tacrolimus being the likely cause of her PRES, we reduced the dose of tacrolimus while adding sirolimus, continuing prednisone at the same dose and stopping azathioprine. The dose of tacrolimus was reduced to 0.5 mg orally twice daily, and sirolimus was started at 0.5 mg orally daily. The subsequent drug levels were 4.8 ng/mL for tacrolimus and 7.0 ng/mL (normal range 4-12 ng/mL) for sirolimus. With this combination of calcineurin and mTOR inhibitors, her renal function was monitored closely and remained normal throughout her clinical course.

With the alternative immunosuppressant regimen, she experienced immediate improvement with no further seizure activity. Repeat MRI of the brain 2 months later demonstrated complete resolution of the T2 and fluid-attenuated inversion recovery signal abnormalities in the cerebrum and the cerebellum (Fig B). Additionally, her pulmonary function remained stable with surveillance transbronchial biopsies showing no evidence of allograft rejection on the combined tacrolimus and sirolimus regimen.

Discussion

Clinical manifestations of PRES after solid organ transplant can be variable, including headache, confusion, altered mental status, vision changes, isolated seizure, generalized seizure, and intracranial hemorrhage, with seizure being the most common.[13,14] Seizures due to PRES are frequently short single grand mal episodes with variable theta/delta slowing on EEG.[15] Focal EEG abnormalities often occur in those patients who experience focal seizures.[15] Seizures typically develop early after disease onset and terminate spontaneously or with therapy during the first 24 hours, with recurrence beyond 24 hours or chronic epilepsy being very uncommon.[15] Although seizures frequently occur with PRES, they are not associated with a worse prognosis and long-term antiepileptic therapy may not be warranted.[15] In a large cohort of patients with PRES due to a variety of reasons, patients on immunosuppression or chemotherapy had lower mean arterial pressures than conditions such as infection, eclampsia, or autoimmune disorders.[16]

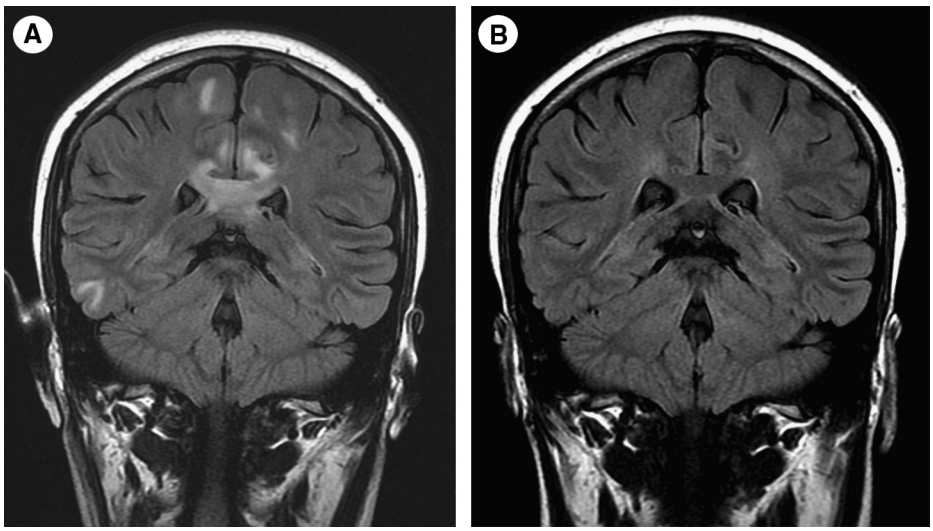

FIGURE.
Fluid attenuated inversion recovery image demonstrates increased cortical signal in the parietal lobes and right posterior temporal lobes and in the corpus callosum (A) with complete reversal of all areas of abnormal signal 2 months later (B).