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Fatal PRES and super-refractory status epilepticus after combined heart and kidney transplant: A case report and literature review

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Prevention of acute allograft dysfunction is the principal focus in the immediate post-transplant period. However, many immune-modulating agents have been associated with posterior reversible encephalopathy syndrome (PRES). We describe a complex case of extended critical illness triggered by PRES in the immediate post-transplant period, leading to super-refractory status epilepticus of unclear etiology and acute rejection of the 2 transplanted organs. Brain autopsy showed findings of multifocal necrotizing leukoencephalopathy (MNL). Our patient differed from previously described cases of PRES after heart transplantation in that our patient did not receive calcineurin inhibitors and had a fatal outcome. A delicate balance must be maintained between the risk of acute rejection in a high-risk patient with inadequate immunosuppression vs the risk of PRES from the use of aggressive immunosuppression. Furthermore, several antiseizure medications interfere with the metabolism of immunosuppressive medications and these potential interactions must be carefully considered to reduce morbidity and prevent mortality. Lastly, our case suggests that perhaps MNL should be considered in the differential diagnosis for refractory seizures in the setting of established risk factors, such as immunosuppression and sepsis.

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Background

Prevention of acute allograft dysfunction is the principal focus in the immediate post-transplant period. This risk is heightened in the setting of high sensitization and multi-organ transplant.[1] Therefore, immunosuppression protocols

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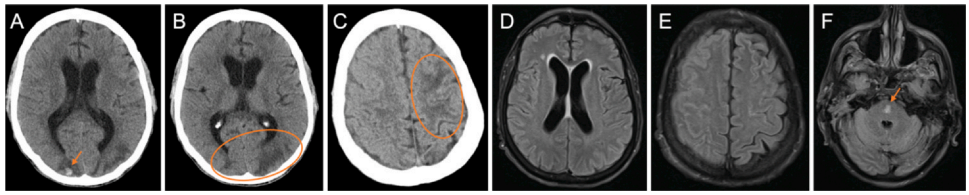

Figure 1 Computed tomography of the brain without contrast performed on post-operative day 9 showing A) a small hyperdense foci in the right occipital lobe consistent with acute hemorrhage (arrow) and B) bilateral parieto-occipital hypodensities (circle) and C) left frontal hypodensities (circle) favored to represent PRES. Magnetic resonance imaging of the brain without contrast performed on post-operative day 29 showed D-E) resolution of the white matter lesions consistent with PRES and F) subacute infarct in the pons (arrow). There were also FLAIR hyperintensities in the right cerebral hemisphere, numerous punctate microhemorrhages in the bilateral cerebral and cerebellar hemispheres, and hemorrhage in the right occipital and left frontal lobes.

utilize multiple agents for induction. While the intention of this aggressive approach is to prevent morbidity and mortality associated with early graft rejection, it can result in posterior reversible encephalopathy syndrome (PRES).[2] As the name suggests, PRES is often clinically and radiographically fully reversible with supportive care and removal of the inciting factor.[2] We present a case of extended critical illness triggered by PRES in the setting of multiorgan transplant, leading to acute rejection of the 2 transplanted organs and super-refractory status epilepticus.

Case presentation

A 58-year-old man with end-stage cardiomyopathy implanted with a left ventricular assist device as a bridge to transplantation 1 year prior (complicated by methicillin-sensitive *Staphylococcus aureus* driveline infection on suppressive doxycycline) and chronic kidney disease presented to the emergency room from clinic for worsening renal parameters noted on routine labs. The patient reported progressive lower extremity edema despite diuretic use and associated fatigue. He was found to be volume overloaded in the setting of worsening right ventricular failure and acute cardiorenal syndrome requiring hemodialysis. He was listed as status 1A for a combined heart and kidney transplant. His hospital course was complicated by catheter-associated *Achromobacter xylosoxidans* bacteremia which was successfully treated with cefepime. Roughly 2 months after admission, he underwent a combined orthotopic heart and deceased donor kidney transplantation. No signs of active infection were visualized during surgical left ventricular assist device removal.

Postoperatively, the patient remained intubated and critically ill on vasopressor support and prophylactic cefepime and vancomycin. Due to elevated panel-reactive antibodies (cPRA = 51) and multiorgan transplantation, the patient received 2 doses each of basiliximab, antithymocyte globulin, and intravenous immunoglobulin (IVIG), plus a 5-day methylprednisolone taper for induction immunosuppression. For maintenance immunosuppression, mycophenolate mofetil was initiated peri-operatively and prednisone was continued following methylprednisolone taper. Tacrolimus was avoided as the patient's transplanted kidney was not functioning well. On postoperative day 5, the patient developed a fever and surveillance blood cultures grew vancomycin-resistant *Enterococcus faecium.* All intravenous catheters were exchanged, antibiotics changed to ampicillin plus daptomycin, and vasopressors maintained for septic shock. Repeat blood cultures were negative.

On postoperative day 9, he developed new-onset seizures. In the days leading up to the first seizure, the patient's creatinine significantly down-trended from 5.78 mg/dl immediately post-transplant to 1.49 mg/dl (normal: 0.66-1.25 mg/dl) on the day of seizure onset. Furthermore, his blood pressure was still being maintained with vasopressors. Ampicillin was discontinued due to its ability to cause seizures and daptomycin was continued as monotherapy. Computed tomography of the brain showed bilateral parieto-occipital and left frontal hypodensities favored to represent PRES, as well as a small hyperdense foci in the right occipital lobe consistent with acute hemorrhage (Figure 1A-C). Electroencephalogram revealed focal status epilepticus in the left temporo-occipital which was considered a manifestation of PRES. The patient had received 2 doses of IVIG on the 2 days prior to the seizures. Thus, a working diagnosis of IVIG-induced PRES was made after multidisciplinary discussion between neurology, transplant cardiology, transplant nephrology, and transplant infectious disease. Subsequent doses of IVIG were held. Since the patient had received aggressive induction immunosuppression, sirolimus was added in place of tacrolimus to the maintenance immunosuppressive regimen. The antiseizure medication (ASM) regimen was quickly escalated to include the combination of levetiracetam, valproic acid, and midazolam infusion for the treatment of refractory seizures.

Due to persistence of status epilepticus after 24 hours of midazolam initiation, he was deemed to have super-refractory status epilepticus. Management goals from the neurology team were to achieve burst suppression for 48 hours and then taper the ASM regimen. However, each time burst suppression was achieved for at least 48 hours, ASMs were unable to be weaned due to recurrence of seizures seen on continuous electroencephalogram monitoring and further escalation of ASMs was required. Due to ongoing super-refractory status epilepticus, lumbar puncture was performed and showed lymphocyte predominance, pleocytosis, and elevated protein level consistent with possible viral infection. Infectious serologies (i.e., *Toxoplasma gondii*, *Mycobacterium tuberculosis,* Cryptococcus, herpes

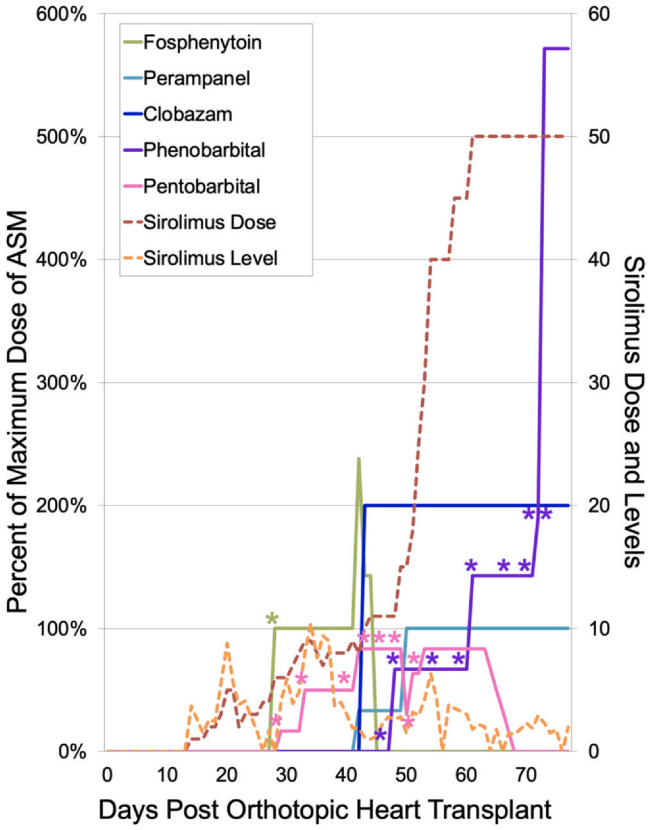

Figure 2 Antiseizure medication dose is reflected as a percentage of the maximum recommended daily dose (fosphenytoin 420 mg/day, perampanel 12 mg/day, clobazam 40 mg/day, phenobarbital 210 mg/day, and pentobarbital 3 mg/kg/hours) and is graphed along the left axis. The dose and level of sirolimus are graphed on the right axis. The star symbol indicates a bolus dose of the corresponding antiseizure medication. ASM, antiseizure medication.

simplex virus 1/2/8, adenovirus, dengue virus, Zika virus, West Nile virus, and chikungunya virus) showed elevated dengue and West Nile virus IgG antibodies, but immunoglobulin M (IgM) antibodies were not detected. Chikungunya IgM was positive and IgG was negative. At this point, the patient had been hospitalized for nearly 3 months in a nonendemic country and did not have clinical features of Chikungunya; thus, additional testing was not further pursued. With viral etiologies largely ruled out, the cerebral spinal fluid (CSF) profile was consistent with ongoing seizure activity.

Magnetic resonance imaging of the brain performed 3 weeks after seizure onset showed resolution of the white matter lesions consistent with PRES, along with a hyperdensity in the pons favored to represent subacute infarct (Figure 1D-F). At this point, his ASM regimen was escalated to midazolam infusion, ketamine infusion, pentobarbital infusion, phenytoin, lacosamide, and levetiracetam. However, pentobarbital severely reduced sirolimus levels (Figure 2) and the excessive volume of the ASM infusions resulted in overt right heart failure leading to abdominal compartment syndrome and subsequent failure of the transplanted kidney, requiring hemodialysis. The patient's first 2 endomyocardial biopsies (EMB) post-transplant demonstrated grade 0R and 1R rejection, respectively (Figure 3). The third EMB showed grade 2R rejection in the setting of increasing pentobarbital dosing which had resulted in subtherapeutic sirolimus levels. Meanwhile, serial echocardiograms demonstrated declining left ventricular systolic function and persistent right ventricular failure. In response, the patient was treated with high-dose methylprednisolone and increased sirolimus and mycophenolate mofetil doses. Gradually, his left ventricular function recovered and repeat EMB showed return to grade 0R rejection.

Unfortunately, the patient continued to be in recurrent status epilepticus despite treatment with 10 different ASMs over the hospital course. In total, the patient achieved 48 hours of burst suppression 7 times over the course of approximately 2 months without ever being able to be weaned off ASMs. Repeat magnetic resonance imaging of the brain performed 6 weeks after seizure onset showed signal changes concerning for anoxic brain injury and in the setting of refractory status epilepticus was suggestive of irreversible brain injury. With the ASM infusions held, the patient did not demonstrate any brainstem reflexes. It was deemed that the patient had a terminal illness, and a decision was made with the family to withdraw care. Prior to withdrawal of care, the patient was on lacosamide, levetiracetam, pentobarbital, clobazam, perampanel, and phenobarbital. Autopsy of the brain revealed multiple microscopic foci of necrosis and focal vacuolization of

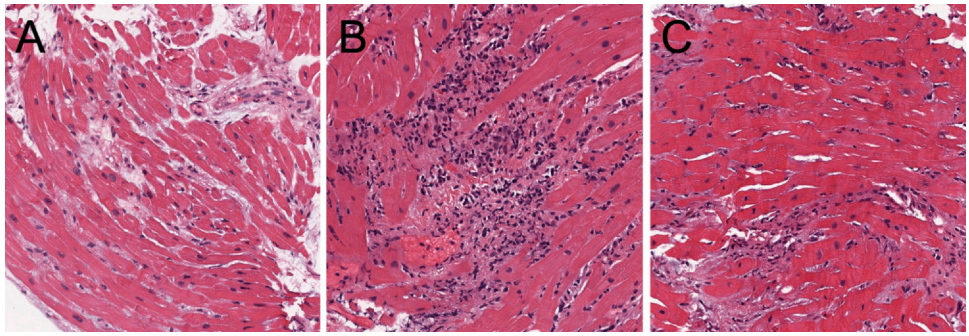

Figure 3 Endomyocardial biopsy showing (A) grade 0R rejection on postoperative day 14, (B) grade 2R acute cellular rejection on postoperative day 28 (preceding sirolimus levels were 10%-50% therapeutic range), and (C) grade 1R rejection on postoperative day 42 (preceding sirolimus levels were 40%-100% of therapeutic range).

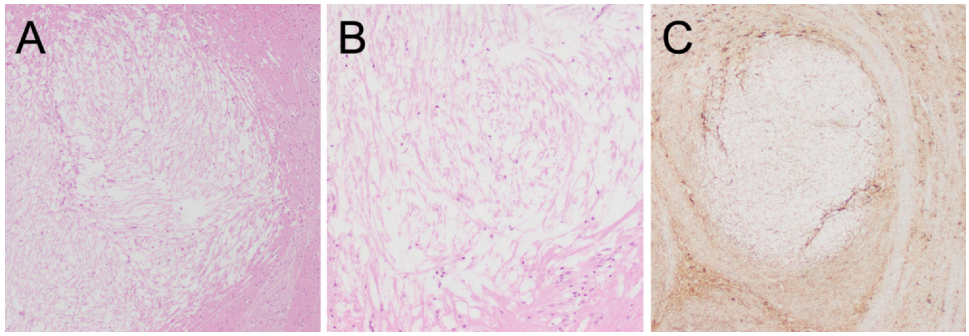

Figure 4 Hematoxylin and eosin stains of the pons showing multiple microscopic foci of necrosis and focal vacuolization of white matter at (A) 4× and (B) 20× magnification. (C) GFAP staining is negative in the areas of necrosis and white matter vacuolization at 10× magnification.

white matter in the pons consistent with multifocal necrotizing leukoencephalopathy (MNL) with pontine involvement (Figure 4).

Discussion

This case illustrates PRES as a devastating complication in the immediate post-transplant period, followed by super-refractory status epilepticus. PRES is often seen in the setting of renal failure and relative hypertension, but PRES has also been associated with the use of many immune-modulating agents. Classically this includes the calcineurin inhibitors, but has been described with mycophenolate mofetil,[3] IVIG,[4-7] antithymocyte globulin,[8] and monoclonal antibodies.[9,10] PRES can present with encephalopathy, headache, seizures, and vision changes but often presents as a forme fruste. The posterior aspect of the brain is not always affected, and the syndrome is not always reversible. PRES should be differentiated from the neurotoxicity (tremor and headache) or aseptic meningitis that can develop from calcineurin inhibitors or IVIG, respectively. The pathophysiology of PRES is hypothesized to be due to vascular leakage from either a rapid rise in arterial blood pressure or cytotoxin-mediated endothelial injury.[2] While there is no specific diagnostic criteria for PRES, it is characterized by unique radiologic findings showing posterior-predominant white matter vasogenic edema.[2] Furthermore, intracranial hemorrhage occurs in about 15% of PRES cases and is most common after bone marrow transplant.[11] Treatment of PRES is aimed at the underlying cause. In the case of immunosuppression-induced PRES, decreased dosing or discontinuation of the medication usually results in complete reversal of the neurologic and radiographic findings.[2] Our patient's characteristic neuroimaging findings with reversal after altering the immunosuppressive regimen and CSF profile not consistent with IVIG-related aseptic meningitis, made PRES the suspected cause of the patient's new onset seizures.

While our patient had resolution of PRES on neuroimaging, our patient continued to have refractory seizures of puzzling etiology. He was critically ill with septic shock and transplant rejection which likely lowered his seizure threshold. He also had intermittently subtherapeutic ASM levels which were eventually discontinued. Inability to achieve therapeutic levels of these drugs was likely caused by drug-drug interactions with his immunosuppressive agents. Although his positive IgM level for Chikungunya suggested acute infection, his lack of preceding clinical symptoms and hospitalization for over 3 months in a nonendemic country made active infection unlikely. Given its rare prevalence in the United States, Chikungunya serologies were not routinely tested prior to transplantation. Notably, our patient's autopsy revealed findings consistent with MNL. MNL is a rare disease usually localized to the pons and diagnosed on microscopy often on autopsy in the setting of immunosuppression and sepsis.[12,13] As a transplant patient in septic shock, our patient had both risk factors for developing MNL. Furthermore, MNL has been reported in another patient who was 3 months postcardiac transplant and in septic shock.[12] Although seizures are thought to arise from the cerebral cortex and not from deep structures, such as the pons, pontine MNL has been described in association with seizures in a few cases.[13] The cerebral cortex appeared normal on autopsy in our patient. Nonetheless, our case suggests that perhaps MNL should be considered in the differential diagnosis for refractory seizures in the setting of immunosuppression and sepsis. Lastly, our patient had atypical hemorrhagic PRES, yet studies have not shown a correlation between hemorrhage and refractory seizure predilection in this setting.[14]

Calcineurin inhibitor-induced PRES has been described after heart transplantation in prior case reports and case series (Table 1).[15-23] All cases occurred within 3 months of transplant with many cases occurring within the first 2 weeks. All patients presented with seizures except for 1 patient who presented with visual disturbance. The offending agent was identified as tacrolimus in 12 cases and cyclosporine in 4 cases. Tacrolimus and cyclosporine levels were not found to be supratherapeutic in any case.

Our case differs from previously described cases in a few ways. First, our patient did not receive calcineurin inhibitors. Since our patient received aggressive induction immunosuppression, the advanced heart failure and transplant nephrology teams felt that sirolimus could be safely used instead of tacrolimus to prevent acute allograft

Table 1 Cases of PRES After Heart Transplantation

Authors, year	Number of cases	Age and sex	Time after OHT	IS	Presentation	IS changes	ASM	Outcome
Dzudie et al. 2009[8]	2 patients	68 yo F	14 days	ATG (induction); CsA, MMF, prednisone	Hypertension, headache, visual disturbance, generalized seizures	CsA stopped, everolimus started	Clobazepam, gabapentin	Recovery
		19 yo M	44 days	CsA, AZA, prednisone	Headache, generalized seizures	CsA reduced	N/A	Recovery
Huenges et al, 2021[9]	1 patient	48 yo F	6 weeks	CsA, MMF, cortisone	Nausea, vomiting, generalized seizures	CsA reduced, everolimus started, cortisone increased	N/A	Recovery
Kapoor et al, 2017[10]	1 patient	37 yo F	16 days	Tacrolimus, MMF, prednisone	Generalized seizures	Tacrolimus stopped, sirolimus started, prednisone reduced	Diazepam, phenytoin	Recovery
Lanzino et al, 1997[11]	1 patient	22 yo F	5 days	ATG, methylprednisolone (induction); CsA, AZA	Focal seizures with secondary generalization	CsA increased (level was subtherapeutic)	Phenytoin	Recovery
Loar et al, 2013[12]	1 patient	10 yo M	10 days	ATG, methylprednisolone (induction); tacrolimus, prednisone, AZA	Hypertension, headache, complex focal seizures with secondary generalization	Tacrolimus reduced, intermittent ATG started	Lorazepam, levetiracetam	Residual speech difficulties, right-sided hemiparesis, homonymous hemianopia
Orgun et al, 2022[13]	3 patients	18 yo M	29 days	Tacrolimus ($n = 3$), no other IS mentioned	Hypertension ($n = 2$), seizures ($n = 3$)	N/A	N/A	Recovery ($n = 3$)
		13 yo M	3 days					
		17 yo F	5 days					
Park et al, 2016[14]	1 patient	50 yo M	4 days	Tacrolimus, no other IS mentioned	Generalized seizures	Tacrolimus reduced	N/A	Short-lived recovery with subsequent reversible cerebral vasoconstriction syndrome and residual bilateral leg and right arm paralysis
Ramirez et al, 2017[15]	1 patient	32 yo F	5 days	Tacrolimus, MMF, prednisone	Hypertension, headache, visual disturbance, generalized seizures	Tacrolimus stopped, CsA started	Lorazepam, divalproex sodium	Recovery
Turnaoglu et al, 2020[16]	5 patients	N/A	5 days to 3 months	Tacrolimus ($n = 5$), no other IS mentioned	Visual disturbance ($n = 1$), seizures ($n = 4$)	N/A	N/A	Recovery ($n = 5$)

Abbreviations: ASM, antiseizure medication; ATG, antithymocyte globulin; AZA, azathioprine; CsA, cyclosporine; F, female; IS, immunosuppression; M, male; MMF, mycophenolate mofetil; OHT, orthotopic heart transplant; yo, year-old.

rejection and preserve the transplanted kidney. While IVIG-induced PRES was the initial working diagnosis in our case, our patient also received mycophenolate mofetil and antithymocyte globulin. Thus, our patient had multiple reasons to have developed PRES and we cannot conclude whether IVIG was the definite or sole etiology. Furthermore, unlike our patient who ultimately died, prior cases described either complete or partial clinical recovery with most patients having return to baseline function. Only 1 other case described associated intracranial hemorrhage and this patient only had partial recovery with residual stroke symptoms.[19] A meta-analysis found hemorrhage to be significantly associated with worse clinical prognosis in PRES.[24]

This case illustrates multiple management dilemmas. First, a delicate balance must be maintained between the risk of acute rejection in a high-risk patient with inadequate immunosuppression vs the risk of PRES from the use of aggressive immunosuppression. Despite aggressive induction immunosuppression, our patient still went into acute rejection due to complications from ASM, which paradoxically were used to treat immunosuppression-induced PRES. Perhaps a less aggressive induction regimen should be considered for dual-organ transplant recipients with negative crossmatch testing, such as our patients. On the other hand, the induction regimen used is well established at multiple centers, including our institution, for dual-organ transplants without prior reports of the outcome seen in this patient. While tacrolimus is often considered the most protective maintenance immunosuppressive agent in the acute post-transplant period, our patient was started on sirolimus instead of tacrolimus. Sirolimus is usually not used in the first 6 months post-transplant due to its adverse effects on wound healing post-operatively and lesser degree of protection from rejection in the acute post-transplant phase. However, due to the poor function of the transplanted kidney and occurrence of PRES, sirolimus was favored over tacrolimus. Second, the volume of drug infusions is an important consideration in heart and kidney transplant patients and hemodynamics should be monitored closely to avoid allograft failure. Third, drug-drug interactions between ASMs and immunosuppressive agents must be considered. Among the 10 ASMs used throughout the treatment of status epilepticus in our patient, fosphenytoin, perampanel, clobazam, phenobarbital, and pentobarbital induce the hepatic metabolism of sirolimus, causing subtherapeutic immunosuppression levels and allograft rejection. Phenobarbital was maintained as an ASM despite its strong interaction with sirolimus because phenobarbital was the agent which yielded the best control of his seizures.

Conclusions

In conclusion, we describe a complex case of extended critical illness triggered by PRES in the immediate post-transplant period, leading to super-refractory status epilepticus of unclear etiology and acute rejection of the 2 transplanted organs. Brain autopsy showed findings of MNL. Multidisciplinary care and intrateam communication are integral to balance drug-drug interactions and iatrogenic complications with the appropriate hemodynamics, sufficient immunosuppression, and multiorgan system health of complex post-transplant patients in the intensive care unit. This balance must be aggressively pursued to improve morbidity and prevent mortality.

Author contributions

C.L.Y. made substantial contributions to the design of the work, acquisition and interpretation of data for the work, drafting the work, and reviewing it critically. H.H. made substantial contributions to the acquisition and interpretation of data for the work and drafting the work. F.R. made substantial contributions to the acquisition and interpretation of data for the work and reviewing it critically. J.M., E.J.B., and S.N. made substantial contributions to the interpretation of data for the work and reviewing it critically. N.T.R. made substantial contributions to the conception and design of the work, acquisition and interpretation of data for the work, and reviewing it critically. All authors approve of the final version for publication and agree to be accountable for all aspects of the work.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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