The Nephrology Quiz and Questionnaire: 2006

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The Nephrology Quiz and Questionnaire (NQQ) occurs at each American Society of Nephrology (ASN) Annual Meeting. Before the meeting, case questions are submitted to Training Program Directors and to the general ASN membership. The results are compiled and displayed at the annual meeting. The general membership of the ASN typically fares as well as teaching program directors. This year, an illustrious team of discussants included Dr. Lee Hamm from Tulane University, Dr. Michelle Josephson from the University of Chicago, Dr. Sharon Adler from Harbor-UCLA, and Dr. Ajay Singh from Brigham and Women's Hospital, illuminating eight intriguing cases that stimulated lively discourse at the recent San Diego meeting.

Case 1: Lee Hamm

A 42-yr-old man with HIV infection diagnosed several years earlier presented to the emergency department with a 1-d history of dyspnea and vomiting. Current medications included lopinavir/ritonavir, tenofovir, and efavirenz. He was given a dose of promethazine and became combative. He was sedated with haloperidol and lorazepam and admitted to the hospital. Initial laboratory studies revealed a sodium of 144, potassium 4.2, chloride (Cl) 104, total CO_2 15, blood urea nitrogen (BUN) 21, creatinine 1.9, and albumin 4.2. No arterial blood gases were drawn. Urinalysis revealed 2 to 3+ ketones.

Question 1A

Which of the following is the MOST LIKELY diagnosis?

A. Pure increased anion gap metabolic acidosis
B. Respiratory alkalosis
C. Metabolic acidosis and metabolic alkalosis
D. Hopeless to decipher without a blood gas

Discussion of Case 1 (Question 1A)

As in many clinical situations, we do not have all of the necessary information in this case. No blood gas was provided. When examining the electrolyte status, the case seems straightforward. Yet, there was a diversity of answers among the respondents. Let's work backwards. Which options were clearly wrong? No one picked respiratory alkalosis (option B). There was no way to call this a respiratory disorder without a blood gas. Let's consider the most popular option that the case is hopeless to decipher without a blood gas (option D). Some experts might agree, but we know that an anion gap >20 is almost always associated with an identifiable metabolic acidosis; indeed, the bicarbonate is reduced (1). We know some things about the patient's condition even without the blood gas. The patient had a high anion gap acidosis. Only a few thought that a pure high anion gap acidosis (option A) could explain the electrolytes. With a pure high anion gap metabolic acidosis, we would have expected a decrease in bicarbonate to approximate the unexplained elevation in anion gap (2). The change in anion gap was probably at least 15 (normal anion gap is approximately 10). The gap was 25, so with a pure high anion gap acidosis we might have expected the bicarbonate to decrease to approximately 10 (normal 25 − 15 = 10). Because the bicarbonate was higher than this, we might imagine that another disorder was raising the bicarbonate in the opposite direction of the metabolic acidosis. The most likely cause would be a metabolic alkalosis, particularly in a patient with a history of vomiting. The correct answer was metabolic acidosis and metabolic alkalosis (option C).

Question 1B

Over the next few hours, the patient became increasingly obtunded and more tachypneic. On transfer to the intensive care unit, respirations were 40, heart rate 130, and BP was 104/43 mmHg. Repeat laboratory studies revealed sodium 146, potassium 5.1, Cl 109, CO_2 8, BUN 27, creatinine 2.7, and albumin 4.5. Arterial blood gas revealed pH of 7.31, pCO_2 13, pO_2 105 on 28% oxygen, and calculated HCO_3^- was 7. Lactic acid level was 11.6, acetaminophen level was 0, serum osmolality was 302, alcohol level was 0, and ketones were negative.

What is the MOST likely diagnosis?

A. Mixed hyperchloremic and increased anion gap acidosis caused by acute renal failure
B. Methanol or ethylene glycol intoxication
C. Salicylate intoxication
D. Tenofovir-induced lactic acidosis

Elimination of wrong options may again be the best way to start. First, renal failure (option A) takes time to develop be-

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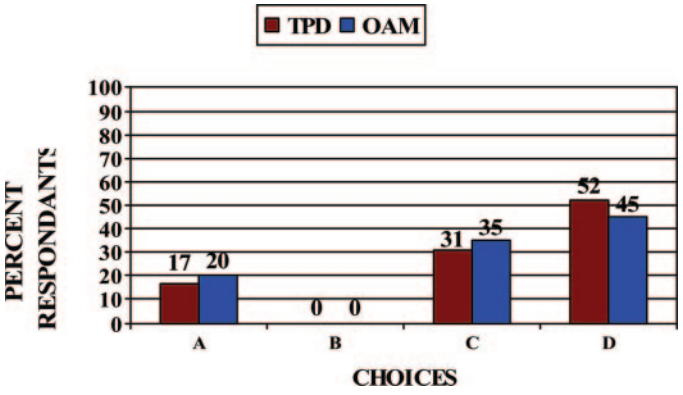

Figure 1. Figures represent answers from the membership. TPD, Training Program Directors; OAM, other ASN members. A, B, C, D refer to the possible options to the question.

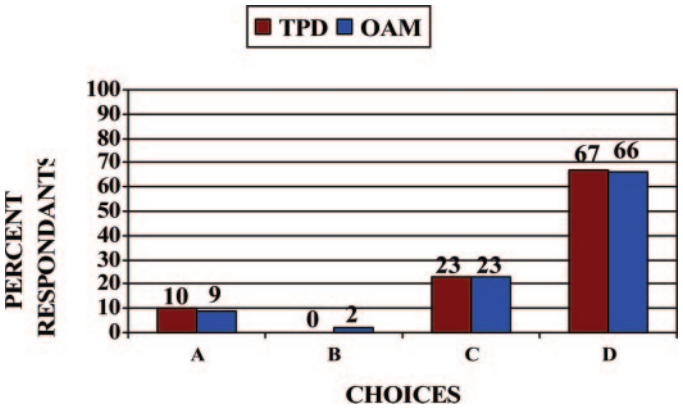

Figure 2. Answers from the membership, question 1B.

cause the primary problem was loss of the ability to excrete the relatively small daily metabolic acid load. Similarly, there was no indication of methanol or ethylene glycol intoxication (option B), and there was no osmolal gap that often accompanies these ingestions. The final two options, an acidosis secondary to salicylate or tenofovir (lactic acidosis), appear reasonable, yet urinary ketones occur in salicylate intoxication. The correct answer is salicylate intoxication (option C).

Question 1C

What should be done next?

A. Sodium bicarbonate infusion
B. Hemodialysis
C. Charcoal hemoperfusion
D. Supportive care

Discussion of Case 1 (Question 1B)

We know that the patient had an elevated salicylate level. Charcoal hemoperfusion (option C) is seldom, if ever, indicated, and not available in most hospitals. Supportive care would only be appropriate with treatment of the underlying condition. For example, if tenofovir had been the offending agent, then the condition would have improved with its cessation; however, tenofovir was not implicated in this case. Supportive care (option D) cannot be a correct option. In mild salicylate intoxication, sodium bicarbonate infusion may help eliminate the drug and lessen entry into the central nervous system, but with severe cases such as this, hemodialysis is indicated (in addition to sodium bicarbonate) (3). Severe cases are associated with salicylate levels >100 mg/dl or clinical deterioration (mental status and renal function decline). The actual level in this case was 46, thus the correct answer is hemodialysis (option B).

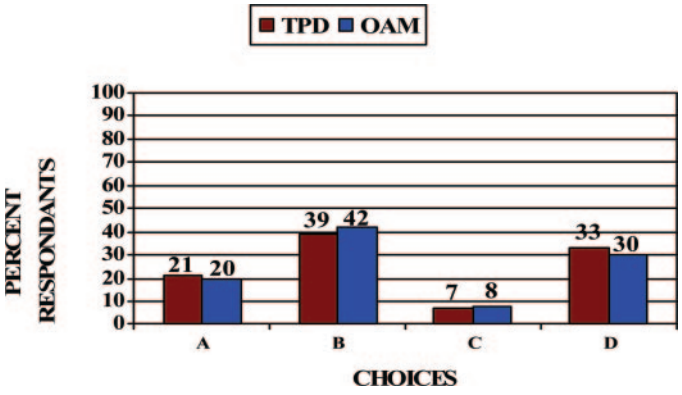

Figure 3. Answers from the membership, question 1C.

Case 2: Michelle A. Josephson

A 43-yr-old female received a simultaneous pancreas-kidney (SPK) transplant from a cytomegalovirus (CMV)-seropositive donor. Her immunosuppressive regimen consisted of thymoglobulin induction and maintenance therapy with tacrolimus, mycophenolate mofetil, and prednisone. She was CMV-seronegative at the time of transplant. She received CMV prophylaxis for a total of 3 mo: intravenous ganciclovir 2.5 mg/kg twice daily was given for 3 wk, then oral valganciclovir 900 mg once daily for the remainder of the 3 mo. Four months postoperatively, her tacrolimus trough was elevated at 13.4 ng/ml, and the tacrolimus dose was reduced. Two weeks later she had diarrhea, and her tacrolimus level was still elevated at 13.1 ng/ml. Her white blood cell (WBC) count dropped precipitously to 1.8 K/L.

Question 2A

The MOST likely cause of her diarrhea is:

A. Elevated tacrolimus level
B. Mycophenolate mofetil
C. Cytomegalovirus colitis
D. Clostridium difficile from antibiotic prophylaxis for urinary tract infections
E. Fluconazole prophylaxis for fungal infections

Discussion of Case 2 (Question 2A)

Diarrhea is a common posttransplant problem. The main causes of posttransplantation diarrhea include infection, immunosuppressive drugs, antibiotics, and other nonimmunosuppressive drugs. Because of the many potential causes, it can be difficult to pinpoint a specific etiology.

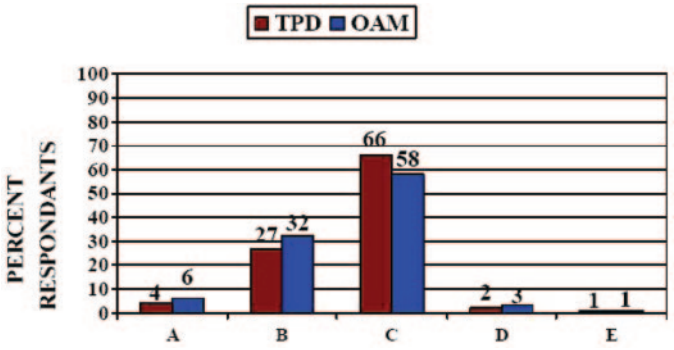

Figure 4. Answers from the membership, question 2A.

The most likely cause of this patient's diarrhea is not an elevated tacrolimus level (option A) or mycophenolate mofetil (option B). Many immunosuppressants have been associated with diarrhea (4). Tacrolimus has been reported to have increased rates of diarrhea when compared with cyclosporine (4). Mycophenolate mofetil has been associated with diarrhea. Studies have noted a dose-dependent trend of increasing diarrhea symptoms reported with 3 g of mycophenolate mofetil when compared with 2 g (4). In multicenter studies, the reported diarrhea incidence was significantly higher for both mycophenolate mofetil 2 g/d and 3 g/d compared with azathioprine (4). Why not an elevated tacrolimus level (option A) or mycophenolate mofetil (option B)? The patient has been on these drugs for 4 mo. Both of these options are possible, although given the clinical picture (in particular the low WBC count), they are not the most likely cause.

What about clostridium difficile from antibiotic prophylaxis for urinary tract infections (option D)? Antibiotics are often associated with diarrhea for a variety of reasons, and not all of these are a consequence of clostridium difficile. In one study, hospitalized kidney and kidney-pancreas transplant recipients had a significantly higher incidence of clostridium difficile than the overall incidence noted in the nontransplant hospitalized population (5). The increased susceptibility to clostridium difficile has been attributed to many factors including the frequent use of antibiotics, more frequent hospital admissions, and immunosuppressant usage (5). Why not option D? Clostridium difficile is a common issue in transplant recipients, but it does not explain the low WBC count.

What about fluconazole prophylaxis for fungal infections (option E)? It is hard to rule out any drug as a potential cause of diarrhea, as most have been associated with diarrhea. Even fluconazole, an antifungal drug, has been reported to cause diarrhea. We are not told that this patient was taking fluconazole and it does not explain the low WBC count.

The most correct answer is cytomegalovirus colitis (option C). There are a number of infectious causes of diarrhea, including bacterial, viral, and parasitic organisms (4). Enteric and or gastric infections with CMV is a common problem (4). CMV was diagnosed in 7.9% of solid organ transplant recipients undergoing colonoscopy for any reason over an 8.5-yr period (6). CMV infection can cause problems in the gastrointestinal tract anywhere from the esophagus all of the way down to the anus (7). The only way to make a diagnosis of CMV enteritis is to obtain endoscopic biopsies. It is important to diagnose invasive CMV disease at an early stage to initiate treatment and prevent further complications and spread. Although CMV can cause pseudo-obstruction, it is more likely to cause enterocolitis. The many potential manifestations of CMV in the gastrointestinal tract includes diarrhea with or without fever, bleeding, perforation, toxic megacolon, and pneumatosis intestinalis (7). This patient was at high risk for CMV because she had a seropositive donor and was herself seronegative for CMV at the time of transplant. She has leukopenia, and thus CMV disease is likely the cause of her diarrhea.

Question 2B

Upon hospitalization, CMV quantitative PCR for blood was sent. The initial stool testing was negative and included shell vial rapid test for CMV, stool culture, and evaluation for microsporidia, cryptosporidium, Giardia lamblia, *Cyclospora*, *Isospora belli*, clostridium difficile, ova, and parasites. Few leukocytes and many yeasts were present in the stool. Mycophenolate mofetil and trimethoprim sulfamethoxazole were stopped. Persistent diarrhea prompted a colonoscopy that demonstrated multiple petechiae/small ulcerations, most severe in the proximal right colon. A biopsy revealed CMV; mycophenolate mofetil toxicity could not be ruled out (Figure 5). CMV was isolated on the shell vial rapid test performed on the colon biopsy sample. The initial quantitative PCR from blood obtained at the time of hospitalization revealed 526,000 copies/ml CMV DNA. The patient was treated with intravenous ganciclovir and then oral valganciclovir, and the diarrhea stopped immediately. The WBC count increased in <1 wk. Blood PCR was negative for CMV within 3 wk.

What is the MOST likely cause of the patient's elevated tacrolimus?

A. Discontinuation of a drug that competes for CYP3A4
B. Decrease in daily grapefruit juice intake
C. Diarrhea
D. Constipation

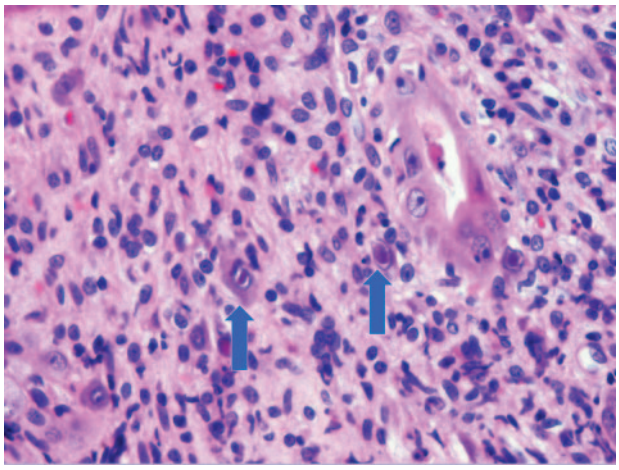

Figure 5. The arrows indicate CMV inclusions.

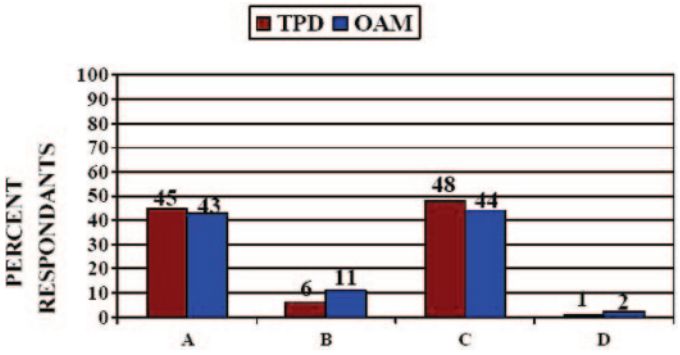

Figure 6. Answers from the membership, question 2B.

Discussion of Case 2 (Question 2B)

The most likely cause of the patient's elevated tacrolimus level is not discontinuation of a drug that competes for CYP3A4 (option A) or decrease in daily grapefruit juice intake (option B). Calcineurin inhibitors (cyclosporine and tacrolimus) are metabolized by the isoenzymes of the cytochrome P-4503A4 (CYP3A4) family (8). Concomitant use of inhibitors of the CYP3A4 system (including grapefruit juice) will result in increased tacrolimus levels (8). Removal of an inhibitor (or a drug that competes for CYP3A4) will cause a decreased level; thus, options A and B cannot be correct. The correct option is diarrhea (option C). Although the absorption of cyclosporine is impaired in patients with diarrhea, (8) this does not always appear to be the case for patients on tacrolimus (9). This patient had an elevated tacrolimus level despite dose reductions in the setting of diarrhea. Given the experience with cyclosporine, the finding of elevated tacrolimus levels during diarrhea is surprising but has been observed by others (10). It is tempting to attribute the diarrhea to the increased tacrolimus level, but timing usually clarifies which came first. Tacrolimus bioavailability after oral administration is determined by intestinal metabolism by CYP3A4 as well as active secretion from enterocytes into the lumen by P-glycoproteins. In the setting of enterocolitis, epithelial cells of the intestine may be injured, thereby paralyzing the P-glycoproteins and increasing the level of tacrolimus (10). Some investigators have noted that decreased intestinal CYP3A4 may play a role in the increased tacrolimus levels seen during diarrhea (10). Another possible explanation for the increased tacrolimus levels is that tacrolimus metabolism is greatest in the duodenum and decreases by the time the drug gets to the colon. The shortened intestinal transit time associated with diarrhea and the ensuing rapid delivery to the colon may lead to higher drug troughs, because CYP3A4 is less active in the colon (7) and thus tacrolimus will be less quickly broken down in the colon.

Case 3: Ajay K. Singh

A 78-yr old black man was referred to the Chronic Kidney Disease Clinic because of an apparently reduced estimated GFR (eGFR). He was otherwise healthy. Past medical history was notable for hypertension diagnosed by his primary care physician about 15 yr ago. He had mildly elevated cholesterol treated with atorvastatin. His BP had been quite stable in the 150 to 160/68 mmHg range. He was status post a recent hip replacement that went well. He had no allergies. Medications included hydrochlorothiazide 50 mg/d, atorvastatin 10 mg qd. He is a former smoker. On physical examination he was a healthy looking obese man. His BP was 152/68 mmHg and his heart rate was 72 beats/min. Weight was 120 kg and jugular venous pressure was 8 cm. The rest of the examination was negative. The urinalysis revealed a specific gravity of 1.015, pH 5.0, 3+ albumin, and was otherwise negative. The urine sediment was bland. His BUN and creatinine were 28 and 1.1 mg/dl, respectively.

Question 3

All of the following statements are true EXCEPT:

A. Estimating his GFR using the Cockcroft-Gault equation will result in a gross overestimation of creatinine clearance.

B. If the chemistry laboratory has calibrated the creatinine measurements using the isotope dilution mass spectroscopy (IDMS)-traceable standards, then one must use the Modification of Diet in Renal Disease (MDRD)-3 equation.

C. The abbreviated MDRD-2 will likely overestimate GFR in this patient.

D. The patient's race and the presence of albuminuria places him at a higher risk of progression regardless of his eGFR.

E. His estimated GFR will be approximately 20% higher than that of a similar white patient.

Discussion of Case 3

Studies indicate that MDRD tends to systematically underestimate rather than overestimate GFR, so option C is false (11,12). Lin *et al.* (11) reported that both MDRD-1 and MDRD-2 (MDRD-2 is the abbreviated MDRD equation) exhibited high negative bias, demonstrating the tendency to underestimate GFR. All of the other options are correct. Weight is part of the Cockcroft-Gault equation; thus, it will grossly overestimate the predicted creatinine clearance. It is important to know whether the laboratory has calibrated the creatinine measurements using the IDMS-traceable standards because the MDRD-3 equation differs quite significantly from the MDRD-1 or MDRD-2 equations. Among the risk factors for kidney progression are

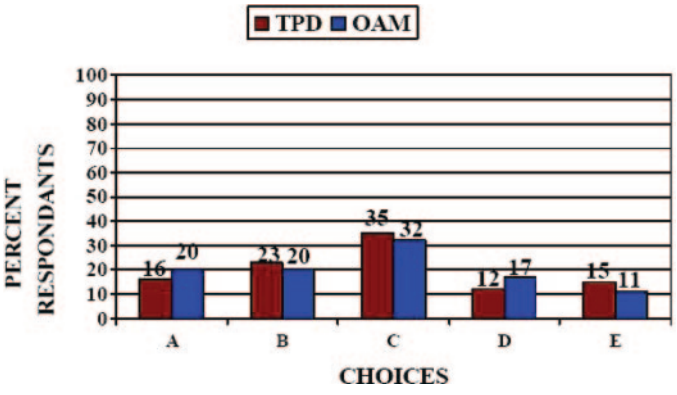

Figure 7. Answers from the membership, question 3.

black race and level of albuminuria. It is important to adjust the eGFR for black race because this was in the original equation.

Although measurement of serum creatinine is the most widely utilized measure for the assessment of kidney function, it has several limitations. Creatinine production is dependent on muscle mass, and it requires cautious interpretation among individuals with low muscle mass, females, and elderly patients. Another source of inaccuracy is the effect of noncreatinine chromogens when the alkaline picrate assay (Jaffe reaction) for creatinine is utilized (13). These factors include acetoacetate, cephalosporins, and high concentrations of furosemide. Modern versions of the Jaffe assay have reduced these effects by adjusting temperature, assay constituents, and various calibration settings. However, to truly reduce the effect of noncreatine chromogens, alternative methods are necessary. These include an enzymatic creatinine assay, high-performance liquid chromatography, or isotope dilution mass spectroscopy. Furthermore, calibration of the serum creatinine is important to reduce intra- and interlaboratory variability.

Given these limitations with serum creatinine as a measure of actual GFR, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) and the National Kidney Disease Education Program (NKDEP) have recommended the use of actual GFR or, when unavailable, the use of a prediction equation for estimating GFR (14). In most situations, direct measurement of GFR is not feasible, thus a prediction equation to estimate GFR is the most practical and accurate method to assess kidney function (14). The MDRD and Cockcroft-Gault equations are now the most popular prediction equations to assess GFR in adults.

The MDRD GFR prediction equation was developed in 1999. The equation is based in 1628 nondiabetic subjects, age 18 to 70 yr, with renal insufficiency. The formula utilizes urea, creatinine (Pcr), albumin (alb), and the demographics of age, gender, and race (black or white). The GFR equation is as follows:

$$GFR = 170 \times Pcr^{-0.999} \times age^{-0.176} \times \text{serum urea nitrogen}^{-0.17} \times alb^{0.318} \times 0.762 \text{ (if female)} \times 1.18 \text{ (if black)}$$

If race is unavailable and white race is assumed, the GFR will be underestimated by 18% if the patient is black. This equation has been validated in black and white racial groups in the United States. It has also been validated in diabetic and predialysis patients and renal transplant recipients. In 2000, a simplified MDRD equation (MDRD-2) was made available based on serum creatinine as the only laboratory value in the absence of urea or albumin. The MDRD formula yields an eGFR normalized to 1.73 m^2 body surface area. Adjusting for body surface area is necessary when comparing a patient's eGFR with normal values or when determining the stage of CKD. However, an uncorrected eGFR may be preferred for clinical use in some situations, such as drug dosing.

Recently, an IDMS-traceable MDRD equation (also known as the MDRD-3 equation) has been developed (13). This modified MDRD equation is used when creatinine values are generated from a laboratory that has calibrated its creatinine measurement to a set of creatinine standards. Until recently, one of the major limitations of using an eGFR equation such as the MDRD equation was the significant variability in the measurement of serum creatinine. This variability results in reduced accuracy of the MDRD equation in the normal to slightly elevated creatinine range (up to 1.5 mg/dl) because assays in most laboratories are not calibrated to the alkaline picrate method used by the Cleveland Clinic laboratory in the MDRD study. Mass spectroscopy is the ideal method to obtain a "true" creatinine value, and therefore creatinine standardization using an IDMS-traceable panel for creatinine is now being recommended. The MDRD-3 equation is as follows:

$$GFR = 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}$$

Case 4: Sharon Adler

A 56-yr-old woman presented with rheumatoid arthritis that was treated with a cyclooxygenase-2 (COX-2) inhibitor, Celebrex (Pfizer Inc., New York, NY), and low-dose chloroquine for 13 mo, followed by an increase in the chloroquine dose to 500 mg/d for 5 mo. The usual initial dose is 400 mg/d with 150 to 300 mg/d for maintenance. The history was remarkable for an absence of acral paresthesias, hypohidrosis, constipation, or the ischemic disease associated with accelerated atherosclerosis. There was no family history of kidney disease.

The physical examination was remarkable for joint changes consistent with rheumatoid arthritis and proximal muscle weakness. There were no angiokeratomas or skin rash. Laboratory tests were significant for an eGFR of 23 ml/min per m^2. Urinalysis showed trace protein and 3+ occult blood. Microscopic examination of the urine revealed few red blood cells/hpf or WBC/hpf and an occasional granular cast. A renal ultrasound revealed a 9.2 cm right kidney and a 10.7 cm left kidney with no hydronephrosis. Creatine phosphokinase and aldolase were normal. Chloroquine and the COX-2 inhibitor were discontinued, but the clinical syndrome did not resolve after some months. A renal biopsy was performed.

Question 4

Which of the following renal biopsy findings is LEAST associated with the clinical condition described?

A. Mesangial and capillary wall deposition of 10 to 12 nm fibrils

B. Subepithelial deposits with podocyte effacement

C. Normocellular glomerular tufts surrounded by crescents

D. Mesangial deposits that are C1q predominant

E. Whorled lipid inclusions in the podocyte

Discussion of Case 4

The correct option is mesangial deposits that are C1q predominant (option D). Rheumatoid arthritis is associated with a variety of different glomerular disorders. Secondary amyloidosis, or amyloid A amyloidosis, remains among the most common histologic lesions in patients with rheumatoid arthritis, and the nephrotic syndrome was seen in 33 of 110 patients in one large renal biopsy series published in 1995 (15). Overall, the most common glomerular disorder associated with rheumatoid arthritis in this series was mesangial proliferative glomerulonephritis caused by immune complex deposition but without C1q predominance. This histologically indistinct form of mes-

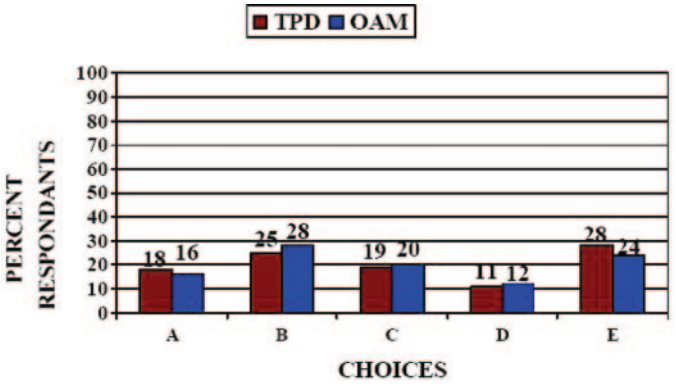

Figure 8. Answers from the membership, question 4.

angial proliferative glomerulonephritis was common in patients with rheumatoid arthritis and hematuria, and was noted in 40 of 100 patients in this biopsy series. Membranous nephropathy, presenting usually with nephrotic-range but occasionally heavy but nonnephrotic proteinuria, was reported in 19 of 100 patients. It is often been associated with gold and d-penicillamine therapy (16). However, membranous nephropathy has also been reported in patients with rheumatoid arthritis in the absence of drug exposure, and some relationship to particular HLA-extended haplotypes has been suggested. Thus, amyloidosis and membranous nephropathy would not be the least likely histologic changes to be seen on the patient's renal biopsy.

Newer therapies may have introduced a new glomerular complication in a small number of patients with rheumatoid arthritis. Rheumatologists have been treating patients with rheumatoid arthritis with inhibitors of TNF-α quite aggressively in recent years, with excellent therapeutic outcomes and substantial improvement in quality of life. The therapeutic administration of TNF-α inhibitors has recently been reported to be associated with immune activation and organ injury in a small number of patients. The TNF-α inhibitor etanercept has been linked to cutaneous vasculitis and to a reversible lupus-like syndrome without renal or central nervous system involvement (17). A number of patients who have been treated with agents that modulate TNF-α, most commonly etanercept (Enbrel, Amgen Inc., Thousand Oaks, CA), but also adalimumab (Humira, Abbott Laboratories, Abbott Park, IL), and infliximab (Remicade, Centocor Inc., Horsham, PA), have been reported to develop temporally associated glomerulonephritis, often with resolution on drug discontinuation. Numerous glomerular lesions have been reported, including IgA nephropathy and Henoch-Schönlein purpura, (18) lupus-like glomerular lesions including patterns similar to focal or diffuse proliferative or membranous lupus nephritis, (19) and pauci-immune crescentic glomerulonephritis (20). Whether this represents cause-and-effect relationships or just chance occurrence is not yet clear, but it is interesting to note the contrast in the 1995 series of 110 patients with rheumatoid arthritis who underwent renal biopsies (15), none of whom had proliferative lupus lesions, lupus membranous glomerulonephritis, or pauci-immune crescentic glomerulonephritis associated with systemic vasculitis. The change in the pattern of renal disease in association with the use of an inhibitor of a known immunomodulator and the temporal patterns of disease presentation with drug onset and disease modulation with drug discontinuation (and therapy) suggest a cause-and-effect relationship.

What about C1q nephropathy? In the study cited above (15), mesangial proliferative glomerulonephritis occurred in 40 of the 110 patients with rheumatoid arthritis, but those patients did not have C1q predominance in their mesangial immune complex lesions. Furthermore, C1q nephropathy usually presents as nephrotic syndrome, and our patient only had trace proteinuria. In C1q nephropathy, there are variable light microscopic appearances, ranging from minimal change to mesangial proliferative glomerulonephritis to focal sclerosis, but so far there have been no cases reported in association with rheumatoid arthritis (21). It is reasonable to argue that C1q nephropathy is the least likely form of glomerulonephritis to be associated with rheumatoid arthritis.

What about whorled lipid inclusions? In the kidney, these inclusions in endothelial cells, podocytes, and interstitial cells are almost pathogenetic for Fabry's disease (22). However, there was no family history of renal disease, no symptoms of Fabry's disease, a normal serum alpha galactosidase level, and no identifiable mutation in the gene. Thus, it seems unlikely that the patient has Fabry's disease.

Could chloroquine have played a role in the development of lipid inclusions in this patient? Chloroquine and hydroxychloroquine have few renal side effects. Fifty-five per cent of patients taking chloroquine and 15% of patients taking hydroxychloroquine experience functional declines in creatinine clearance of >10%. Whorled inclusions typical for Fabry's disease were reported in 2003 in a patient with hypertension and Sjögren's syndrome taking chloroquine. The lack of a family history, systemic signs or symptoms typical of Fabry's disease, and normal activity of α-galactosidase A in isolated leukocytes (56 nmol/mg; range, 33.2 to 109 nmol/mg) ruled out Fabry's disease (23). Indeed, the patient that is the subject of this discussion represents another such patient (24). Although her renal biopsy showed typical lipid inclusions, she had no family history of Fabry's disease; no angiokeratomas; no cornea, lens or retinal lesions; and no hypohidrosis or acral paresthesias. Her plasma α-galactosidase A activity was within the normal range, and she had no mutations in the DNA sequence of all protein coding regions and intron-exon boundaries as performed at the Mt. Sinai School of Medicine (New York, NY). One difference between true Fabry's disease and the pseudo-Fabry's disease seen in the chloroquine-induced cases is that the latter have lipid inclusions in macrophages, whereas the former do not (24).

Case 5: Lee Hamm

A 52-yr-old man presented with 1 wk of worsening extremity pain and weakness. The patient reported that he went to bed the prior night with painful legs, and he was unable to move his legs the next morning. His arms felt heavy, and the extremity pain was described as "constant burning pain" made worse

with palpation. A past history of seizures treated with diphenylhydantoin was elicited, but he had not taken the medication in over a month. There was no history of nausea, vomiting, diarrhea, or change in his oral intake. There was no history of diuretic or laxative use. On physical examination, his temperature was 37.3°C, pulse 80, respirations 14, and BP was 124/72 mmHg. The examination was remarkable for 2/5 strength in upper and lower extremities, whereas sensation was preserved in all extremities. He had no edema, erythema, or evidence of trauma. The extremity muscles were tender to light palpation. His laboratory results are shown in Table 1.

Question 5A

Regarding the patient's hypokalemia, which of the following is the MOST CORRECT statement?

A. The trans-tubular potassium gradient (TTKG) cannot be calculated, and hence no inferences regarding the renal origin of the hypokalemia can be made

B. The low urine potassium clearance indicates that the kidneys are not the problem

C. The urine anion gap is most consistent with vomiting

D. A component of redistribution of potassium is likely

Discussion of Case 5 (Question 5A)

The options here may frustrate nearly everyone, but this case will increase our "electrolyte skills." We will return to our tactic of eliminating wrong options first. The urine anion gap is not helpful in potassium disorders. Its main utility is in distinguishing hyperchloremic metabolic acidosis from diarrhea (urine anion gap Na+K-Cl negative as a result of appropriate ammonium in urine) when compared with a metabolic acidosis from renal disease or renal tubular acidosis (urine anion gap typically >0). Thus, option C is incorrect. Urine K <15 to 20 typically indicates that the kidneys are appropriately conserving K^+ in a K-deficient state because urine K cannot be lowered further. With the polyuria that may be occurring here (with the very low urine specific gravity), urine losses may still be high despite a relatively low K concentration (1), so option B is incorrect. The TTKG cannot be calculated without a urine osmolality, thus option A may be correct. Many experts do not recommend the use of TTKG in hypokalemia, but by substituting the values of the case, TTKG = $U_K/P_K \div U_{osm}/P_{osm}$ = $1273/x$, which equals >2 with U_{osm} <600, is likely considering the low specific gravity. This value would be considered inappropriately high during K deficiency, thus the "we can make no inferences" choice (option A) may not be the best option (2). A component of redistribution of K is the best answer (option D). Admittedly, redistribution from a pH of 7.51 will not cause plasma K of 1.6, so something else is occurring.

Table 1. Laboratory findings

	Value
Sodium	138 mEq/L
Glucose	97 mg/dL
Potassium	1.6 mEq/L
Calcium	10.3 mg/dL
Chloride	83 mEq/L
Magnesium	1.7 mg/dL
HCO3–	40 mEq/L
CPK	11,031 U/L
BUN	5 mg/dL
TSH	2.84 mU/L
Creatinine	0.6 mg/dL
Phosphate	0.9 mg/dL
Arterial blood gas	
pH	7.51
pCO2	51
pO2	83

	Urine	Serum
Sodium	29 mEq/L	138 mEq/L
Potassium	7.2 mEq/L	1.6 mEq/L
Chloride	36 mEq/L	83 mEq/L
Calcium	<2.0 mEq/L	
Osm	Lost by lab[a]	290 mOsm/kg

[a]Urine specific gravity was <1.005.

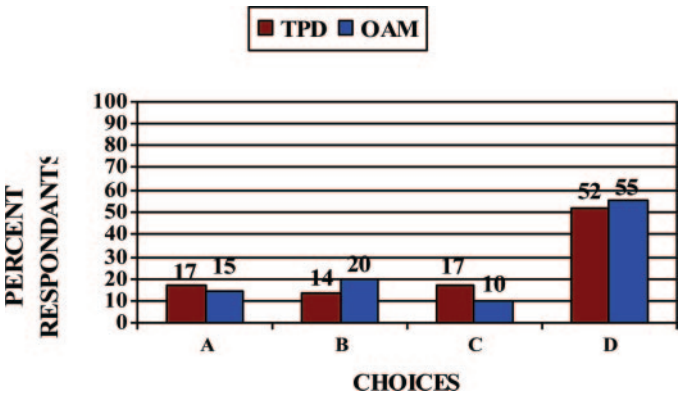

Figure 9. Answers from the membership, question 5A.

Question 5B

The MOST LIKELY origin of the electrolyte disorder is:

A. Gitelman syndrome

B. Primary hyperaldosteronism

C. Surreptitious vomiting

D. Inadequate intake

E. Laxative abuse

Discussion of Case 5 (Question 5B)

To approach the origin of the disease, it is useful to look for all the clues in the case. Of particular note, there are a variety of rather severe chemical disturbances in addition to the serum K and metabolic alkalosis. Most remarkable are the hypophosphatemia (phosphate 0.9), the very low BUN, and elevated creatine phosphokinase. The latter is consistent with rhabdomyolysis, a likely cause of the muscle pain and tenderness, which may have resulted from either severe hypokalemia or severe hyperphosphatemia. What might cause both hypokale-

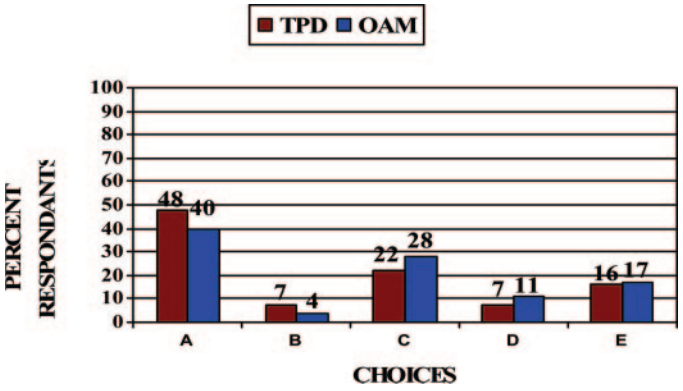

Figure 10. Answers from the membership, question 5B.

mia and hypophosphatemia? First, consider the causes of hyperphosphatemia in Table 2.

Most of the listed options for this question are not associated with hypophosphatemia, including options A, B, and C. The most popular option, Gitelman syndrome (option A), does not cause hypophosphatemia. This option was undoubtedly chosen because of recent epidemiologic evidence that Gitelman syndrome is significantly more common on tests than in emergency rooms. This leaves the options of inadequate intake and chronic diarrhea. Because diarrhea is usually associated with acidosis, inadequate intake seems the more likely diagnosis. This diagnosis is consistent with poor protein intake and a low BUN. The best answer is "inadequate intake" (option D), despite the fact that this seldom causes marked hypophosphatemia. Diarrhea is rarely associated with metabolic alkalosis. Clearly, examination of the laboratory values contrasts with the history of no dietary change and no gastrointestinal problems, thus the history has to be considered suspect—a valuable conclusion in treating the patient.

Case 6: Michelle A. Josephson

A 54-yr-old female received a SPK transplant from a 20-yr-old donor. The immunosuppressive regimen consisted of basiliximab induction and maintenance therapy of tacrolimus, mycophenolate mofetil, and prednisone. The patient was not yet on dialysis at the time of transplantation; thus, her preoperative serum creatinine was 2.7 mg/dl. Her serum creatinine increased to 3.7 mg/dl 2 d after transplant but was down to 2.8 mg/dl by discharge on postoperative day 7. She required some insulin until postoperative day 6. On postoperative day 9, her serum creatinine was 4.1 mg/dl, amylase and lipase were normal, and glucose was 106 mg/dl. A kidney biopsy revealed a Banff IIA rejection.

Thymoglobulin was administered, and the patient's serum creatinine fell to 1.2 mg/dl. During treatment, she required insulin for glucose control. During the last few days of the rejection treatment course, the patient complained of abdominal pain and was febrile. A CT scan was consistent with pancreatic necrosis and the patient underwent pancreatectomy.

Table 2. Causes of hypophosphatemia

Redistribution
Insulin, refeeding
Respiratory alkalosis
Hungry bone
Decreased intestinal absorption
Inadequate intake
Chronic Al or Mg containing antacids
Chronic diarrhea
Vitamin D deficiency
Renal losses
Hyperparathyroidism, vitamin D deficiency
Renal leak

Question 6A

What is the MOST likely cause of the pancreas necrosis?

A. Rejection of the pancreas simultaneous with rejection of the kidney

B. Ischemia

C. Thymoglobulin complication

D. Pancreatic pseudocyst

E. Presence of antiphospholipid antibodies

Discussion of Case 6 (Question 6A)

While islet transplantation is still in its infancy, solid organ transplantation is the established treatment for some type I diabetic patients (25). Pancreas graft survival has improved slightly over the past few years when performed with a SPK. In 2003, the 1-yr pancreas graft survival rate (for those receiving a SPK) was 85.8% compared with 82.2% in 1995 (26). The survival rates for pancreas allografts in the setting of pancreas after kidney and pancreas transplant alone improved more than the survival rate for a pancreas transplant performed during a SPK. Between 1995 and 2003, the 1-yr pancreas graft survival increased from 70.1% to 77.9% for pancreas after kidney transplants (26). In the case of pancreas transplant alone, 1-yr graft survival over that same time period rose from 63.9% to 74.4% (26).

Enteric exocrine drainage is the most common surgical approach now, replacing bladder drainage to avoid urological and metabolic complication (27). Despite surgical advances,

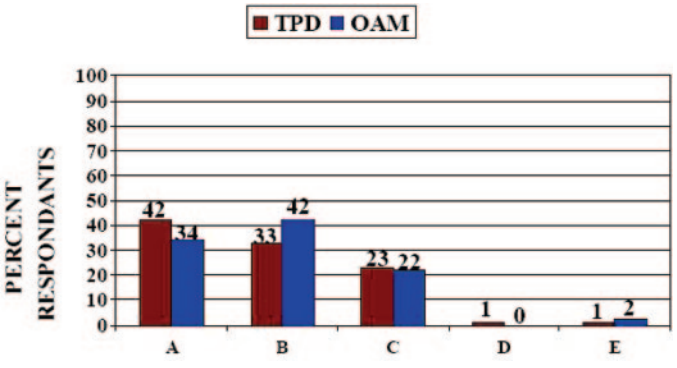

Figure 11. Answers from the membership, question 6A.

pancreatic grafts continue to be susceptible to surgical complications, more so than other solid organs (25). Acute vascular thrombosis is the leading cause of early graft pancreatectomy. In a review of 580 bladder-drained pancreas transplants performed at the University of Minnesota between 1995 and 1997, recipients receiving preemptive SPK transplants (recipients not yet on dialysis), like this patient, had an 11.4% incidence of thrombosis, a higher rate than in recipients of SPK transplants already on dialysis (28).

The most likely cause of the pancreas necrosis is not rejection of the pancreas simultaneous with rejection of the kidney (option A). Given the greater technical difficulty of a pancreas biopsy compared with a kidney biopsy, pancreas allograft rejections are often diagnosed presumptively or inferred because of biopsy-proven kidney allograft rejection. Pancreas rejection is usually suspected in the setting of elevated pancreatic enzymes (amylase and lipase), not the case with our patient. In this patient, very early pancreas rejection could have been present, although unlikely because the amylase and lipase were never elevated. Even if present, pancreas rejection would not likely cause necrosis of the pancreas.

Thymoglobulin complication (option C) is not correct. Although thymoglobulin is associated with potential adverse side effects, allograft necrosis is not one of them. Pancreatic pseudocysts are complications of pancreas transplantation (option D). In one series of 118 patients undergoing portal-enteric drainage, 10 patients at the University of Pisa (8.5%) were diagnosed with peripancreatic fluid collections (29). In this case, the imaging study did not demonstrate a fluid collection. Antiphospholipid antibodies are associated with an increased incidence of thrombosis (option E). In this case, no information or other clues are given to make this diagnosis. The most likely cause is ischemia (option B). Ischemic injury and thrombosis are the most likely causes of the pancreatic necrosis. Thrombosis is a relatively common reason for pancreatectomy. In a case series of 159 pancreas transplantations performed at the University of Tennessee, 37 (23%) required pancreatectomy; 62% of the 37 pancreatectomies were performed for thrombosis (27). The early insulin requirements in this patient make one suspicious of an early event.

Question 6B

After pancreatectomy, the patient's serum creatinine hovered around 1.0 mg/dl when volume replete. Ten days after pancreatectomy, her creatinine started to increase and reached a level of 4.0 mg/dl by postoperative day 17. The patient noted increased abdominal girth. A kidney biopsy was obtained that revealed mild calcineurin inhibitor toxicity, and an ultrasound performed during the procedure revealed ascites.

The MOST likely diagnosis is:

A. Urinary leak

B. BK nephropathy

C. Calcineurin inhibitor toxicity

D. Kidney allograft compression from the ascites

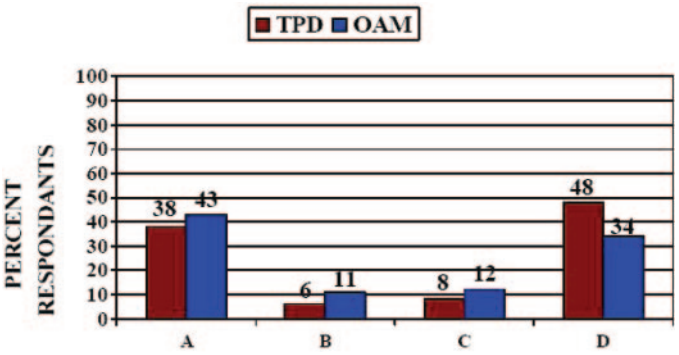

Figure 12. Answers from the membership, question 6B.

Discussion of Case 6 (Question 6B)

The differential diagnosis for acute renal failure in a patient with a kidney transplant is similar to that of the non–kidney transplant patient, broadly dividing the differential diagnosis into prerenal, intrinsic renal, and postrenal (30). With prerenal causes, the calcineurin inhibitor effect of afferent arteriolar vasoconstriction needs to be considered. In intrarenal processes, the potential for calcineurin inhibitor toxicity as well as rejection or recurrent disease must be considered. With postrenal causes, the association of BK with ureteral stenosis needs to be considered. Potential technical complications with lymphoceles or leaks need to be considered as well.

The most likely diagnosis is not BK nephropathy (option B). Given the timing and absence of evidence of BK on kidney biopsy in this case, BK nephropathy was not high on the differential. Given the mild nature of the calcineurin inhibitor toxicity on biopsy, it was unlikely to cause such quick and profound acute renal dysfunction (option C). The presence of ascites brings up consideration of compression of the kidney allograft (option D), although this diagnosis seems less likely for several reasons. We would likely need to invoke a lot of pressure or tension for such a profound change in kidney function. There are no findings such as ischemia on biopsy, and no associated new-onset or worsening of hypertension, characteristic the of so-called "Page" kidney.

The most likely diagnosis is urinary leak (option A). The sudden increased abdominal girth and acute renal failure after a surgical procedure makes this diagnosis highly suspicious. The elevated creatinine in the ascites fluid pointed toward a leak, later demonstrated by the nuclear medicine scan and antegrade nephrostogram.

Paracentesis was performed and the fluid creatinine was 16 mg/dl. Two cystograms showed no evidence of a leak. A ^{99m}Tc-MAG 3 tracer nuclear medicine scan (Figure 13) was performed. Antegrade nephrostogram revealed florid extravasation of contrast from the proximal ureter. A percutaneous nephroureterostomy and internal stent were placed, and the patient's creatinine fell to 0.7 mg/dl within 5 d.

Case 7: Ajay K. Singh

A 72-yr-old diabetic man had been on hemodialysis for 8 yr, dialyzing on a 2.5 mEq/L calcium bath. A recent Kt/V was

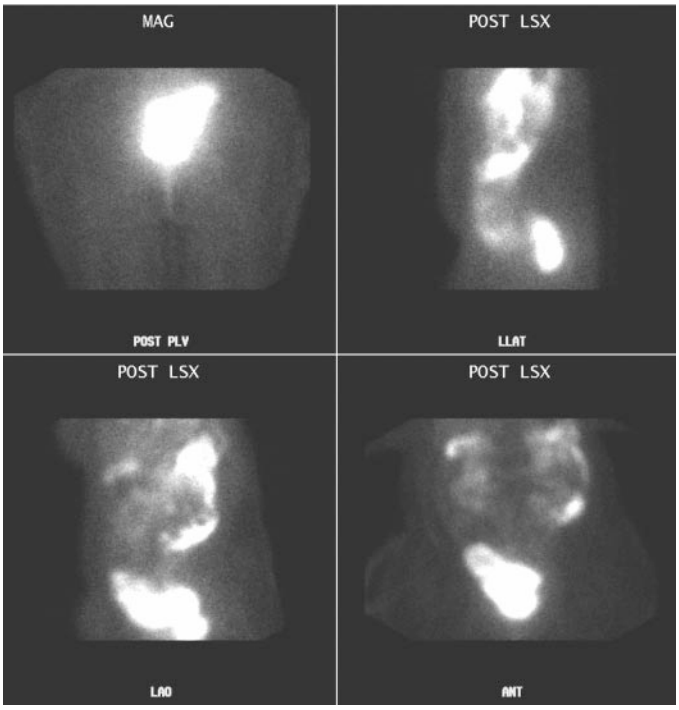

Figure 13. ^{99m}Tc-MAG 3 tracer nuclear medicine scan. Images were taken after the ^{99m}Tc-MAG 3 tracer went through the kidney, and the free radiotracer is seen tracking around and shifting with patient position changes instead of in the bladder.

1.54. He had problems with phosphorus control requiring close dietary counseling. He denied bone pain. Medications included calcium acetate 667 mg, two tablets with each meal, and calcitriol 4 μg at each dialysis treatment. The results of the lab studies are shown in Table 3.

Question 7

Which of the following statements represents the MOST appropriate management of this patient?

A. The patient should continue on his present medications; no changes are needed.

B. The patient's calcitriol dose should be doubled.

C. Calcium acetate should be stopped in 3 mo if his parathyroid hormone (PTH) level is <100 pg/ml.

D. The patient should be started on a low dose of paricalcitol to reduce the risk of a cardiovascular event or death.

Table 3. Laboratory studies: Serum electrolytes

Sodium	139 meq/L
Chloride	99 meq/L
Calcium	10.2 mg/dL
Potassium	4.9 meq/L
Bicarbonate	20 meq/L
Phosphorus	6.9 mg/dL
Intact Parathyroid hormone (iPTH)	40 pg/mL
25 (OH) D	47 ng/ml

E. The patient should stop his calcitriol and calcium acetate, and start sevelamer 1600 mg three times daily.

Discussion of Case 7

Because of the patient's calcium × phosphorous product, the calcitriol and calcium should be stopped in an effort to reduce positive calcium balance (option E). The PTH level in this patient is also quite low and would be another reason to discontinue the calcitriol and consider starting the non–calcium-containing binder sevelamer. The other options are all incorrect. This case raises the topic of the management of secondary hyperparathyroidism (SHPT) in dialysis patients. The role of calcium and phosphorus balance interfaced against vitamin D–deficiency make management of secondary hyperparathyroidism complex and frequently quite challenging.

SHPT is a multifactorial syndrome that begins early in CKD but is present in most patients with ESRD (31). Bone disease in CKD and ESRD patients frequently represents a spectrum from low- and high-turnover disease and osteomalacia and osteoporosis; a detailed discussion is beyond the scope of this review. The central abnormality is an excess secretion of PTH by the parathyroid glands. Circulating calcitriol levels begin to fall when the GFR is <40 ml/min. By the time patients have progressed to ESRD, the calcitriol level is markedly reduced. The removal of the normal suppressive effect of calcitriol on the parathyroid glands results in PTH secretion. Reduced 1α-hydroxylase activity, a consequence of worsening kidney function, results in decreased levels of calcitriol (1,25-dihydroxyvitamin D).

As a consequence of calcitriol deficiency, there is reduced absorption of calcium in the gut and reduced mobilization of calcium. In addition, excess extracellular phosphorus binds to calcium and further reduces the ionized plasma calcium concentration. Excess extracellular phosphorus induces hyperplasia of the parathyroid glands independent of calcium and calcitriol. The initial hyperplasia of the parathyroid gland is followed in later stages by nodularity with evidence of monoclonal cellular expansion. The lack of calcitriol is thought to cause downregulation of vitamin D receptors, which then promotes parathyroid chief cell hyperplasia and nodule formation. The resistance of parathyroid cells to calcitriol appears to serve

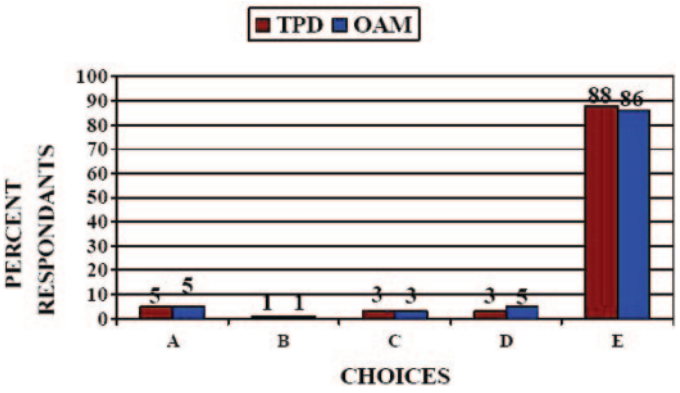

Figure 14. Answers from the membership, question 7.

as second stimulus for PTH secretion in patients with advanced CKD.

GFR declines with advancing CKD, renal phosphate excretion is reduced, and serum levels of phosphate rise. Circulating levels of phosphate are influenced by other factors: dietary phosphorus intake, intestinal absorption, and exchange with bone reservoirs. The major hormones that regulate phosphate homeostasis through these mechanisms are 1,25(OH)2D3 and PTH. A role for a novel class of proteins termed phosphatonins has also emerged (32,33). Phosphatonins are a group of proteins discovered in the characterization of a group of pathologic conditions characterized by phosphate wasting.

Management of calcium and phosphorous balance are important elements in the management of SHPT. Management of hyperphosphatemia in dialysis patients almost always involves the use of phosphate binders in addition to dietary restraint in phosphorous intake (34). Phosphorus binders taken with meals decrease absorbed phosphorus and have effects similar to dietary phosphorus restriction. Calcium-based phosphorous binders are often used (such as calcium carbonate or calcium acetate), but the dose of elemental calcium should not exceed 1500 mg/d. Use of calcium further suppresses PTH by increasing serum calcium, possibly resulting in a chronically positive calcium balance and vascular calcification. Non–calcium-based binders such as sevelamer HCl 800 mg three times daily or lanthanum carbonate 250 mg three times daily offer effective phosphorus control without the dangers of calcium loading, but are more costly than calcium-based binders (35). Maintenance of calcium $\times$ phosphorous product of <55 is recommended because of the high risk of vascular calcification. The burden of vascular calcification in the dialysis population is reflected by the higher prevalence and severity of coronary artery calcification when compared with age-matched controls in healthy subjects (36). In addition to abnormalities in serum calcium and phosphorus, risk factors for the development for vascular calcifications also include increased age, longer duration of dialysis, inflammation, hypertension, dyslipidemia, and calcium-based phosphate binders. In the Treat to Goal study, which compared calcium-based phosphate binders to the non–calcium-based phosphate binder sevelamer, (36) similar goals were achieved (serum P, Ca $\times$ P, and PTH), but coronary artery and aorta calcification increased in the group that used calcium-based binders.

Treatment with vitamin D or one of its analogs is a key element in management. One of these agents should be used whenever PTH is above the target range despite vitamin D repletion and phosphorus control (34). Vitamin D analogs reduce the stimulation of intestinal calcium and phosphorus absorption. Paricalcitol (Zemplar, Abbott Laboratories) appears to have the least effect on intestinal mineral absorption and in randomized trials had an incidence of hypercalcemia and hyperphosphatemia similar to placebo. Doxercalciferol (Hectorol, Genzyme Corp., Cambridge, MA) is a prohormone (1(OH)D2) and is metabolized constitutively by the liver to 1,25(OH)2D2, an active form of vitamin D. Other metabolites of doxercalciferol may also be formed and may account for the apparently lower incidence of hypercalcemia and hyperphosphatemia seen with this analog. Evidence from observational studies suggests there may also be a survival benefit with use of a vitamin D analog over calcitriol. The introduction of cinacalcet has heralded more effective medical therapy for refractory SHPT. Cinacalcet (Sensipar, Amgen Inc.) is the first calcimimetic approved by the US Food and Drug Administration for the treatment of SHPT in patients with CKD. Calcimimetic agents target the calcium sensing receptor to mimic or potentiate the effect of extracellular calcium on the calcium sensing receptor.

Case 8: Sharon Adler

A 45-yr-old woman without systemic systems had recurrent gross hematuria that began before age 30. Episodes were accompanied by anemia but hemolysis studies had not been done. Three recent episodes of acute renal failure, one requiring dialysis, all resolved either spontaneously or with prednisone. There was no diarrhea and no consistent drug exposure with the episodes. One episode each was preceded by sulfamethoxazole/trimethoprim or aspirin use. She had an extensive history of recreational drug use, mostly marijuana and methamphetamine, but none since the illness had worsened. She used cocaine rarely in the past, but not for many years, and she smokes tobacco. There was no family history of renal disease. She has a sister with lupus, but no nephritis. She has four children, one with Crohn's disease and one with tuberculosis. She had an appendectomy, a hysterectomy, and a cholecystectomy in the past year, and none showed changes of thrombotic microangiopathy. She developed steroid-induced diabetes mellitus associated with the treatment of the recurrent acute renal failure. She was taking a long list of medicines. The only remarkable finding on physical examination was a cushingoid appearance. Lab tests that were normal or negative included hepatitis B and C antibodies, anti-neutrophil cytoplasmic antibodies, anti-nuclear antibodies (ANA) and anti-dsDNA antibody, lupus anticoagulant, anti-SCL70, anti-Jo1, and anti–glomerular basement membrane. ADAMTS13 activity was also normal (Quest Laboratories, Lyndhurst, NJ). Her complement C3 was transiently low on one measure in August 2005 during an active episode. Two renal biopsies showed thrombotic microangiopathy. On light microscopy, the capillary walls all showed double contours. There was fibrin in the urinary space in some glomeruli and a fibrocellular crescent in some. There was acute tubular injury shown by loss of proximal tubule brush border and mitotic figures in tubular cells. In some fields, an interstitial inflammatory infiltrate was seen. Ischemic collapse of one of the glomeruli was evident by some chronicity, and there were tubulointerstitial fibrotic changes demonstrating lesion chronicity. There was fibrin in arterioles and also linearly in the glomerulus by immunofluorescence microscopy. On ultrastructural examination, there was a swollen endothelium with mesangial interposition and subendothelial fibrin. The swollen endothelial cell virtually occluded some of the glomerular capillary lumina. The histopathologic diagnosis was an acute thrombotic microangiopathy with acute interstitial nephritis and acute tubular necrosis. The underlying cause of this patient's disease was unknown.

Question 8

Which of the following pathogenetic operative mechanisms is MOST LIKELY responsible for the clinical syndrome?

A. Inhibition of von Willebrand cleaving factor protease
B. Deposition of circulating DNA–anti-DNA antibodies
C. Dysregulation of complement pathway
D. Deposition of cryoglobulins

Discussion of Case 8

The majority of respondents chose "inhibition of von Willebrand cleaving factor protease" (option A). Is this thrombotic thrombocytopenic purpura (TTP) then? The clinical features and pathogenesis of TTP have recently been reviewed (37). TTP classically presents as a pentad with microangiopathic hemolytic anemia, TTP, renal disease, central nervous system disease, and fever. Historically, TTP and hemolytic uremic syndrome (HUS) were viewed as different presentations within a single spectrum of disease. TTP is now recognized as a heterogeneous disorder that is distinct from HUS. It is defined as a syndrome associated with diminished activity of the enzyme product of the gene ADAMTS13, or von Willebrand cleaving factor protease. ADAMTS13 cleaves von Willebrand factor into small fragments, leaving these small fragments to circulate. However, when this cleavage does not occur, an "ultra-large" von Willebrand factor protein is present, which facilitates adhesion and aggregation of platelets. Attenuated function of the gene product of ADAMTS13 (*e.g.*, von Willebrand factor) is the unifying feature of all forms of TTP.

TTP displays mechanistic heterogeneity. Diminished activity of the von Willebrand cleaving factor may be caused by either the presence of a low amount of protein or the presence of an abnormally functioning protein. The latter may be the result of the presence of an inherited mutation or the *de novo* development of an antibody against the protein preventing its normal function. This patient does not have TTP, even though it is one of the more common forms of recurrent thrombotic microangiopathy, because there was no fever, no thrombocytopenia, no purpura, no central nervous system changes, no consistent drug exposure, and, most importantly, the ADAMTS13 activity was normal.

Almost no one chose lupus nephritis, and this is not lupus.

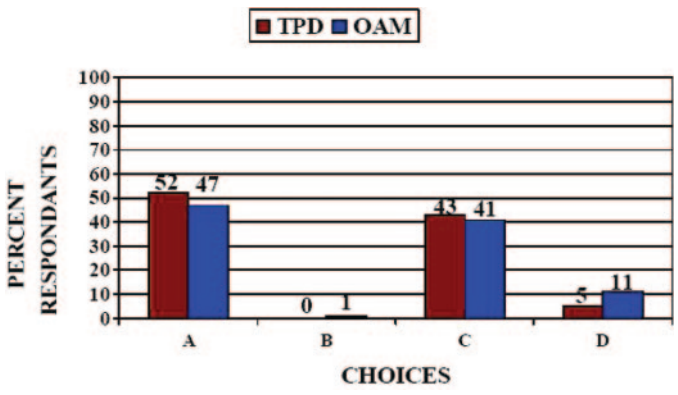

Figure 15. Answers from the membership, question 8.

She did have a sister with lupus, and she did have transient hypocomplementemia, but she lacked any of the classic clinical features of lupus. She had a normal ANA and a normal anti-dsDNA, she had no lupus anticoagulant, and no other serologic features to suggest lupus.

A few nephrologists chose cryoglobulinemia. This is unlikely to be a thrombotic microangiopathy caused by cryoglobulinemia. She did not have hepatitis C. The protocol did not mention the presence of a paraproteinemia. There was no cryoglobulin deposition on the renal biopsy, and she had normal serum complement C4 and no rheumatoid factor.

The second most popular choice, "dysregulation of the complement pathway" (option C), is another way of inferring atypical HUS. After ruling out TTP, lupus, cryoglobulinemia, and environmental triggers for the recurrent thrombotic microangiopathy (TMA) with acute renal injury, an additional diagnostic possibility was entertained. We considered that this was a complement factor H mutation or an environmentally triggered disease, but was this HUS?

There are two forms of HUS. Both forms are histopathologically identical to TTP, but neither has ADAMTS13 involvement. One form of HUS, the diarrheal form (formerly D^+ HUS), is now called typical HUS. The alternative form was designated D^- HUS but is now called atypical HUS. In typical HUS, a Shiga-like toxin binds to the colonic epithelium and renders it permeable. The toxin then circulates, binds to renal receptors, and induces local inflammation, endothelial injury, thrombosis, and acute renal failure (38). Although there is a rare case of Shiga-positive HUS that presented without diarrhea, it is extremely unlikely, and especially unlikely to occur recurrently. Thus, this is not typical HUS.

Can it be atypical HUS? Recent reviews of atypical HUS have been published (39,40). The atypical form presents with the classic triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal disease, as in typical HUS, but without a diarrheal prodrome. There are numerous nonfamilial precipitants, such as collagen-vascular disease, neoplasms, systemic vasculitis, pregnancy, infections including HIV and *Streptococcus pneumoniae*, bone marrow transplantation, and numerous medications including ciprofloxacin, calcineurin inhibitors, mitomycin-C, rapamycin, and oral contraceptives.

Recent research in this area has shown that atypical HUS is associated with complement pathway dysregulation. The best understood of these are the results of mutations in complement factor H, factor I, and membrane cofactor protein. These mutations cause complement activation and complement consumption. Complement factor H and I stabilize the C3 convertase of the alternate pathway. When these proteins are mutated or their activity is attenuated by the presence of antibodies, complement activity proceeds in an unregulated fashion. Similarly, complement factors H, I, and membrane cofactor protein cleave and inactivate surface-bound C3b and C4b. When mutated or nonfunctional, continued complement activation at cell surfaces occurs. These disorders are very uncommon, numbering in the tens (complement factor I and membrane cofactor protein) to a few hundred (complement factor H) in the literature. Some clinical features are common to all genotypes. For

instance, hypertension, acute renal failure, and neurologic complications are characteristic of all three genotypes (39). Recurrence is less likely in the transplanted kidney of patients with the membrane cofactor protein mutation (39,41).

If we return to the original question and are limited by the choices proposed in the question, by process of elimination thrombotic microangiopathy with acute renal failure would most likely be caused by atypical HUS because the ADAMTS13 was normal and there was no evidence for lupus or cryoglobulinemia.

Disclosures

None.

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