American Society of Nephrology Quiz and Questionnaire 2013: Transplantation

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Abstract
The nephrology quiz and questionnaire remains an extremely popular session for attendees of the Annual Meeting of the American Society of Nephrology. As in past years, the conference hall was overflowing with interested audience members. Topics covered by 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 by a panel of experts. Before the meeting, program directors of United States nephrology training programs answered questions through an Internet-based questionnaire. A new addition to the nephrology quiz and questionnaire was participation in the questionnaire by nephrology fellows. To review the process, members of the audience test their knowledge and judgment on a series of case-oriented questions prepared and discussed by experts. Their answers are compared in real time using audience response devices with the answers of nephrology fellows and training program directors. The correct and incorrect answers are then briefly discussed after the audience responds, and the results of the questionnaire are displayed. This article recapitulates the session and reproduces its educational value for the readers of CJASN. Enjoy the clinical cases and expert discussions.


Introduction: Mark A. Perazella and Michael J. Choi (Comoderators)
For most American Society of Nephrology 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 Atlanta, with full-house attendance, was no exception. Each of the discussants prepared vignettes of puzzling cases, each illustrating 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 expert American Society of Nephrology faculty. Subsequently, each discussant prepared a manuscript summarizing his or her discussion of the cases, which serves as the main text of this article.

In this NQ&Q, Dr. Michelle Josephson presents her 2 challenging transplant cases and discusses the appropriate diagnostic and management approach for these complicated cases. The audience responses are reviewed along with the training program director and nephrology fellow responses obtained prior to the meeting, giving an interesting perspective into the thought processes of nephrologists with varying levels of training and experience. Dr. Josephson reviews essential clinical, laboratory, and renal pathology data, and walks the reader through the diagnosis and appropriate management of two challenging transplant cases with unusual complications. Overall, it was an educational experience for all who participated. We hope that this distillate from Atlanta will serve CJASN subscribers 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)
In October of 2012, a 66-year-old Laotian man who immigrated to the United States after spending 2 years in a refugee camp received a deceased donor kidney transplant. His medical history included ESRD secondary to hypertension, hyperlipidemia, and chronic hepatitis B. He started dialysis in 2004, at which time he was also found to have a mediastinal mass that was subsequently diagnosed as a thymoma. In 2007, while being evaluated for kidney transplantation, the mass was noted to be enlarging. Although the routine pre-transplant screening, including stress test, echocardiogram, colonoscopy, and tuberculin skin test (TST), were all acceptable, the thymoma was a contraindication to activation on the kidney transplant waiting list. To be transplant-eligible, the patient agreed to surgical resection. He received adjunctive radiation therapy after resection. Approximately 5 years after the thymectomy, he was activated on the transplant list.

Post-transplant immunosuppression included induction thymoglobulin and maintenance therapy with prednisone, tacrolimus, and mycophenolate mofetil. The kidney worked immediately. Four days after the transplant,
an infectious disease evaluation was obtained when donor blood cultures were reported to be growing *Staphylococcus lugdunensis*. Therapy with intravenous vancomycin was initiated followed by conversion to cefepime. He did well for the first few months after transplant, except for persistent hyperparathyroidism and BK viruria. His baseline creatinine was 1.2 mg/dl.

Approximately 3 months post-transplant, he developed a nonproductive cough associated with right flank pain that was felt to be musculoskeletal in origin. It persisted, and after 2 weeks, he was evaluated at an outside emergency room, where a computed tomography (CT) scan of the abdomen and pelvis was obtained and interpreted as follows: “Transplanted kidney with surrounding perinephric stranding; pyelonephritis cannot be excluded; no hydrenephrosis or stones; no appendicitis, no colitis, no diverticulitis.” He was given levofloxacin and transferred to the transplant center for additional management, where on arrival, he was given cefepime for treatment of pyelonephritis. On physical examination, he was found to have a large area of swelling and tenderness in the right posterior rib cage area, which was fluctuant but without an obvious area to drain. Blood cultures were negative for bacteria, but viral studies of the blood revealed 17,000 copies/ml BK virus by PCR. His calcium was 9.7 mg/dl, phosphorous was 2.7 mg/dl, and parathyroid hormone was 76 pg/ml. A CT scan revealed a 7.2×3.9-cm mass encasing a lower right posterior rib with bony destruction (Figure 1), which was a new finding from a CT scan obtained 7 months before. An enlarged right hilar lymph node and scattered mediastinal nodes were also noted. A positron emission tomography scan showed multiple new markedly hypermetabolic mediastinal lymph nodes. A large markedly hypermetabolic right flank mass with destruction of the 11th rib was also seen.

The patient underwent resection of the right chest wall mass. Samples from surgery were sent to pathology and microbiology.

**Question 1A**

What is the most likely diagnosis in this patient?

A. Recurrent thymoma
B. Post-transplant lymphoproliferative disorder (PTLD)
C. Malignant BK nodule
D. Extrapulmonary tuberculosis (TB)
E. Brown tumor

**Discussion of Case 1, Question 1A**

A rapidly growing painful flank mass in a recently transplanted patient is uncommon, and it evokes a broad differential diagnosis that spans the gamut from malignancy to infection. In these situations, putting the patient’s past history into context is important. With this in mind, extrapulmonary TB is the mostly likely diagnosis in our patient, and it was the cause of the mass (choice D is correct) (Figure 2). The acid-fast bacillus smear of the surgical specimen sample was positive for acid-fast bacilli, and the culture grew *Mycobacterium tuberculosis*. His sputum sample also had 4+ acid-fast bacilli.

Our patient’s largest risk factor for TB was his country of origin (Laos), a highly endemic area (1). Furthermore, he spent years in a refugee camp, making his risk for latent TB even greater. The period of highest risk for TB reactivation in foreign-born residents of the United States is the first few years after arrival, although the risk persists for many years (1–3). His immunosuppression also predisposed him to reactivation of latent TB. Corticosteroids can lead to reactivation of TB (1), and tacrolimus has also been implicated (4). Although not applicable to our patient, cyclosporine hastens presentation (5). The temporal course of our patient’s case, with disease presentation within the first post-transplant year, is consistent with what others have observed (1,6) (Figure 3). Atypical presentations are common in solid organ transplant recipients (7), with frequent occurrence of extrapulmonary and disseminated TB (1). Most cases consist of reactivation, in which latent disease had not been appreciated. Even when the TST is performed, it may not be a useful screening tool in patients with ESRD, because its sensitivity and specificity are on the order of 50% (6). False positives may occur from exposure to non-TB mycobacteria or prior Bacille Calmette–Guerin vaccination. False negatives may occur from cutaneous anergy (5). The latter is the case for our patient. He had been given yearly skin tests in his dialysis unit, all of which were negative, in hindsight, because of anergy. New TB tests have been developed that can be used in lieu of the TST. These tests, so-called IFN-γ release assays (IGRAs) use ELISAs (e.g., QuantiFERON) or enzyme-linked immunosorbents spots (e.g., T-SPOT.TB) to measure INF-γ release of T cells after stimulation with *M. tuberculosis*–specific antigens. A systemic review of the literature compared...
the performance of TST and IGRA for detecting latent TB. There were insufficient data to compare and contrast the performances of these two tests. The review suggested that, compared with the TST, the ELISA-based IGRA is more sensitive and specific in the setting of ESRD [8].

TB is a major cause of morbidity and mortality worldwide. In 2010, there were an estimated 8.8 million new cases, resulting in 1.1 million deaths. In solid organ transplant recipients, the prevalence of TB ranges between 0.2% and 15% depending on the geographic region (with renal transplant recipients on the Indian subcontinent at the high end and North American populations at the low end). These ranges are 20–74 times greater than that reported in the general population [5–7]. Studies support the benefit of chemoprophylaxis with isoniazid (INH) for renal transplant recipients at risk for active infection, despite its known potential for hepatotoxicity, neurotoxicity, and drug-drug interactions. Prophylaxis should be given to individuals who are at highest risk for developing active TB but not those individuals at low risk to avoid complications in individuals unlikely to develop disease [5,6].

The Kidney Disease Improving Global Outcomes Clinical Practice Guideline for the Care of Kidney Transplant Recipients acknowledges that dialysis and transplant patients frequently have false negative TSTs. The guideline notes that some experts recommend INH treatment in select patients with a negative TST, including those patients with a history of active TB who were not adequately treated, those patients with radiographic evidence of previous TB but without prior treatment, and those patients who receive an organ from a donor with a history of a positive TST. The guideline does not address the issue of patients (like ours) who come from endemic regions but have negative TSTs [9].

As mentioned above, malignancy must be considered in transplant recipients. Given his history, it is important to consider that thymomas can recur even years after treatment. Our patient could develop recurrent thymoma, especially because he received adjuvant radiotherapy for the disease, indicating that resection alone was not felt to be sufficient treatment. However, thymoma is a largely indolent tumor, and our patient’s mass developed quickly after transplant. The rapidity of the onset of the lesion makes recurrent thymoma, while not impossible, less likely (choice A is incorrect). The incidence of thymomas is not increased in solid organ transplant recipients, indicating that there is no reason to think that immunosuppression would increase the likelihood of a recurrence or alter its usually slow tempo of growth [10,11].

Post-transplant lymphoproliferative disorder is another malignancy that must always be considered. It is the most common malignancy complicating solid organ transplantation (excluding nonmelanoma skin cancer and in situ cervical cancer), accounting for approximately 20% of all cancers. More than one half of PTLD presents with extranodal masses. Involved organs include the gastrointestinal tract, lungs, skin, liver, central nervous system, and the allograft itself [12]. A mass encasing a rib is not usually seen. Although PTLD could occur and should be included on the differential diagnosis list, given the patient’s history, it is not the most likely diagnosis [13] (choice B is incorrect).

A malignant BK nodule is an entity that I fabricated for this quiz, and thus, it cannot be the correct answer and...
should not be in the differential diagnosis (choice C is incorrect).

Bone and mineral metabolism derangements afflict patients with end stage kidney disease and may continue after transplant. A Brown tumor is a benign bone lesion occurring from excess osteoclast activity caused by primary or secondary hyperparathyroidism. Brown tumors are usually radiolucent on x-ray from subperiosteal and subchondral resorption. With transplantation of a well functioning kidney allograft, hyperparathyroidism improves or persists, but it does not worsen. De novo development of a Brown tumor is unlikely. Brown tumors can occur in ribs, and an atypical Brown tumor resembling a malignancy has been reported (14). Occurrence of a Brown tumor after transplant is rare and given our patient’s parathyroid hormone level, is not a likely diagnosis (choice E is incorrect).

Returning to our patient: treatment with rifampin, isoniazid, pyrazinamide, and ethambutol was initiated for TB, and mycophenolate mofetil was discontinued to manage the BK viremia.

**Question 1B**
How might TB treatment affect the tacrolimus level?

- A. Decrease the tacrolimus level, because rifampin is a CYP3A4 inducer
- B. Increase the tacrolimus level, because INH is a CYP3A4 competitor
- C. Decrease the tacrolimus level, because ethambutol is a CYP3A4 inducer
- D. No marked change, because by using INH and ethambutol, they will cancel each other’s effect
- E. Increase the tacrolimus level, because pyrazinamide is a CYP3A5 inducer

**Discussion of Case 1, Question 1B**
Tacrolimus is metabolized by CYP3A4, a member of the cytochrome P450 mixed function oxidase system; treatment with rifampin will induce this enzyme and decrease tacrolimus levels (choice A is correct) (Figure 4).

The cytochrome P450 superfamily is a large and diverse group of enzymes that catalyzes the oxidation of organic substances. CYP3A4 is involved in the oxidation of the broadest range of substrates of all the cytochromes. CYP3A4 is present in the largest quantity of all the cytochromes in the liver. The rate of metabolism of tacrolimus is influenced by the presence of other drugs that are also broken down by CYP3A4. Any agent that induces the enzyme will increase the enzyme activity and lead to enhanced tacrolimus metabolism and reduced circulating levels. By contrast, any medication that competes for CYP3A4 will reduce the enzyme’s activity, and an increase in circulating tacrolimus levels will follow (15).

Our patient was placed on four new medications: INH, ethambutol, pyrazinamide, and rifampin. Clinical studies have shown that INH, ethambutol, and pyrazinamide do not affect calcineurin inhibitor levels (16–18) (choices B, C, D, and E are incorrect). Rifampin is clinically the most important agent. It induces CYP3A4 in the liver, causing a drop in calcineurin inhibitor levels (19). After rifampin was started, our patient’s tacrolimus dose was increased to counteract the accelerated breakdown of the drug caused by rifampin.

**Transplantation Case 2: Michelle A. Josephson (Discussant)**
A 30-year-old man (blood type AB) with ESRD secondary to hypertension received a deceased donor kidney. After initial delayed graft function, our patient did well and had a baseline serum creatinine of 1.9 mg/dl with no proteinuria. Medications included sirolimus, mycophenolate mofetil, prednisone, metoprolol, amlodipine, famotidine, and trimethoprim/sulfamethoxazole.

Two and a half years after transplantation, a deep vein thrombosis (DVT) developed in his upper extremity, and he was started on oral anticoagulation with warfarin. One month after the DVT occurred, his creatinine increased, warfarin was held, and a kidney biopsy (Figures 5–8) revealed (1) acute T cell–mediated rejection, type 2A, (2) chronic allograft arteriopathy (chronic rejection, T cell–mediated), and (3) chronic transplant glomerulopathy.
and peritubular capillaritis with diffuse C4d staining, consistent with chronic antibody-mediated rejection. Moderate interstitial fibrosis and tubular atrophy was present. Our patient had donor-specific antibodies to A1, DQ5, and DQ6, with measured mean fluorescent intensity values of 2764, 4147, and 1841, respectively.

Warfarin was restarted, and therapy with pulse intravenous methylprednisolone and intravenous Ig (IVIG) was initiated. Nineteen days after the biopsy, the patient returned to the clinic complaining of progressively worsening fatigue, dyspnea on exertion, and feeling that he was having fevers in the evening. Differential diagnosis for the cause of the fatigue, dyspnea, and fever included infection from recent increased immunosuppression, pulmonary vascular congestion from IVIG, pulmonary embolism during warfarin discontinuation, and acute anemia from blood loss after the reinitiation of warfarin.

On physical examination, our patient was an obese man with a temperature of 36.5°C, BP of 149/93 mmHg, pulse of 105/min, and respiratory rate of 20/min. Cardiovascular examination was notable for a 2/6 systolic ejection murmur, his lungs were clear to auscultation, the site of the kidney biopsy was nontender, and he had trace edema of his lower extremities and marked enlargement of his right upper extremity compared with the left extremity. Laboratory studies are shown in Tables 1 and 2.

**Question 2A**
Which of the following is the most likely mechanism of anemia in this patient?

A. Iron deficiency anemia secondary to a bleed
B. Decreased production anemia caused by bone marrow suppression
C. Dilutional anemia caused by volume overload
D. Intravascular hemolysis

**Discussion of Case 2, Question 2A**
Anemia after transplant is a common finding and may have a number of potential etiologies. The underlying cause of the anemia can be divided into destruction, blood loss, and underproduction. Our patient has laboratory findings...
production, and his inflammatory state, which could be secondary to the immune rejection of his kidney allograft. The strongest indicator of hemolysis in our patient is the positive direct Coombs test. The direct Coombs test (also known as the direct antiglobulin test) is used to detect whether antibodies or complement system factors have bound to red blood cell (RBC) surface antigens in vivo. The test is performed as follows: the patient’s RBCs are washed to remove the patient’s own serum. The cells are then centrifuged with antihuman globulin (also known as Coombs reagent). If Ig or complement factors have been fixed on the RBC surface in vivo, the antihuman globulin will agglutinate the RBCs, and the direct Coombs test will be positive. The results of our patient’s Coombs test indicate the presence of antibodies bound to his RBCs. The elevated lactate dehydrogenase is also a marker of hemolysis, because lactate dehydrogenase is abundant in RBCs; however, it is nonspecific, because it can be increased with the turnover of other types of cells. The absence of urine hemosiderin in our patient does not support hemolysis, but it does not rule it out either. Hemosiderinuria occurs when hemoglobin is released from RBCs into the bloodstream in excess of the binding capacity of haptoglobin. The excess hemoglobin is filtered by the kidney and reabsorbed in the proximal convoluted tubule, where iron in the hemoglobin is removed and stored in ferritin or hemosiderin. The cells of the proximal tubule slough off with the hemosiderin and are excreted into the urine, producing a brownish color. It is usually seen 3–4 days after the onset of hemolytic conditions. The urine hemosiderin test is most sensitive for diagnosing chronic intravascular hemolysis. Another marker that can point to hemolysis is an elevation of unconjugated bilirubin in the serum, which can be determined by measurements of total and direct bilirubin levels. However, these tests were not performed.

Iron deficiency anemia secondary to a bleed is a reasonable consideration here, because our patient is on warfarin. However, the lack of history of gastrointestinal blood loss and the subacute nature of his symptoms make acute bleeding unlikely. His serum iron of 79 μg/dl (reference normal=40–160 μg/dl) and percent iron saturation of 39.5% (14%–50%) are normal and argue against iron deficiency anemia. Furthermore, the low total iron binding capacity of 200 μg/dl (reference normal=230–430 μg/dl) is more consistent with inflammatory block rather than iron deficiency. In addition, his international normalized ratio (INR) is 1.8, which is slightly below the target level for treating a thrombus; this finding indicates that the warfarin level is subtherapeutic and not supratherapeutic, making bleeding, although not impossible, a bit less likely (20,21) (choice A is incorrect).

Underproduction anemia, a common problem for transplant recipients, can often be attributed to medication-induced suppression of the bone marrow or kidney dysfunction-associated decreased erythropoietin production. Our patient’s reticulocyte count is 1.7% (reference range=0.5%–1.5%). Although his level seems high, the percent reticulocyte count, in fact, is low given his level of anemia. As noted above, the lower than expected reticulocyte count can be explained by his kidney dysfunction and/or an inflammatory block. This degree of suppression of his erythrocyte production is not enough to cause the drop in his hematocrit seen over 19 days;

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**Table 1. Selected laboratory studies at the time of kidney biopsy and 19 days later**

<table>
<thead>
<tr>
<th>Laboratory Studies</th>
<th>Day of Kidney Biopsy</th>
<th>19 d Later</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC, cells/µl</td>
<td>6.5</td>
<td>11.2</td>
</tr>
<tr>
<td>Hgb, g/dl</td>
<td>10.4</td>
<td>9</td>
</tr>
<tr>
<td>HCT, %</td>
<td>33.9</td>
<td>27.8</td>
</tr>
<tr>
<td>Platelet count, /µl</td>
<td>211,000</td>
<td>157,000</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Anisocytosis noted/no schistocytes seen</td>
<td></td>
</tr>
<tr>
<td>Na, mEq/L</td>
<td>144</td>
<td>138</td>
</tr>
<tr>
<td>K, mEq/L</td>
<td>5.1</td>
<td>3.9</td>
</tr>
<tr>
<td>Chloride, mEq/L</td>
<td>114</td>
<td>110</td>
</tr>
<tr>
<td>HCO₃, mEq/L</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>3.6</td>
<td>4.1</td>
</tr>
<tr>
<td>Sirolimus, ng/ml</td>
<td>17.1</td>
<td></td>
</tr>
</tbody>
</table>

WBC, white blood cell count; Hgb, hemoglobin; HCT, hematocrit.

**Table 2. Selected additional laboratory studies**

<table>
<thead>
<tr>
<th>Laboratory Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron, μg/dl</td>
<td>79</td>
</tr>
<tr>
<td>TIBC, μg/dl</td>
<td>200</td>
</tr>
<tr>
<td>Percent saturation</td>
<td>39.5</td>
</tr>
<tr>
<td>Reticulocyte count, %</td>
<td>&lt;20</td>
</tr>
<tr>
<td>DAT, Anti-IgG Coombs</td>
<td>Positive 1+</td>
</tr>
<tr>
<td>Lactate dehydrogenase, IU/L</td>
<td>857</td>
</tr>
<tr>
<td>INR</td>
<td>1.8</td>
</tr>
<tr>
<td>Urine hemosiderin</td>
<td>Negative</td>
</tr>
</tbody>
</table>

TIBC, total iron binding capacity; DAT, direct antiglobulin test; INR, international normalized ratio.

indicative of destruction, specifically intravascular hemolysis (choice D is correct) (Figure 9).

During intravascular hemolysis, free hemoglobin is released from erythrocytes into the circulation. Haptoglobin binds free hemoglobin with high affinity, and consequently, the haptoglobin level drops. The resulting haptoglobin–hemoglobin complex is removed by the reticuloendothelial system (mostly the spleen). Haptoglobin levels fall significantly, even in response to very small amounts of free hemoglobin in the plasma. The finding of a low haptoglobin level is consistent with but not diagnostic of intravascular hemolysis, because the level can be low secondary to liver disease, which can complicate the interpretation of test results. The reticulocyte count is usually elevated in patients with hemolytic anemia. Our patient’s reticulocyte count is lower than expected for someone with hemolysis. This finding can be explained by our patient’s renal insufficiency, which is associated with depressed levels of erythropoietin
however, it contributes to his inability to compensate for the hemolytic anemia. His normal neutrophil count is another clue that his marrow is functioning, and, thus, the underlying process is less likely to be decreased production (choice B is incorrect).

One last consideration is dilution that makes the anemia look worse. The patient is volume overloaded as evidenced by his BP, leg edema, and enlarged arm. Given the other laboratory findings, dilution alone is unlikely to be causing the anemia (choice C is incorrect).

**Question 2B**

What is the most likely cause of the hemolytic anemia in this patient?

A. The rejection episode
B. Solumedrol
C. IVIG
D. Occult infection
E. Sirolimus toxicity

**Discussion of Case 2, Question 2B**

IVIG is the most likely cause of hemolytic anemia in this patient (choice C is correct) (Figure 10). With intravascular hemolysis implicated, considerations in our patient’s history for the underlying cause include rejection, IVIG, infection, and sirolimus. IVIG is pooled from approximately 1000 donors who encompass all blood types (22). Donors with type O blood can contribute blood group antibodies directed against A and B blood group antigens, donors with type B blood can provide antibodies to blood group A, and donors with type A blood can contribute antibodies to blood group B. There is passive transfer of anti-A and anti-B hemagglutinins, because these hemagglutinins are
not removed during the manufacture of IVIG. The antibodies that are present in IVIG preparations can coat the recipient’s RBCs and cause hemolysis (22–26). As illustrated in Figure 7, the amount of anti-A and anti-B varies in different IVIG preparations (26).

Our patient’s blood type is AB, making his RBCs a target for antibodies to both blood groups A and B antigens. He received Gammagard, which contains among the highest level of isohemagglutinin titers of all of the IVIG products (Figure 11) (26). Case reports of IVIG-mediated hemolytic anemia in the literature provide other examples of IVIG-induced hemolytic anemia (27). Given the amount of IVIG used therapeutically, it is surprising that we do not see this phenomenon more often and that it has been described as rare. To explain this discrepancy, a two-hit hypothesis has been proposed. The first hit is passive transfer of AB isohemagglutinins to non–O blood group patients and coating of the RBCs. The second hit proposed is enhanced activity of the immune system in patients with an underlying inflammatory state associated with accelerated removal of sensitized RBCs from the circulation (25). This hypothesis fits our patient’s presentation: our patient had non–O blood group (AB) and an inflammatory state caused by the episode of transplant rejection as well as a recent DVT.

Predicting who will develop hemolytic anemia from IVIG is difficult. Predisposing factors that have been identified include high cumulative IVIG dose (≥2 g/kg in one study [27] and 100 g or 1–2 g/kg in another study [25]), the titer of anti-A and anti-B antibodies in the administered preparation, non–O blood type, and women (23). Our patient received 130 g IVIG (approximately 1.3 g/kg IVIG). Management includes stopping the offending agent (the IVIG) and transfusing type O blood if needed. In our patient’s case, IVIG was stopped. A blood transfusion was not required.

Although rejection is a known cause of hemolytic anemia, primarily through the development of thrombotic microangiopathy associated with antibody-mediated rejection (28), the timing of the symptoms makes it an unlikely cause of hemolytic anemia in this patient, and rejection-related hemolytic anemia would not be Coombs-positive (choice A is incorrect). Unlike IVIG and rejection, solumedrol is a treatment for hemolytic anemia (29) (choice B is incorrect). Occult infection should always be considered in immunosuppressed transplant recipients, and infection associated with hemolytic anemia has been reported (30). However, it is not the most likely cause of hemolytic anemia in this patient (choice D is incorrect). Finally, whenever a patient experiences a complication, it is important to consider whether medications may be contributing to or causing the problem. It is particularly true in patients taking immunosuppression, such as transplant recipients, because immunosuppressants have many unintended side effects. Our patient’s medications included sirolimus. Like cyclosporine and tacrolimus, the mammalian target of rapamycin inhibitors sirolimus and everolimus have been implicated in causing thrombotic microangiopathy (TMA) (31–33). Our patient’s sirolimus level was elevated at 17.1 ng/mL. However, given that he has been on long-term sirolimus without prior TMA and that he was recently treated with IVIG, sirolimus is not the most likely cause of our patient’s anemia. In addition, in a patient with TMA, one would expect to see schistocytes on the peripheral blood smear and would not see a positive direct Coomb test (choice E is incorrect).

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Disclosures
None.

References