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Case Report
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Tacrolimus Induced Cerebral Hemorrhagic Posterior Reversible Encephalopathy Syndrome in a Post-Cardiac Transplant Patient

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Abstract

Tacrolimus (FK-506, Prograf) is a potent immunosuppressant agent used in organ and bone marrow transplantation. It is associated with a variety of neurotoxicities that include leukoencephalopathy and posterior reversible encephalopathy syndrome (PRES). Radiological features of white matter changes with high tacrolimus levels are documented but there are no case reports of hemorrhagic posterior reversible encephalopathy syndrome in adult patients after heart transplant. Here, we describe the case of a 50 year old gentleman who developed hemorrhagic PRES while taking tacrolimus, 1 month following cardiac transplant for coronary artery disease with serial magnetic resonance imaging showing bilateral subcortical changes consistent with PRES which had interval resolution after the discontinuation of tacrolimus. A brief review of the proposed mechanism underlying PRES and a literature review of hemorrhagic PRES in the context of organ transplantation are also described. This case illustrates hemorrhagic posterior reversible encephalopathy syndrome in the setting of normal tacrolimus levels in an adult patient after cardiac transplantation which has never been reported in the literature.

Keywords: Tacrolimus; Posterior Reversible Encephalopathy Syndrome; Cerebral Hemorrhage; Post-Cardiac Transplant

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Introduction

Posterior reversible encephalopathy syndrome usually presents in those with hypertension, uremic encephalopathy, eclampsia, and during immunosuppressive therapy. Headache, blurriness in vision/blindness, hemiparesis, or seizures was the most common presentations that led to a neurological evaluation. Magnetic resonance imaging of these patients revealed symmetrical edema of white matter tissue in the parieto-occipital regions of both cerebral hemispheres and cerebellum. We present the following case in a patient with well-controlled blood pressure and normal tacrolimus levels who develops acute hemiparesis and hemorrhagic posterior reversible encephalopathy which has never been reported in a post-cardiac adult transplant patient.

Case Presentation

We evaluated a 50-year-old right-handed man with a history of hypertension and hypercholesterolemia who received a heart transplant one month prior to our neurologic evaluation. He was transferred from an outside hospital after a myocardial infarction (MI) and underwent an emergency coronary artery bypass graft (CABG). The following day he required the help of biventricular assist devices (BIVAD) because of failed bypass. He then received a heart transplant 4 weeks later. His post-operative course was uneventful and he remained in the hospital for the next 4 weeks. He was getting ready to be discharged when he acutely developed painless left hemiplegia without hemiparesthesias or headaches. He was awake, alert, and oriented to person, place and time but was dysarthric in speech with full comprehension of commands. The cranial nerve exam was normal except for a mild left facial droop, and a decreased shoulder shrug on the left. His motor strength was flaccidly plegic in the left arm and leg while the right side was normal. He was hyperreflexic on the left, with normal sensation and coordination. On plantar stimulation, his left toe was upgoing and the right was down going.

His international normalized ratio (INR) was 1.1 (0.8–1.1), partial thromboplastin time (PTT) 26.8 (11.9–14.9), and prothrombin time (PT) 11.5 (22.3–36.7). His blood pressures were stable

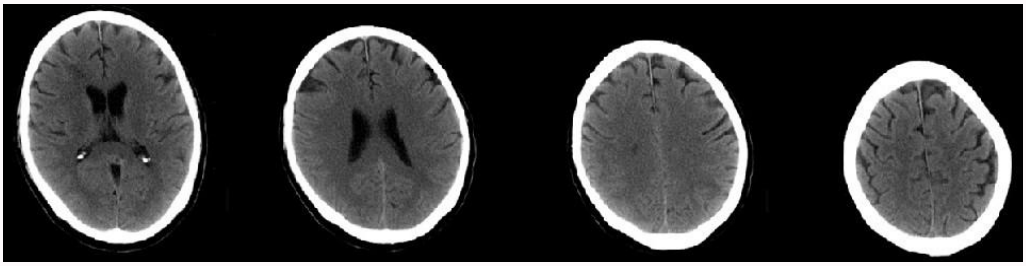

Figure 1: CT head without contrast, pre-transplantation, demonstrating chronic injury of the right frontal and centrum semiovale.

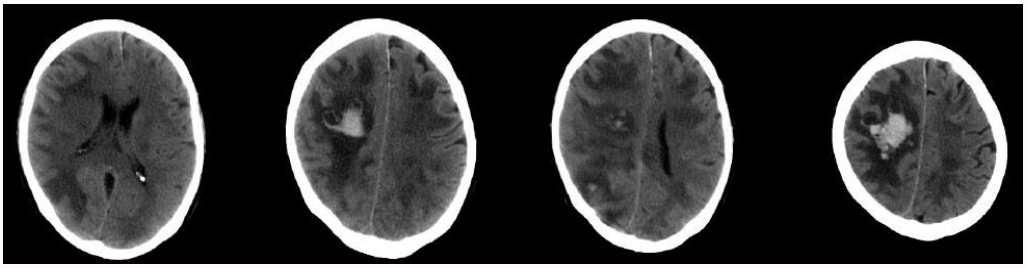

Figure 2: CT head without contrast, post-transplantation, demonstrating an area of hemorrhage in the right frontoparietal lobe with bilateral white matter edema consistent with HPRES.

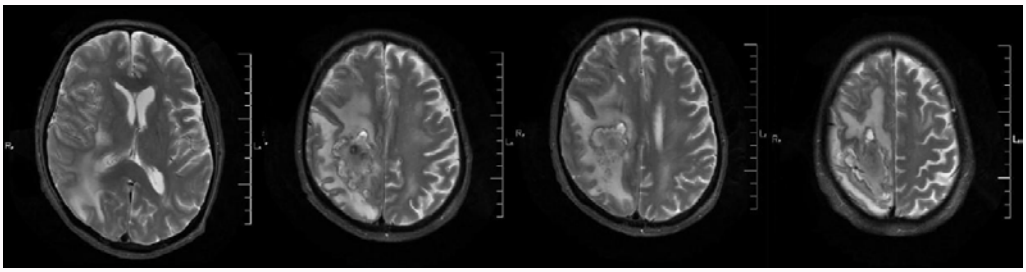

Figure 3: MRI head, T2 sequence, demonstrating bilateral posterior leukoencephalopathy.

throughout his hospitalization and increased only after the onset of his hemiplegia. His medication administration record was reviewed and no antithrombotics or anticoagulants had been given. At the time of his acute event his blood pressure was 150/90 mmHg.

Serial computed tomography (CT) head studies were reviewed from prior to transplantation (Figure 1) and after this event (Figure 2). A pre-operative CT head from 2 months prior to the heart transplant done after a syncope episode showed 2 areas of fairly well defined decreased attenuation within the right centrum semi ovale and right frontal lobe which were non-specific but had the appearance of remote ischemic injury. After the event, a non-contrast CT head showed a right frontoparietal intraparenchymal hemorrhage with mass effect and mild midline shift. There was also an additional small focus of hemorrhage in the subcortical right parietal lobe. Bilateral parietal hypodensities were also present.

Subsequent magnetic resonance imaging (MRI) revealed patchy multifocal areas of vasogenic edema with a predominance for the posterior aspects of the frontal, temporal and parietal lobes, as well as the bilateral cerebellar hemispheres. There were two discrete areas of intraparenchymal hemorrhage within the right frontoparietal region as well as a smaller focus in the right parietal lobe laterally with significant right frontal perihematomal edema, as reflected on the MRI. Magnetic resonance spectroscopy (MRS) revealed vasogenic edema in the above characterized regions of the brain and magnetic resonance arteriography (MRA) was normal, ruling out vascular etiologies of hemorrhage including arteriovenous malformations or aneurysms, which helped solidify our diagnosis of posterior reversible encephalopathy syndrome (PRES).

Serial brain MRIs were reviewed after this event. A repeat study four days after the initial event and after the cessation of tacrolimus showed no changes in the right frontal and parietal hemorrhages but showed slight improvement in the T2 and FLAIR hyper intensities in the frontal, parietal and temporal lobes with resolution of the abnormal signals in the cerebellum. We repeated an additional MRI brain on post event day #11, which showed a resolving hematoma and continued improvement in the leukoencephalopathy.

Tacrolimus levels were therapeutic prior to this event (10-20 ng/ml) and were more often sub-therapeutic with only 2 values above 20 ng/ml more than 2 weeks prior to this event. The patient's tacrolimus dose was immediately decreased after this event and was discontinued 2 weeks after this event. The patient was bridged to cyclosporine and did very well with physical and occupational therapy. He was discharged to a rehabilitation unit ambulating but still with significant residual left hemiparesis.

Our patient's pre-operative scans were essentially normal, except for some evidence of old injury in the right frontal and centrum semiovale (Figure 1). The post-event HCT revealed a large right

fronto-parietal intracerebral hemorrhage with bilateral white matter edema (Figure 2). Serial MRI's showed striking bilateral subcortical changes consistent with PRES which had interval resolution after discontinuing tacrolimus (Figure 3).

Conclusion

Posterior reversible encephalopathy syndrome (PRES) has been described in the literature since 1988 but not introduced into clinical practice until 1996 [1,2]. Since its initial appearance in the medical literature, multiple case studies and series have been described in association with solid organ as well as bone marrow transplantation, immunosuppressive treatments, specifically calcineurin inhibitors, renal failure, sepsis, eclampsia of pregnancy, and acute elevations in blood pressure. Patients present with variable symptoms, including seizures, headache, encephalopathy and cortical blindness, with seizures being the most common presentation in at multiple case series [3-6]. In general, recovery is expected.

One review of immunosuppressive-associated PRES found the incidence ranged from 0.4 to 6% at individual institutions, with immunosuppressive-associated PRES accounting for 12-27% of all central nervous system lesions after organ transplantation; however, the role of immunosuppressants such as cyclosporine and tacrolimus in causing PRES is still not fully understood [6]. Two traditionally cited models of PRES are that 1) Severe hypertension exceeds the limits of autoregulation, leading to breakthrough cerebral edema; and 2) Hypertension leads to cerebral autoregulatory vasoconstriction, ischemia and subsequent brain edema, although neither seems to fully explain immunosuppressive-associated PRES nor cases of PRES which occur in the absence of hypertension. A newer model proposes that systemic toxicity, whether from immunosuppressive therapy or from other complex underlying comorbidities such as renal failure or sepsis, leads to endothelial dysfunction via cytokine dysregulation and increased leukocyte trafficking, resulting in altered intrinsic vascular tone and brain hypoperfusion [7]. This may account for the MRI lesions and clinical deficits as well as their reversibility.

Posterior reversible encephalopathy syndrome with hemorrhage has been previously described in several case series in association with underlying coagulopathies, in the setting of transplantation, most often with non-solid organ transplantation, hypertension and toxicity from immunosuppressive medications [8-10]. One radiologic case series identified the incidence of hemorrhage (including microhemorrhages) in PRES of 15%, suggesting that it may be under diagnosed [8]. In one case series of patients with hemorrhagic PRES, an underlying coagulopathy was present in seven of eight patients, while only half of the patients were on calcineurin inhibitors [9]. Case reports of hemorrhagic PRES with tacrolimus have largely been confined to patients undergoing stem cell or bone marrow transplantation [11-13]. There has been one case report of hemorrhagic PRES occurring in a pediatric patient after cardiac transplantation in the setting of tacrolimus use, but none thus far have been reported in the adult population [14].

We believe that the cause of our patient's leukoencephalopathy was from the immunosuppressant itself and that the hemorrhage may have been secondary to the PRES itself. Hypertension cannot be entirely discounted in this case since blood pressures were not continuously monitored, but all reported vital signs had been normal for 22 days. Other vascular etiologies were ruled out with an MRA of the head and no antiplatelets or anticoagulants were given prior to the event. The bilateral leukoencephalopathy, hemorrhage and right frontal perihematomal edema that were seen on MRI resolved over time, consistent with hemorrhagic PRES.

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