American Society of Nephrology Quiz and Questionnaire 2014: Transplantation

Michelle A. Josephson, Mark A. Perazella,† and Michael J. Choi‡*

Abstract

The Nephrology Quiz and Questionnaire remains an extremely popular session for attendees of the Annual Kidney Week Meeting of the American Society of Nephrology. Once again, the conference hall was overflowing with audience members and eager quiz participants. Topics covered by the expert discussants included electrolyte and acid-base disorders, glomerular disease, ESRD/dialysis, and transplantation. Complex cases representing each of these categories along with single best answer questions were prepared and submitted by the panel of experts. Before the meeting, program directors of United States nephrology training programs and nephrology fellows answered the questions through an internet-based questionnaire. During the live session, members of the audience tested their knowledge and judgment on a series of case-oriented questions prepared and discussed by experts. They compared their answers in real time using audience response devices with the answers of the nephrology fellows and training program directors. The correct and incorrect answers were then discussed after the audience responses and the results of the questionnaire were displayed. As always, the audience, lecturers, and moderators enjoyed this educational session. This article recapitulates the session and reproduces its educational value for the readers of *CJASN*. Enjoy the clinical cases and expert discussions.

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Introduction: Michael J. Choi and Mark A. Perazella (Comoderators)

For most American Society of Nephrology (ASN) Kidney Week attendees, case-based clinical nephrology talks are the most exciting venues of the meeting. The Nephrology Quiz and Questionnaire (NQ&Q) is the essence of clinical nephrology and represents what drew many of us into the field of nephrology. This year's NQ&Q in Philadelphia, with full-house attendance, was no exception. The discussants prepared vignettes of puzzling cases, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of various areas of nephrology. These eight interesting cases were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her discussion of the cases.

In this NQ&Q, Michelle Josephson presents her two challenging transplant cases. The audience responses are reviewed along with the responses of training program directors and nephrology fellows obtained before the meeting. Michelle Josephson reviews essential clinical, laboratory, and imaging data and walks the reader through the diagnosis and appropriate management of two challenging transplant cases with unusual complications. Overall, an educational experience was had for all who attended the session. We hope that this distillate from Philadelphia will serve the *CJASN* readers well and provide some fresh insights into the complexity and vibrancy of clinical nephrology for those who were unable to attend the meeting.

Transplantation Case 1: Michelle A. Josephson (Discussant)

A 50-year-old man with ESRD secondary to diabetes mellitus and hypertension received a deceased donor kidney transplant. Thymoglobulin was administered for induction immunosuppression. His kidney functioned immediately, and his creatinine dropped from 5.8 to 1.4 mg/dl within 5 days post-transplant. By 4 months, his hematocrit was up to 40.2% without the use of any erythropoiesis-stimulating agents. The patient was medically stable: his sustained post-transplant hyperparathyroidism was controlled, hypertension was treated, hyperlipidemia was managed, and diabetes mellitus was regulated. He was seen in the clinic on a monthly basis and did not experience any complications until 9 months post-transplant, at which time he presented to the clinic complaining of fever, fatigue, and lightheadedness. His medications included tacrolimus, mycophenolate mofetil (MMF), prednisone, trimethoprim sulfamethoxazole, amlodipine, minoxidil, carvedilol, aspirin, atorvastatin, cinacalcet, insulin, pantoprazole, and cholecalciferol. Review of systems was notable for loose stool and right upper quadrant pain with defecation. He denied black or overtly bloody stools or yellowing of his eyes or skin. On examination, he was alert and oriented. His supine BP was 110/60 mmHg with a heart rate (HR) of 62 beats/min, and his standing BP after 2 minutes was 100/60 mmHg with an HR of 68 beats/min. His left forearm arteriovenous fistula was patent. The kidney transplant in his right lower quadrant was nontender. Laboratory values are displayed in Table 1.

He was anemic. As depicted in the solid portion of the hematocrit curve in Figure 1, his hematocrit had increased during the first 3–4 months after transplant and then,

Table 1. Laboratory findings

Hematology	Chemistry
WBC: 7.3×10^3 per 1 μl	Sodium: 141 mEq/L
Hemoglobin: 8.0 g/dl	Potassium: 4.5 mEq/L
Hematocrit: 24.5%	Chloride: 109 mEq/L
MCV: 87.2 fl	Bicarbonate: 21 mEq/L
MCH: 28.5 pg	BUN: 24 mg/dl
MCHC: 32.7 g/dl	Creatinine: 1.4 mg/dl
Platelet count: 247×10^3 per 1 μl	Glucose: 128 mg/dl
	Calcium: 9.6 mg/dl
	Phosphorous: 3.1 mg/dl
	Magnesium: 1.6 mg/dl

WBC, white blood cell count; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

plateaued followed by a precipitous drop after about 7 months postoperation. The patient's hematocrit was documented as low as 24.5%. He underwent an anemia evaluation. Results are shown in Table 2. Of note are the adequate iron stores and low reticulocyte count consistent with an underproduction anemia. His blood smear was unremarkable. Two years earlier, he had undergone colonoscopy and esophagogastroduodenoscopy (EGD) studies at an outside hospital. These procedures had not revealed any evidence for malignancy, ulcerations, or bleeding. One benign polyp had been removed. After reviewing his anemia laboratory evaluation, the patient's MMF and trimethoprim sulfamethoxazole were held.

Question 1a

Testing for which of the following may be most helpful in evaluating the underproduction anemia?

A. *Cytomegalovirus (CMV)*
B. *BK virus*
C. *Parvovirus B19*
D. Clostridium difficile
E. *JC virus*

Discussion of Question 1a

Between 1% and 12% of recipients of kidney transplants are reported to have symptomatic parvovirus infection during the first post-transplant year. The virus targets erythroid progenitors in the bone marrow, causing acute anemia (choice C is correct) (Figure 2). Our patient's parvovirus B19 DNA PCR was positive, although IgM and IgG antibodies to parvovirus were not detected.

Parvovirus is a nonenveloped single-stranded DNA virus. Identified in 1975, it was first associated with human disease in 1981 (1,2). Infection is common, usually occurring during childhood. Approximately 70%–80% of adults have serologic evidence of past infection (3). Transmission primarily occurs by inhalation, although parvovirus can also be acquired through vertical transmission from mother to fetus, transfusion of blood products, and bone marrow and solid organ transplantation (4). Parvovirus B19 targets the erythroid progenitors in the bone marrow, binding to blood group P antigen. Blood group P antigen is abundant in erythroblasts (5). Viremia can last several days, during which time the reticulocyte count can plummet to zero. Clinical manifestations cover the spectrum from benign to life threatening. In children, infection often manifests as erythema infectiosum (fifth disease) with low-grade fever, malaise, slapped-cheek facial appearance, and a lacy maculopapular rash on the trunk and limbs. Adults can present with sudden onset of symmetric polyarthralgia or polyarthritis in a rheumatoid-like pattern with ankle, knee, wrist, and metacarpophalangeal joint involvement. The anemia is normochromic, normocytic, lacking reticulocytes, and resistant to erythropoietin therapy (4).

The first case report of parvovirus B19 in a recipient of a kidney transplant was published in 1986 (6). Routes of infection for recipients of transplants include transfusion and viral reactivation as well as donor-derived disease (7). The lack of effective humoral and/or cellular immune systems in recipients of transplants predisposes them to delayed viral clearance. Acute anemia and chronic pure red cell aplasia are the most common manifestations seen in recipients of solid organ transplants. Recipients of transplants often lack a rash and arthritis (4).

CMV infection may aggravate anemia; however, its effect is predominately one of leukopenia and thrombocytopenia

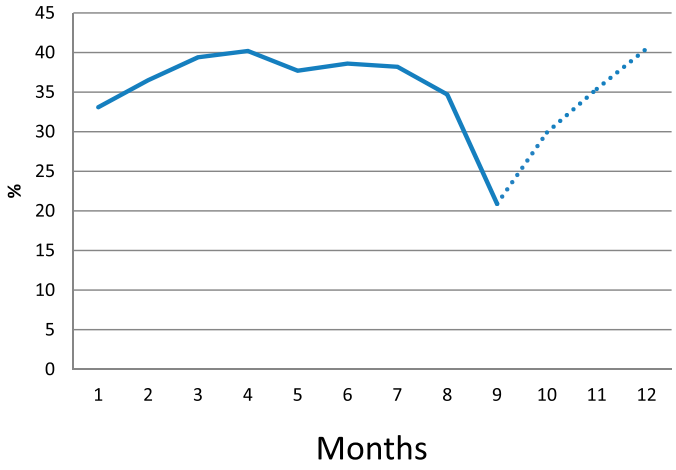

Figure 1. | **Post-transplant hematocrit.**

Table 2. Anemia laboratory evaluation

Laboratory Values	Reference Range
MCV (fl): 86.7	81–99
MCH (pg): 28.3	26–33
MCHC (g/dl): 32.7	32–35
Iron (μg/dl): 241	40–150
TIBC (μg/dl): <253	230–430
Ferritin (ng/ml): 1686	20–300
Haptoglobin (mg/dl): 49	51–192
Reticulocyte count (%): 0.2	0.5–1.5
Absolute reticulocyte count (K/μl): 5.06	22–89
Reticulocyte production index: 0	
Direct antiglobulin test: negative	
LDH (units/L): 174	116–245
Stool for occult blood: negative	

MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TIBC, total iron-binding capacity; LDH, lactic dehydrogenase.

rather than anemia (8). Consequently, testing for CMV is less helpful in evaluating the anemia (choice A is incorrect). Polyoma viruses BK and JC do not typically cause anemia, although leflunomide treatment for BK has been reported to cause hemolytic anemia (9) (choices B and E are incorrect). *C. difficile* is characterized by leukocytosis rather than anemia (10) (choice D is incorrect).

Question 1b

Which of the following is most effective in treating Parvovirus B19?

A. *Intravenous Ig (IVIG)*
B. *Cidofovir*
C. *Valganciclovir*
D. *Acyclovir*
E. *Immunosuppression reduction*

Discussion of Question 1b

Immunocompetent patients do not usually require treatment for parvovirus infection, because their symptoms are temporary and they can mount an immune response against the virus. Individuals who are immunocompromised may have diminished or absent parvovirus B19–directed antibody responses (11), which was the case with our patient, who had neither detectable IgM nor IgG. Consequently, although immunosuppression reduction may be helpful, it is not usually sufficient for effective management. Immunosuppressed patients with parvovirus B19 benefit most from active treatment. Commercial Ig (IVIG) offers a significant source of anti-B19 antibodies (4). Although clinical trials have not been performed to establish its efficacy, case reports and case series suggest that IVIG is most effective in treating parvovirus B19 (12–15) (choice A is correct) (Figure 3).

At the time of the NQ&Q, the antiviral effect of cidofovir against parvovirus B19 had not been described. Subsequent to the ASN NQ&Q session, a study has been published indicating that cidofovir can inhibit parvovirus B19 replication *in vitro* (16). The *in vivo* antiviral efficacy of cidofovir against parvovirus B19 has not been described (choice B is incorrect). Choices C and D are not correct because of the lack of published studies examining the anti–parvovirus B19 activity of these antiviral medications. Immunosuppression reduction is a reasonable adjunctive measure. In clinical practice, it may not be sufficient to control parvovirus B19 replication (choice E is incorrect).

Clinical responses from IVIG treatment include reticulocytosis, increased hemoglobin levels, and declines in serum viral DNA. Our patient received two infusions of IVIG several days apart at doses of 1 g/kg each. One month later, his parvovirus B19 titer was still positive, and another two doses of IVIG (1 g/kg) were given. Our patient's MMF was also held. The response that he experienced is depicted in the dashed part of the hematocrit curve in Figure 1.

Six months later, he presented with 3–4 days of fatigue, fever, shaking chills, nausea, joint pains, and an erythematous nonpalpable petechial rash on his shins and ankles. His hematocrit was 30.4%. Parvovirus B19 had not yet cleared. Even with the use of IVIG, complete eradication of viremia may not occur, and relapses can occur (11). Our

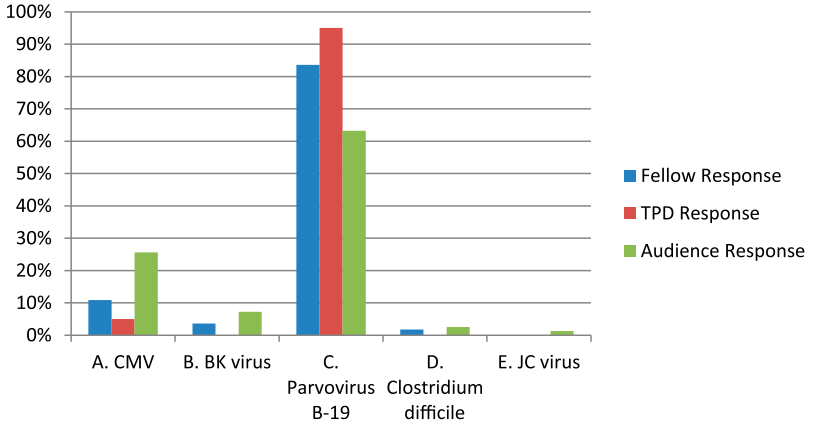

Figure 2. | Answer for Case 1, Question 1a. Testing for which of the following may be most helpful in evaluating the underproduction anemia? The correct answer is C. CMV, cytomegalovirus; TPD, training program directors.

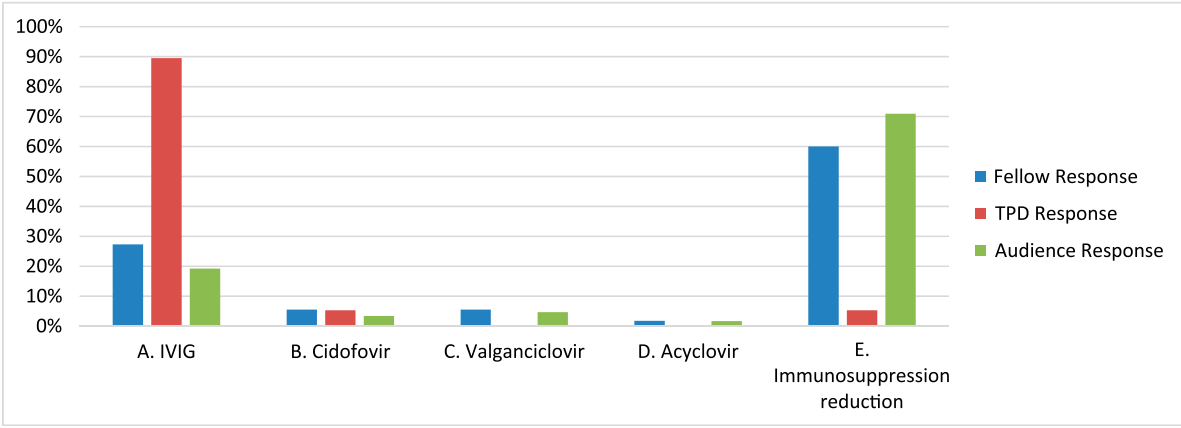

Figure 3. | **Answer for Case 1, Question 1b. Which of the following is most effective in treating Parvovirus B19?** The correct answer is A. IVIG, intravenous Ig; TPD, training program directors.

patient's rash and joint pains were most likely secondary to immune complex formation. He was given more IVIG. His symptoms subsided, and hematocrit increased.

Transplantation Case 2: Michelle A. Josephson (Discussant)

A 52-year-old woman with a history of hypertensive nephrosclerosis received a deceased donor kidney transplant after 7 years of hemodialysis. The allograft functioned immediately. She received thymoglobulin for induction treatment. She was discharged on postoperative day 4, by which time her serum creatinine had dropped from 5.2 to 2 mg/dl. Medications at discharge included tacrolimus, MMF, prednisone, valganciclovir, fluconazole, trimethoprim sulfamethoxazole, famotidine, simvastatin, and furosemide.

She felt well for the first 2 weeks after surgery, after which time she was readmitted to the hospital with pancreatitis and a loculated peripancreatic fluid collection that required placement of a percutaneous drain. One week after discharge, she returned to the clinic complaining of increasing drain output and abdominal pain. Her creatinine was 2.6 mg/dl (up from a nadir of 1.4 mg/dl at the time of her last hospital discharge). On physical examination, she had pitting edema up to her midthighs. Her tacrolimus trough was 10 ng/ml. The patient was readmitted, and an EGD was performed to evaluate for the possibility of peptic ulcer disease or gastritis.

Later on the day of the EGD, the patient was found to have an altered mental status. She was unresponsive to sternal rub, not tracking with her eyes, and not following commands. She was afebrile, oxygen saturation was over 94%, BP was 138/84 mmHg, HR was in the 120s, and her glucose was 220. Naloxone was administered, after which she had a tonic clonic seizure. She was intubated and transferred to the intensive care unit. On neurologic examination, she was lethargic and opened her eyes to voice but did not follow commands. Cranial nerve examination revealed that she had a dysconjugate gaze, her pupils were 6 mm bilaterally and reactive to light, and she blinked to threat bilaterally. Her tongue was midline. On motor examination, her muscle bulk was normal, although her overall muscle tone was reduced. Her left upper extremity had spontaneous movement; otherwise, no movement was observed. She did not respond to noxious stimuli in any extremity, and she was hyporeflexive throughout. Toes were downgoing bilaterally on Babinski testing. A lumbar puncture was performed. The opening pressure was 49 mm H_2O (normal pressure is 60–250 mm H_2O). Her cerebrospinal fluid laboratory values are depicted in Table 3. Results of additional laboratory testing to evaluate her altered mental status included a nonreactive rapid plasma reagin, thyroid-stimulating hormone of 2.75 μunits (normal is 0.3–4 μunits), B12 of 484 pg/ml (normal is 240–900 pg/ml), folate of 4.2 ng/ml (normal is 4–26 ng/ml), ammonia of 62 μg/dl (normal is 20–70 μg/dl), and lactate of 1.3 mEq/L (normal is 0.7–2.1 mEq/L).

An electroencephalogram study revealed frequent diffuse polyspike and sharp wave discharges mostly posteriorly. In addition, there were frequent periods of electrodecrement lasting up to 2 seconds and diffuse slowing consistent with moderate to marked encephalopathy. No seizures were recorded.

A computed tomography (CT) scan was obtained (Figure 4A). If the patient had undergone a magnetic resonance imaging scan, it would likely have shown the findings shown in Figure 4B.

Question 2A

What is the most likely diagnosis?

A. *Posterior reversible encephalopathy syndrome (PRES)*
B. *CMV encephalitis*
C. *Progressive multifocal leukoencephalopathy (PML)*
D. *Herpes simplex virus (HSV) encephalitis*
E. *JC virus encephalitis*

Table 3. Cerebrospinal fluid results

Cell Counts, Glucose, and Protein
23 WBCs (0–5) 6 RBCs 87% PMNs (0–6) 2% Lymphocytes (40–80) 11% Monocytes (15–45) Protein: 51 mg/dl (15–45) Glucose: 156 mg/dl (50–70)

WBC, white blood cell; RBC, red blood cell; PMN, polymorphonuclear leukocyte.

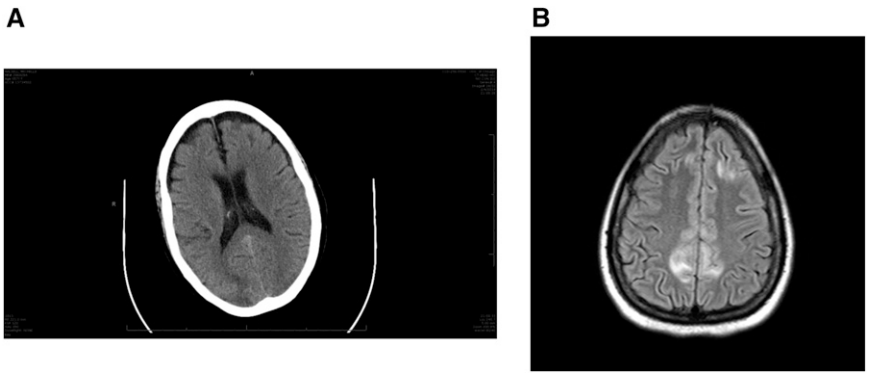

Figure 4. | **Brain imaging studies.** (A) Head CT. (B) Brain MRI. CT, computed tomography; MRI, magnetic resonance imaging.

Discussion of Question 2A

This patient has developed PRES (also referred to as reversible posterior cerebral edema syndrome, posterior leukoencephalopathy syndrome, hyperperfusion encephalopathy, and brain capillary leak syndrome; choice A is correct) (Figure 5). PRES is a form of acute encephalopathy caused by vasogenic edema in the posterior cerebral hemispheres. It is a clinicoradiologic diagnosis. Modern neuroimaging modalities are sensitive to changes in the distribution of white matter edema in the posterior circulation, even early on (17).

The introduction of neuroimaging studies revealed that some individuals with an altered mental status had brain edema, predominantly in the posterior area of white matter. These findings were often associated with a variety of underlying clinical conditions, including hypertensive encephalopathy and immunosuppression. Wide recognition of the syndrome occurred in 1996 with the publication of a case series in the *New England Journal of Medicine* describing 15 hospitalized patients with clinical findings that included headaches, vomiting, confusion, seizures, cortical blindness and other visual abnormalities, and motor dysfunctions (18). CT and magnetic resonance imaging studies in these individuals revealed predominately white matter abnormalities, likely indicating edema in the posterior regions of the cerebral hemispheres (18). The clinical and imaging abnormalities were reversible (18).

Clinical features associated with this syndrome include encephalopathy with a headache, altered sensorium, seizures, and cortical blindness. A seizure is often the presenting symptom. Neuroimaging studies reveal symmetric white matter edema in the posterior cerebral hemispheres, particularly in the parietooccipital regions. The syndrome was initially characterized as always reversible, with neuroimaging studies returning to normal, often within weeks, with control of BP and withdrawal of inducing drugs. Although not common in recipients of transplants, it has been described in this population (19).

CMV encephalitis is very rare in recipients of solid organ transplants (20). Furthermore, our patient was receiving prophylaxis against CMV, making CMV encephalitis less likely (choice B is incorrect). PML can occur after transplantation, although rarely, and the radiologic findings may mimic those found in PRES (21). However, the mean time to diagnosis is 1 year, making our patient's neurologic presentation early for the diagnosis and PML less likely (22) (choice C is incorrect) Furthermore, the definitive diagnosis is on the basis of a brain biopsy, which our patient did not

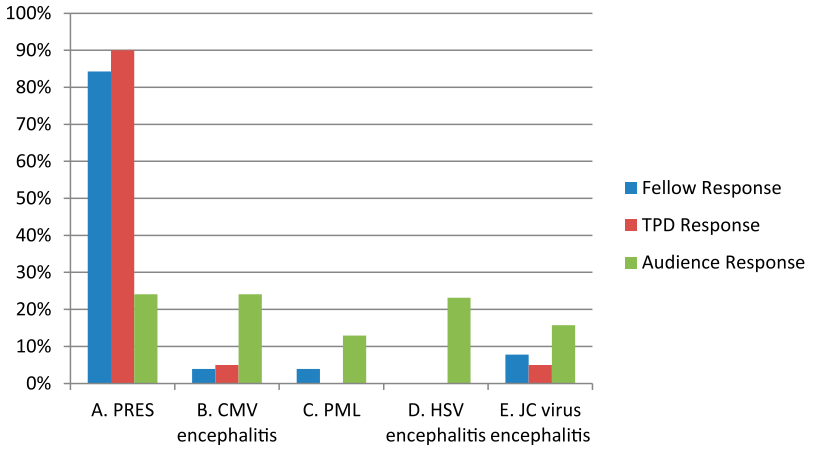

Figure 5. | **Answer for Case 2, Question 2a. What is the most likely diagnosis?** The correct answer is A. CMV, cytomegalovirus; HSV, herpes simplex virus; PRES, posterior reversible encephalopathy syndrome; PML, progressive multifocal leukoencephalopathy; TPD, training program directors.

Table 4. Cerebrospinal fluid studies

Infection Work-Up
Cultures: negative No VZV DNA No HSV No EBV No CMV No JC Negative enterovirus

VZV, varicella zoster virus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; CMV, cytomegalovirus.

undergo. Although HSV reactivation occurs early post-transplant, encephalitis is a rare event (23), and our patient was receiving prophylaxis with ganciclovir. Thus, HSV encephalitis is less likely (choice D is incorrect). JC virus is the cause of PML, and thus, JC virus encephalopathy should be considered similarly to PML; as noted above, it is less likely than PRES (choice E is incorrect).

Results of cultures and viral studies obtained on her cerebrospinal fluid are depicted in Table 4.

Question 2B

Which of our patient's medications has most commonly been associated with PRES?

A. *Valganciclovir*
B. *Famotidine*
C. *Tacrolimus*
D. *Simvastatin*

Discussion of Question 2B

Case reports and review articles of PRES occurring post-transplant have implicated calcineurin inhibitors in the development of PRES (17,24–27) (choice C is correct) (Figure 6). Valganciclovir, famotidine, and simvastatin have not been identified in the literature as predisposing to the development of PRES (choices B–D are incorrect).

The explanation for the association between calcineurin inhibitors and PRES is the direct toxicity of the immunosuppressants on vascular endothelium leading to capillary leakage and blood-brain barrier disruption, which may then trigger vasogenic edema. The cause of this leak may be sudden elevations in systemic BPs exceeding the autoregulatory capability of the brain vasculature, leading to vasodilation and vasoconstriction occurring in areas with perturbations of the blood-brain barrier (17,24–26). Case reports have also implicated rapamycin as predisposing to PRES. Akin to the case of calcineurin inhibitors, rapamycin-associated PRES is a consequence of vasculopathy with abnormal cerebral perfusion and vasogenic brain edema (28).

Risk factors that have been identified in PRES include significant fluid overlaod, mean BP >25% above baseline, and a creatinine >1.8 mg/dl. Our patient was volume overloaded. Her systolic BP at the time of hospitalization for the EGD was, at times, as high as 145 mmHg whereas in the initial weeks after the transplant, her systolic BP ran between 105 and 110 mmHg. Although 145 mmHg systolic BP is not particularly high, it was higher than her baseline. Whether these recorded BP elevations contributed to her developing PRES is unclear. Our patient had AKI with a creatinine of 2.6 mg/dl when she was admitted (18).

When originally described in 1996, PRES was defined as reversible within weeks (18). At least one case report describes a patient with a history of PRES left with permanent neurologic deficits, possibly a consequence of delayed intervention (24). Over the many months since her seizure, our patient has slowly improved, although severe neurologic impairments, including visual deficits, persist. She has been off of calcineurin inhibitors since presentation, and mammalian target of rapamycin inhibitors were never started. Her last CT scan showed improvement.

Disclosures

None.

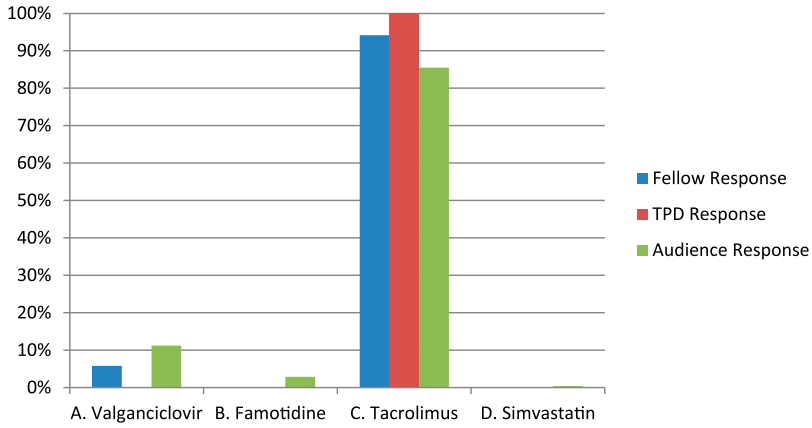

Figure 6. | Answer for Case 2, Question 2b. Which of our patient's medications has most commonly been associated with posterior reversible encephalopathy syndrome? The correct answer is C. TPD, training program directors.

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