ESRD and Dialysis Case 1: Joanne M. Bargman (Discussant)

The patient is a 47-year-old woman of African-Caribbean descent who has been on conventional thrice-weekly hemodialysis since 1997. The cause of her kidney disease was hypertensive nephrosclerosis. She was refused listing for a deceased donor kidney transplant because of problems with compliance. The patient refused attempts at permanent vascular access until 2005, when she had a left brachio-cephalic arterio-venous (AV) fistula constructed. However, she developed stenoses of the left cephalic, subclavian, and innominate veins, and a right-sided tunneled internal jugular catheter was placed through which she has dialyzed for the last 4 years. Other past medical history included a ruptured appendix with surgical peritonitis in 2000 and a recent breast lump for which a biopsy was pending.

During a routine hemodialysis session, the patient complained of the sudden onset of severe headache and dizziness. This was followed by acute deterioration in her level of consciousness (Glasgow Coma Scale score 11/15) without any lateralizing signs or focal deficits. The patient was afibrile, and the vital signs were normal.

What is it about the hemodialysis session that could contribute to the sudden change in her sensorium (Figure 1)?

A. Internal jugular catheter-related sepsis.
B. Acute intravascular hemolysis.
C. Acute intracranial hypertension.
D. Pulmonary leukostasis syndrome.
E. Dialysis disequilibrium syndrome.

ESRD and Dialysis Question 1B

Which ONE of the following would be the MOST appropriate immediate action (after protecting airway) (Figure 2)?

A. Blood cultures.
B. Hemodialysis line change over a guide wire.
C. Lengthen the hemodialysis session by 1 hour to optimize solute clearance.
D. Neurology opinion.
E. Computed tomography (CT) of the brain.

Discussion of Case 1 (Questions 1A and 1B)

The correct answer for Question 1A is C. The sudden occurrence during the hemodialysis session strongly suggests that the neurologic event is related to the dialysis process itself. However, as can be seen from the choices in Question 1A, there are multiple adverse events that can occur during hemodialysis. The best choice would be an event that leads to a generalized decline in sensorium without focal neurologic deficit or other symptoms and signs, including shortness of breath or fever. The patient complained of severe headache soon after the initiation of hemodialysis, which was followed by decline in level of consciousness to precoma. Although the differential diagnosis is broad, the symptoms and signs suggest raised intracranial pressure.

What is it about the hemodialysis session that could have increased the intracranial pressure? With the attendant anticoagulation during hemodialysis, the patient is at risk for an intracranial bleed or subarachnoid hemorrhage. The patient under discussion had a newly diagnosed breast mass awaiting biopsy. If this mass were cancerous, it is conceivable that she could have had an

ESRD and Dialysis Question 1B

Which ONE of the following would be the MOST likely cause of the sudden change in her sensorium (Figure 1)?

A. Internal jugular catheter-related sepsis.
B. Acute intravascular hemolysis.
C. Acute intracranial hypertension.
D. Pulmonary leukostasis syndrome.
E. Dialysis disequilibrium syndrome.

Discussion of Case 1 (Questions 1A and 1B)

The correct answer for Question 1A is C. The sudden occurrence during the hemodialysis session strongly suggests that the neurologic event is related to the dialysis process itself. However, as can be seen from the choices in Question 1A, there are multiple adverse events that can occur during hemodialysis. The best choice would be an event that leads to a generalized decline in sensorium without focal neurologic deficit or other symptoms and signs, including shortness of breath or fever. The patient complained of severe headache soon after the initiation of hemodialysis, which was followed by decline in level of consciousness to precoma. Although the differential diagnosis is broad, the symptoms and signs suggest raised intracranial pressure.

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D. Pulmonary leukostasis syndrome.
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intracranial bleed from a metastasis. Another explanation for intracranial hypertension, however, could be related to impaired venous drainage from the brain. It was already known from previous venous mapping studies that this patient had stenoses of the left cephalic, subclavian, and innominate veins. That meant that the major drainage pathway could occur only through the right internal jugular vein to the superior vena cava, and this is where the dialysis catheter was situated. If the right-sided venous drainage were compromised, venous congestion and consequent intracranial hypertension could ensue.

Other hemodialysis-related emergencies have to be considered in a patient with a sudden decline during the treatment. Options B, acute intravascular hemolysis, and D, pulmonary leukostasis syndrome, are rare but important events that can occur during dialysis. The former is characterized by circulatory collapse accompanied by pinkish discoloration of the dialysate from erythrocyte destruction, and the latter by shortness of breath and hypoxemia (1). The patient, on the other hand, maintained good BP and had no breathing difficulties, and the organ dysfunction was clearly confined to the central nervous system. Therefore, options B and D are much less likely. Dialysis disequilibrium can lead to altered level of consciousness but would be extremely unlikely in this patient on routine dialysis for years.

Line sepsis (Option A) unfortunately remains a serious complication of hemodialysis. Well functioning arteriovenous fistulas cannot be successfully developed in many patients on hemodialysis (2), and a high percentage of patients, such as the one under discussion, continue to dialyze via a tunneled internal jugular catheter. Any patient with this kind of catheter presenting with fever on hemodialysis has a greater than 75% chance of having catheter-related bacteremia (3), even in the absence of obvious exit site infection. Signs of infection can present either off or on dialysis, but certainly the sudden onset of fever during a hemodialysis run, especially if accompanied by chills or rigors, strongly suggests line sepsis. The patient described in this case complained of headache, which could be a prodrome of sepsis, but proceeded to neurologic deterioration without fever or circulatory collapse. Despite the very high prevalence of line sepsis as a complication of hemodialysis, the absence of fever, rigors, and chills argue against this diagnosis. However, given how common line sepsis is, our first consideration (and that of many of the respondents in the quiz) was that this presentation was a particularly severe form of catheter-related sepsis.

The best answer for Question 1B is E. As discussed above, the presentation was principally neurologic, and a CT would be important to rule out intracranial bleed, metastasis, cerebral edema, and other central nervous system catastrophes.

The CT scan showed generalized edema without any focal lesions. The patient continued to have a decline in level of consciousness and needed intubation for airway protection. She was transferred to the Neuro Intensive Care Unit.

**ESRD and Dialysis Question 1C**

Which ONE of the following statements is MOST correct (Figure 3)?

A. She should be started on broad-spectrum antibiotics for a presumed central nervous system bacterial infection.

B. Anti-neutrophil cytoplasmic auto-antibodies should be urgently measured to rule out vasculitis and pulse corticosteroid given empirically.

C. She should be put on the priority list for deceased donor renal transplant.

D. She has superior vena cava syndrome and should have dilation of the stenotic veins.

E. She is intolerant of hemodialysis and should be transitioned to peritoneal dialysis.

**Discussion of Case 1 (Question 1C)**

The most correct answer is D. If the reader thought that the deterioration was a result of line sepsis, then broad spectrum antibiotics would be the obvious choice. Indeed,
in the face of such a catastrophic event, if the working diagnosis were line sepsis, it would be tempting to remove or exchange the line as more definitive therapy (reviewed in 4) in addition to antibiotics. Although vasculitis has protean manifestations, including those referable to the central nervous system, the presentation is not usually so dramatic unless there were an accompanying major bleed or thrombotic event, which was not seen on the CT scan. Furthermore, empiric high-dose corticosteroid would be risky in this patient without a working diagnosis. Answers C and E suggest a change in modality to either deceased donor kidney transplant or peritoneal dialysis. Indeed, as a “long-term” issue, the patient appears to be running out of venous access for hemodialysis, so consideration should be given to proactively transition to another form of renal replacement therapy. However, given the history of compliance problems she may not be a candidate for transplant or a home-based dialysis modality. Furthermore, the past episode of surgical peritonitis (ruptured appendix) may mean that the patient does not have a usable peritoneal cavity. In any case, modality change will not address the current problem.

The superior vena cava (SVC) syndrome results from obstruction of venous drainage from the head and upper limbs. It typically presents with edema of the face and arms, plethora, or hyperpigmentation of the face. In severe cases, there can be venous hypertension of the brain, leading to cerebral edema. The magnetic resonance imaging study in this patient showed diffuse cerebral edema and early tonsillar herniation. The cause of SVC syndrome has changed over the last decades. It was originally described when venous drainage was compressed by tumors or other diseases such as fibrosing mediastinitis from histoplasmosis or pressure from an aneurysm in syphilitic aortitis. In the modern era the cause is principally from the use of intravascular devices leading to secondary venous stenosis. Risk factors include longer duration of the intravascular devices, multiple catheter insertions, subclavian vein catheters, and left (versus right) internal jugular catheters. The latter risk can be explained by the tortuous route that the catheter placed on the left has to traverse crossing midline via the innominate vein to reach the SVC. The mechanism of stenosis is not clear, but may be related to abrasion of the device against the venous wall, leading to inflammation and consequent hyperplasia of the endothelial and vascular smooth muscle cells. Interestingly, however, venous stenosis can occur distant from the catheter itself. The patient under discussion had stenoses of the left cephalic, subclavian, and innominate veins, without ever having indwelling catheters in those locations. These venous stenoses may be a complication of distal fistulae causing high flow and turbulence in the proximal stenotic vein.

The patient underwent CT angiography, which showed complete occlusion of the right internal jugular vein and severe stenosis of the innominate vein. Pressure in the innominate vein was 75/36 mmHg (normal: 5 to 10 mmHg) proximal to the stenosis. The stenosis was crossed using a guide wire. Venoplasty was performed using a 14-mm followed by a 16-mm Atlas balloon (www.bardpv.com) (5). Repeat measurement of pressure in the innominate vein after dilation was 18/11 mmHg. After the procedure the patient's level of consciousness rapidly improved and a follow-up CT scan showed resolution of the cerebral edema.

**ESRD and Dialysis Case 2: Joanne M. Bargman (Discussant)**

The patient is a 74-year-old woman with CKD (stage 5) on the basis of diabetic nephropathy. She has been on continuous ambulatory peritoneal dialysis (PD) for the last 4 years. In her third year she had an episode of peritonitis that resolved quickly with antibiotics. Routine clinic visits in her fourth year had been unremarkable. However, one day the patient’s daughter called the PD unit to report a problem with both inflow and outflow of the dialysate. They had noticed the flow to be slower for the past 3 days, and on the day of the phone call there was very little flow observed. The patient came to the unit and had a supine x-ray of the abdomen, which showed that the PD catheter was in good position in the deep pelvis. There was a moderate amount of feces in the colon. The patient was prescribed cathartics on the assumption that constipation was the cause of the catheter malfunction. However, even with several bowel movements and follow-up radiography showing clearing of the colon, there was still very poor inflow and outflow.

**ESRD and Dialysis Question 2A**

Which ONE of the following is LEAST likely to be the cause of the catheter dysfunction (Figure 4)?

A. Constipation.
B. Intraluminal clot of the PD catheter.
C. Encapsulating peritoneal sclerosis (EPS).
D. Kink in the PD catheter.
E. Omental wrap of the catheter.

**Discussion of Case 2 (Question 2A)**

The “correct” answer is C. EPS is a rare but devastating complication of PD characterized by accelerated fibrosis and sclerosis of the peritoneal membrane and submesothelial tissue (7,8). In advanced cases “cocooning” of the bowel ensues, leading to recurrent bowel obstruction and malnutrition. Therapy with anti-inflammatory and antifibrotic agents has been used, and in the worst cases lysis of surgical adhesions and capsule release has been undertaken.

Poor catheter flow should be approached as “one-way” or “two-way” obstruction. The patient described has two-way
obstruction (no inflow or outflow). This kind of obstruction is typically caused by narrowing or obliteration of the catheter lumen. Examples include a blood clot in the lumen or a kink in the catheter itself. The more common problem is one-way obstruction, where there is satisfactory inflow of dialysis fluid, but sluggish or no outflow. The commonest causes of one-way obstruction are constipation or wrapping of the omentum around the catheter. In both instances the flow of dialysis fluid out of the catheter into the peritoneal cavity is sufficient to push the blockage (colon filled with feces, omentum) away. However, when the fluid is drained out of the peritoneal cavity, the suction draws the impediment up against the catheter, resulting in compromise to dialysate outflow. Other causes of one-way obstruction include the first-ever infusion of dialysis fluid, which may not drain because of its movement into the para-colonic gutters, filling up the peritoneal “dead-space,” and leaks of dialysate out of the peritoneal cavity (for example, into the pleural space thorough subdiaphragmatic stomata). Because the patient had two-way obstruction, the most likely diagnosis was either a kink in the catheter or intraluminal obstruction.

Case 2 additional findings: The patient, who is now anuric, has now been 4 days without dialysis. She feels well, but her BP is 150/105 mmHg, and her potassium is now 6.0 mEq/L.

ESRD and Dialysis Question 2B
ALL of the following steps could be taken EXCEPT which ONE (Figure 5)?
A. Catheter study with radiocontrast media.
B. Immediate catheter placement for hemodialysis.
C. Oral potassium exchange resin for the hyperkalemia.
D. Peritoneal dialysis catheter removal and replacement.
E. Addition of an angiotensin converting enzyme inhibitor for the hypertension.

Note: This question was not included in the Program Director’s Questionnaire.

The “correct” but wrong answer is E. Although the BP is higher than ideal, it is temporary and will resolve with resumption of dialysis. Furthermore, there is a risk that renin-angiotensin system inhibition may worsen the hyperkalemia (9,10), although this is not consistently reported (11,12). All of the other choices are reasonable for this patient. She was very opposed to temporary hemodialysis, so attempts were made to try to repair and return function to the PD catheter. The patient underwent a catheter radiocontrast study which, surprisingly, showed a patent PD catheter. Radiocontrast material injected through the catheter traveled freely into the peritoneal cavity with no evidence of intraluminal obstruction. Because we were unable to elucidate the cause of the catheter dysfunction, the patient was scheduled for an urgent PD catheter removal and replacement the next day.

ESRD and Dialysis Question 2C
In the meantime, one of the PD nurses suggests which ONE of the following (Figure 6)?
A. Instill tissue plasminogen activator (tPA) into the catheter lumen.
B. Change the catheter transfer set and connector.
C. Use a stronger cathartic.
D. Change from a coiled to a straight intraperitoneal portion of the catheter when it is replaced.
E. Use icodextrin instead of conventional peritoneal dialysis solution.

Discussion of Case 2 (Question 2C)
The correct answer is B (see Figure 7). The transfer set was removed and a flush of dialysate through the catheter showed normal inflow and outflow. The transfer set was replaced with a new one, and inflow and outflow remained unimpeded. The problem that caused the obstruction in the first place was an accumulation of fibrin in the transfer set. Interestingly, for the radiocontrast study, the radiologist removed the transfer set to inject the dye, and that is why the study showed normal inflow. However, the old transfer set was put back onto the catheter, and the problem recurred. Note that the strong majority of training program directors chose instillation of tPA, whereas the radiocontrast study showed that there was no intraluminal obstruction. The patient resumed her PD and continues to do well on this therapy.

Disclosures
None.

References
Glomerular Disorders Case 1: Fernando C. Fervenza (Discussant)

A 72-year-old white woman with a 20-year history of treated hypertension was referred for further evaluation of impaired kidney function. She was feeling well until 3 months ago when easy fatigability was noted and severe anemia (hemoglobin of 8.4 g/dl) and a serum creatinine of 2.4 mg/dl were discovered. A renal ultrasound was said to be “normal.” She received 2 units of packed red blood cells (RBCs) and was recommended to have a gastrointestinal evaluation. A colonoscopy revealed multiple polyps that were removed and proved to be benign. A week later, she noticed some blood in the stool and received another blood transfusion. The serum creatinine was now 4.2 mg/dl. Urinalysis showed 20 to 50 RBC/high-power field (hpf) and 1+ protein. Repeat colonoscopy showed a postpolypectomy ulcer with a large visible vessel protrusion for which she underwent in hospital photocoagulation. Kidney failure was believed to be of prerenal origin secondary to gastrointestinal (GI) bleeding superimposed on CKD due to long-standing hypertension. She was sent home with a serum creatinine of 3.9 mg/dl. Two weeks later, creatinine rose further to 4.6 mg/dl. She was referred for further evaluation. Physical examination is unremarkable except for edema 1+ bilaterally. The laboratory evaluation included the following: hemoglobin 10.6 g/dl, leukocytes 5.4 × 109/L, platelets 120,000 × 109/L; sedimentation rate 65 mm/h; creatinine 5.3 mg/dl, BUN 75 mg/dl, endogenous creatinine clearance (CrCl) 16 ml/min; urinalysis 20 to 30 RBC/hpf, <25% dysmorphic, protein 1.8 g/24 h; C3 109 mg/dl (nl 70 to 175 mg/dl), C4 17 mg/dl (nl 14 to 40 mg/dl); rheumatoid factor 81 IU/ml (nl 0 to 39 IU/ml), ANA 1.2 (<1.0); pANCA (anti-neutrophil cytoplasmic antibodies) +; myeloperoxidase (MPO)-ANCA 62.9 EU/ml (nl <5 EU/ml).

A renal biopsy was performed (Figure 8, A and B). Ten glomeruli were identified on serial section, with more than one being globally sclerosed. All glomeruli showed segmental capillary loop consolidation, with matrix replacement and tuft-capsular adhesions. Silver stains show segmental fragmentation of peripheral capillary loop basement membranes. No immune complex type deposits were found along capillary loop basement membranes. Viable regions of glomeruli showed focal endocapillary proliferation, with leukocyte accumulation and localized fibrin deposition. Silver stains show segmental fragmentation of Bowman’s capsule surrounding several glomeruli. Focal interstitial fibrosis with associated tubular atrophy, involved over two-thirds of the biopsy area. Focally intense lympho-plasmacytic infiltrates are identified within the expanded interstitial regions. Tubules contained red blood cells and red cell casts. The final diagnosis was a focal segmental proliferative and necrotizing glomerulonephritis, of the “pauci-immune” type.

Glomerular Disorders Question 1

Which ONE of the following therapies would you NOW recommend (Figure 9)?

A. Angiotensin-converting enzyme inhibitors (ACEi) plus low-protein diet.
B. High-dose corticosteroids plus oral or intravenous cyclophosphamide.
C. High-dose corticosteroids plus mycophenolate mofetil.
D. High-dose corticosteroids plus oral or intravenous cyclophosphamide and plasmapheresis.
E. High-dose corticosteroids plus rituximab (RTX).
Discussion of Case 1 (Question 1)

If one restricts the answer strictly to evidence-based medical practice, then the correct answer is B. However, as will be discussed below, answer D can also be accepted as correct, under certain circumstances.

ANCA-associated vasculitis (AAV) comprises three heterogeneous syndromes: Wegener granulomatosis (WG), now known as granulomatous polyangiitis (GPA), microscopic polyangiitis (MPA), and the Churg-Strauss syndrome (CSS) (1). These three multisystem disorders are characterized by necrotizing small vessel vasculitis with predilection for kidney, lungs, and peripheral nervous system involvement that share the occurrence of ANCAs in most patients at the time of initial presentation (2–5).

Untreated, systemic AAV follows a progressive course with a fatal outcome due to vital organ failure. Glucocorticosteroids (GCS) alone do not induce disease remission in the great majority of patients. This fact was initially demonstrated by Hollander and Manning who reported on 26 patients with GPA treated with GCS alone, and although mean patient survival was extended from 5 to 12 months, eventually every patient died despite high-dose GCS (6). A similar experience was describe by Fauci and Wolff who in 1973 wrote: “Although corticosteroids may decrease inflammatory reactions and improve symptoms early in the disease, they ceased to be of any benefit when the disease progressed to significant pulmonary and renal involvement.” (7). The introduction by Fauci and coworkers of combined therapy with the use of high-dose GCS and cyclophosphamide (CYC) revolutionized the treatment of AAV (8–10). The use of this combined therapy was capable of inducing remission in 65% to 90% of cases and quickly became the standard of care for patients with severe AAV (4,9–13).

However, it was soon recognized that GCS combined with CYC do not regularly cure the disease but rather turn it into a chronically relapsing disease process, with up to 50% of the patients who respond to initial therapy relapsing within the first 3 to 5 years (11). In addition, not all patients respond to CYC, and CYC is associated with serious acute and long-term adverse effects, e.g., bone marrow suppression, infection, infertility, secondary malignancies, hemorrhagic cystitis, which result in treatment-related morbidity and mortality rivaling that caused by the underlying disease (8,9).

Therefore, approaches that could minimize the toxicity of CYC have been vigorously sought. One of these approaches has been to use intravenous pulse rather than oral CYC. A recent randomized, controlled trial found intravenous pulse CYC combined with GCS equally effective as daily oral CYC combined with GCS in inducing remission in patients with newly diagnosed severe AAV with renal involvement (88.1% versus 87.7% at 9 months) (14). The absolute cumulative CYC dose in the daily oral group was approximately double that in the pulse group (15.9 versus 8.2 g; \( P < 0.001 \)), and not surprisingly, leukopenia was more frequent in the oral CYC group. There was no difference in overall mortality rate, with five deaths in the pulse CYC group versus nine deaths in the daily oral group (\( P = 0.79 \)). Thirteen patients in the pulse CYC group and six in the daily oral group relapsed after achieving remission. Unfortunately, the limited follow-up of the study precludes an evaluation of the long-term rate of remission in patients treated with pulse CYC. This is an important issue based on previous publication by the same group, suggesting that lower cumulative doses with the use of pulse CYC may come at the expenses of higher relapse rates (15).

Another approach has been to avoid CYC altogether by using mycophenolate mofetil (MMF) for remission induc-
tion in patients with AAV who have failed or are intolerant of CYC. This approach has been associated with a variable degree of success (16–18). On the other hand, in a recent uncontrolled trial MMF used in combination with GCS was capable inducing remission in 76% of patient with MPA who were MPO-ANCA positive and had mild to moderate renal involvement (19). The discrepancy among study outcomes may be related to the fact that in studies where MMF performed poorly, the majority of patients had GPA (17,18). Furthermore, these studies enrolled only patients who were either relapsing, resistant to CYC, or had contraindications for CYC use (17,18). In contrast, Silva et al. focused solely on patients with MPO-ANCA positive MPA with active renal disease, and the majority of enrolled patients were newly diagnosed and CYC-naive (19).

In recent years, a number of single case reports and small case series have suggested that targeting B cells with the use of RTX was effective in the treatment of patients with GPA, MPA, and CSS who had been refractory or had contraindications to the use of CYC (20–33). These preliminary observations have now been confirmed by two randomized controlled studies that have examined the efficacy of RTX in inducing remission in patients with severe AAV (34,35). The major findings and differences between the two studies have been recently reviewed (36). In the first study, RITUXVAS, Jones et al., randomized 44 patients with newly diagnosed AAV and renal involvement in a 3:1 ratio to receive standard GCS regimen plus either RTX (375 mg/m² intravenous weekly four times) with two intravenous CYC pulses (33 patients, the RTX group) or intravenous CYC for 3 to 6 months followed by azathioprine (11 patients, the control group) (34). Sustained remission (defined as BVAS of 0 for ≥6 months) at 12 months was achieved in 25 patients in the RTX group (76%) and nine patients in the CYC group (22%) (P = 0.68). Severe adverse events occurred in 14 patients in the RTX group (42%) and four patients in the control group (36%) (P = 0.77). It is possible that RTX used in combination with CYC leads to a higher frequency of adverse events than standard therapy with CYC, but the small number of patients involved in this trial precludes any firm conclusion. Six of the patients in the RTX group (18%) and two of 11 patients in the control group (18%) died (P = 1.00).

Simultaneously published in the same journal were the results of the RAVE trial: a multicenter randomized, double-blind, double placebo-controlled trial conducted to evaluate the efficacy and safety of RTX for remission induction in severe AAV in comparison to CYC (35). A total of 197 patients with severe GPA or MPA (3:1), all positive for PR3-ANCA or MPO-ANCA (2:1), were randomized on a 1-to-1 ratio to receive treatment with RTX (375 mg/m² intravenous weekly four times) or CYC (2 mg/kg per day, by mouth) in combination with GCS. Initial GCS treatment was the same in both groups (1 to 3 g intravenous methylprednisolone) and was followed by rigorously protocol-determined GCS tapering, aimed at complete discontinuation of GCS by month 5. Sixty-three (64%) of the patients in the RTX arm versus 52 (53%) in the CYC arm achieved the primary endpoint of the study, defined as disease remission with a BVAS of 0 in the absence of GCS therapy at month 6, a result that met the criterion for noninferiority (P < 0.001). A larger proportion of patients in the RTX group achieved the primary endpoint than in the CYC group, and the results came close to meet the criteria for superiority (P = 0.09). Similarly, 71% of the patients in the RTX group versus 62% of the patients in the CYC group reached the secondary outcome of disease remission while receiving a daily prednisone dose <10 mg. RTX was more effective than CYC in inducing remission in patients with relapsing disease. This is an important point to consider because it is in this patient population that minimization of the cumulative CYC exposure might be beneficial. Preliminary analysis of the long-term follow-up of the RAVE trial shows that the benefits of RTX therapy are maintained for at least 18 months (37).

The results of these two randomized trials demonstrate, without question, that RTX, either combined with GCS alone or with GCS and CYC, is not inferior to standard therapy for the induction of remissions in patients with newly diagnosed severe AAV and is in fact the superior to standard therapy in patients with relapsing disease. Major contraindications to the use of RTX include history of severe allergic reactions to humanized or chimeric monoclonal antibodies or murine-derived protein, active systemic infection (including hepatitis B and HIV), severe liver disease (alanine aminotransferase or aspartate aminotransferase level >2.5 times the upper limit of normal that cannot be attributed to underlying AAV disease), active malignancy or history of malignancy in the last 5 years, total white blood cell count that is <4000/mm³, platelet count that is <120,000/mm³, pregnancy, and the use of a live vaccine fewer than 4 weeks before receiving RTX.

For ethical reasons, patients with severe alveolar hemorrhage or with serum creatinine >4.0 mg/dl at the time of screening were excluded from participating in the RAVE trial, and although the RITUXVAS trial included nine patients who were dialysis dependent (five of the eight patients treated with RTX actually came off dialysis), further research is needed to evaluate the efficacy of RTX in the group of patients, as the one currently presented, whose renal disease severity recommends the use of plasma exchange (38). A large multicenter, international, open label, factorial design, randomized control trial to further evaluate the efficacy of plasma exchange in addition to immunosuppressive therapy and GCS in reducing death and ESRD in severe AAV (PEXIVAS trial ISRCTN07754794) is currently under way.

Although renal biopsy findings correlate, in general, with the renal outcome in patients with AAV, the correlation is not great (39). In the opinion of the writer, a decision regarding initiation of immunosuppression treatment in patients with AAV and renal involvement depends more on the levels of renal function before the development of AAV, the rapidity of rise in serum creatinine, and the evidence of active vasculitis on renal biopsy, as well as the overall clinical status of the patient. In the present case, renal function had been lost relatively quickly and the presence of red cell casts suggested ongoing active vasculitis. This together with the overall good clinical status of the patient helped in making a decision to treat the patient...
despite the renal biopsy finding showing severe tubulo-interstitial damage.

Treating the patient only with an ACEi + low-protein diet (option A) could be considered in patients whose disease is clearly in remission, which is not the case here. Also, the elevated serum creatinine makes it unlikely the patient could tolerate an ACEi.

High-dose corticosteroids plus oral or intravenous cyclophosphamide (option B) can be considered the most correct answer in view that the patient has systemic disease and severe renal involvement, and if we strictly abide by the fact that the MEPEX trial, which evaluated and supported the use of plasmapheresis (plasma exchange [PLEX]) in severe AAV, only included patients with a serum creatinine >5.8 mg/dl (40). The use of high-dose corticosteroids plus oral or intravenous cyclophosphamide plus PLEX (option D) might also be considered a correct choice, based on current clinical practice in a number of centers with extensive experience in treating patients with severe AAV, including the author’s own center. Indeed, given the severity and speed of decline in the patients renal function, the addition of PLEX to treatment with oral GCS and CYC could be justified by extrapolation from the results of the MEPEX trial. However, the evidence for this practice needs closer examination. Early studies of PLEX in rapidly progressive glomerulonephritis due to AAV gave mixed results (40–42). On the other hand, the MEPEX trial (38) strictly examined the benefits of the addition of PLEX versus intravenous methylprednisolone pulses to standard CYC-based therapy in 137 patients with AAV and severe renal failure (serum creatinine >5.8 mg/dl or dialysis dependent at presentation). The MEPEX trial demonstrated an absolute reduction in the development of irreversible ESRD of 24% (95% CI 6.5% to 41%) at 12 months for patients treated with PLEX. There were no demonstrable differences in mortality at 12 months among the treatment groups (25% in both). Longer-term follow-up of the MEPEX trial shows identical outcomes between the treatment groups for ESRD or death beyond 12 months (P = 0.57) (43,44). Furthermore, Walsh et al. recently published a systematic review and meta-analysis of randomized controlled trials comparing standard CYC-based care plus adjuvant PLEX in adult patients with either renal vasculitis or rapidly progressive glomerulonephritis (45). These authors concluded that there is insufficient information to reliably determine whether PLEX decreases the composite outcomes of ESRD or death. If adding PLEX would help patients with lesser degrees of renal insufficiency is not clear, and this issue is currently being evaluated in a large multicenter, international, open-label, factorial design, randomized controlled trial (PEXIVAS, ISRCTN07757494). In the present case the patient was actually treated with GCS and CYC without PLEX. Ten years later she is in complete remission of her AAV with a serum creatinine of 1.5 mg/dl and a creatinine clearance of 37 ml/min. Clearly, more research is needed to better define the role of PLEX in patients with severe AAV. PLEX may be life-saving in those patients with AAV who present with severe pulmonary hemorrhage (46). As discussed above, the use of high-dose GCS plus mycophenolate mofetil (option C) has been disappointing, and preliminary results showed success only in patients with MPA and with serum creatinine levels <3 mg/dl. Finally, high-dose GCS plus RTX (option E) was not considered as a correct answer in the present case because the RAVE trial did not include patients with serum creatinine >4 mg/dl. On the other hand, the RITUXVAS trial did include nine patients who were dialysis dependent, with six of the eight patients in the RTX group achieving sustained remission, whereas five actually came off dialysis. Thus, RTX appears to be effective in the group of patients whose renal disease severity suggests the use of PLEX, but further research is needed to define better evidence-based guidelines.

Disclosures
None.

References


Glomerular Disorders Case 2: Fernando C. Fervenza (Discussant)

A 73-year-old man was referred for evaluation of edema starting in November 2009. During this time his urine became tea-colored and foamy. He had no prior history of hypertension, but in October 2009 his systolic BP was found to be in 160 mmHg and continued to increase to 213 mmHg in January 2010. During an evaluation for hypertension a serum creatinine of 2.1 mg/dl was noted, increased from a baseline of 1.0 to 1.2 mg/dl the previous year. Urinalysis showed >50 RBC/hpf; >25% dysmorphic. Urinary protein excretion was 1.7 g/d. Fluorescence antinuclear antibody was 1:40, C4 was 15 mg/dl (normal), and C3 was 52 mg/dl (low). Renal ultrasound showed a right kidney 10.9 cm and a left kidney 12.4 cm in length with no masses, renal artery stenoses, or hydronephrosis. BP was well controlled, and a kidney biopsy was performed. Light, immunofluorescence (IF), and electron microscopy (EM) are shown in Figure 10, A through D. The IF was positive only for C3.

Glomerular Disorders Question 1

Based on these clinical and pathologic findings, which ONE of the following would be the MOST useful diagnostic test (Figure 11)?

A. Serum free light-chain assay.
B. Hepatitis B and C serology.
C. Complement Factors H, I, membrane co-factor assays.
D. Anti-streptolysin O titer.
E. Anti-double-stranded DNA antibody.

Discussion of Case 2 (Question 1)

The correct answer is C. The renal pathology in this case reveals a pattern of membranoproliferative glomerulonephritis (MPGN) by light microscopy with electron-dense mesangial and subendothelial deposits by EM, resembling type I MPGN. The IF findings are crucial for proper diagnosis. The IF is negative for IgG, kappa and lambda light chains, and is strongly positive for C3 without C1q deposition. These findings are indicative of a diagnosis of C3 glomerulonephritis (C3 GN), most often due to an underlying deficiency of complement factor H causing persisting dysregulation of activation of C3.

MPGN, or mesangiocapillary glomerulonephritis, refers to a specific histologic pattern of glomerular injury most frequently resulting from deposition of immune complexes in the mesangium and subendothelial regions (1) (see Table 1). Based on electron microscopy findings, at least three distinct pathologic patterns of injury have been described and are designated as MPGN types I, II, and III. Patients with all three types of MPGN can present in a variety of ways including hematuria (can be syphaphingitic), proteinuria, hypertension, nephrotic syndrome, or a rapidly progressive glomerulonephritis.

MPGN type I is the most common pattern of injury and is characterized by glomerular hypercellularity, increased matrix and mesangial cells, capillary endothelial swelling, and accumulation of eosinophilic material representing precipitated immune complexes. The duplication and splitting of the basement membranes are the result of new basement membrane formation due to the interposition of...
the mesangial cell, mesangial matrix, and endothelial cell debris along the subendothelial side of the lamina densa and give the glomeruli loops the appearance of “double contours.” IF usually demonstrates deposition of IgG, IgM, C3, and C4 in the mesangium and capillary walls. On EM, the deposits are primarily subendothelial (2–4).

MPGN type I can be idiopathic or secondary to a variety of diseases (4) Traditionally, MPGN has been associated with the presence of chronic infections including hepatitis C (5,6), shunt nephritis (7), and abscesses and endocarditis (8–11). Of these, hepatitis C virus (HCV) is by far the commonest with kidney involvement due to type II cryoglobulinemia in 50% to 60% of cases (6,12–15). In addition to chronic infections, autoimmune diseases such as systemic lupus erythematosus, Sjögren syndrome, and rheumatoid arthritis are also associated with persistent circulating immune complexes and the development of MPGN (16–18). More recently, monoclonal gammopathies have also been associated with development of a MPGN (19–21). In fact, Sethi et al., found that MPGN type I were as or more commonly associated with a monoclonal gammopathy than with HCV (21). As it stands, idiopathic MPGN type I appears to be a vanishing disease because a possible underlying etiology is likely to be found in the majority of cases (4).

In MPGN type II or dense deposit disease (DDD), findings on light microscopic examination can vary widely from mild mesangial hypercellularity through a membranoproliferative pattern to crescentic glomerulonephritis. C3 is present in an interrupted band pattern along the glomerular and tubular basement membranes and the basement membranes of Bowman’s capsule. C3 in the mesangial areas can result in a prominent spherule or ring-like pattern. However, the presence of confluent and extremely electron-dense intramembranous deposits within glomerular, tubular, and vascular basement membranes that are the pathognomonic feature of MPGN II or DDD. In fact, DDD is a more accurate description than MPGN II because dense deposits are diagnostic, but capillary wall thickening or hypercellularity are not always present on the biopsy (22). DDD is associated with partial lipodystrophy (Dunngan-Koeblering disease) and the presence of extensive retinal degenerative changes (drusen) on indirect retinoscopy (22). These retinal changes are commonly seen in elderly patients and rarely cause visual impairment, but it is their presence in young patients that is noticeable in cases of DDD. In type III MPGN, the deposits are both subepithelial and subendothelial, and lucent areas are present within the glomerular basement membranes.

More recently, cases with an MPGN pattern of injury and with extensive C3 deposition along the capillary walls and mesangium along with the absence of immunoglobulins deposition on IF microscopy have been described: the so-called glomerulonephritis with isolated C3 deposits or C3 glomerulonephritis (C3 GN) (23–25). On light microscopy and on IF evaluation, these cases resemble DDD but EM examination in C3 GN does not show the typical electron-dense intramembranous deposits characteristic of patients with DDD. Instead the deposits appear similar to the immune deposits noted in immune complex-mediated MPGN.

In cases of MPGN that are due to deposition of circulating immune complexes, complement is activated via the classical pathway, leading to the generation of chemotactic factors (C5a), opsonins (C3b), and the membrane attack complex (C5b-9; MAC). In these patients, classical pathway activation

### Table 1. Conditions associated with a membranoproliferative pattern of injury

<table>
<thead>
<tr>
<th>Chronic infections</th>
<th>Viral: hepatitis C, hepatitis B (rarely)</th>
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</thead>
<tbody>
<tr>
<td>Bacterial: endocarditis, infected ventriculo-atrial shunt, visceral abscesses, leprosy, meningococcal meningitis</td>
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<tr>
<td>Protozoa/other infections: malaria, schistosomiasis, mycoplasma, leishmaniasis</td>
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<td>Autoimmune diseases</td>
<td>SLE</td>
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<td>Sjögren syndrome</td>
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<td>Rheumatoid arthritis</td>
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<td>Antibodies against complement cascade proteins, e.g., C3 nephritic factor, antibody against factor H (see C3 GN)</td>
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<tr>
<td>Genetic/hereditary causes</td>
<td>Inherited complement deficiencies/dysregulation: e.g., mutations on factors H, I (see C3 GN)</td>
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<tr>
<td>Monoclonal gammopathies</td>
<td>C3 glomerulopathy (C3 GN)</td>
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<td></td>
<td>C3 glomerulonephritis</td>
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<td></td>
<td>Dense Deposit Disease (DDD)</td>
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<td>Chronic and healed thrombotic angioiopathies</td>
<td>Healing phase of HUS/TTP</td>
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<td></td>
<td>Anti-phospholipid (anti-cardiolipin) antibodies syndrome</td>
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<td>POEMS syndrome</td>
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<td>Radiation nephritis</td>
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<td>Nephropathy associated with bone marrow transplantation</td>
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<td>Drug-associated thrombotic angioiopathies</td>
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<td>Sickle cell anemia and polycythemia</td>
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<td></td>
<td>Dysfibrinogenemia and other prothrombotic states</td>
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<td></td>
<td>Transplant glomerulopathy</td>
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<tr>
<td>Idiopathic forms of MPGN</td>
<td>Need to prove that none of the conditions above are present</td>
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</tbody>
</table>

HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes; MPGN, membranoproliferative glomerulonephritis.
is reflected by the presence of a normal or low C3, low C4, and low CH50.

On the other hand, MPGN type II/DDD is not due to immune complex deposition but results from inherited or acquired dysregulation of proteins (e.g., factor H, I, MCP) involved in regulation of the alternative pathway (AP) complement cascade (Figure 12) (22, 26–28). Once activated, the AP generates effector compounds that are delivered indiscriminately to all membrane surfaces. Multiple complement regulators and inhibitors operate at every level controlling progression of the cascade and preventing self-induced damage (29). Mutations in factors H and I, or the presence of antibodies against C3 convertase enzyme (C3bBb), also known as C3 nephritic factor (C3Nef), result in persistent complement activation and development of MPGN. In this situation, patients may present with low C3, normal C4, and low CH50.

Similarly, the majority of the cases of C3 glomerulonephritis are related to the dysregulation of the alternative complement pathway due to loss of regulatory mechanisms at different steps in the alternative pathway. In the study by Servais et al., 19 patients were identified as having C3 GN and were divided into two groups based on renal pathology: group I (n = 13) was classified as showing MPGN Type I (C3GN + MPGN), and group II (n = 6) was classified as having mesangial and intramembranous C3 deposits in the absence of mesangial proliferation (C3GN without MPGN) (24). Mutations in complement regulatory genes were detected in four of six patients identified as C3 GN without MPGN (heterozygous mutations in Factor H [two patients] and in factor I gene [two patients]) and in two of 13 patients diagnosed as C3GN + MPGN (heterozygous mutations in factor H gene [one patient] and double heterozygous mutations in CD46 gene [one patient]) (24). In contrast, C3Nef was present in five of 13 patients with C3GN with MPGN and in two of six patients with C3GN without MPGN, one of whom had a factor H mutation. However, the presence of autoantibodies, e.g., against factor H or I, was not assessed and functional assays of AP activity were not performed. We have recently evaluated five cases of C3 GN (30). In all these cases, AP complement cascade evaluation showed loss of regulatory control of the AP complement cascade. Thus, AP dysfunction results in not only DDD, but in C3 glomerulonephritis, a type of MPGN that lacks the classic electron microscopic hallmarks of DDD. It is important to recognize that review of the histology of these cases suggests that dysregulation of the AP of complement produces a spectrum of morphologic patterns that range form a mesangial proliferative GN (early stages) to the classic pattern of MPGN with double contours or even sclerosing GN (late stages). Thus, the pattern of injury likely depends on the timing of the renal biopsy as the disease progresses from a proliferative to a sclerosing lesion. Failure to recognize this phenomenon, led, in the view of this author, to Servais et al. (24) to divide their patients into two groups while they likely represent a continuum of the same pathologic process.

Evaluating the AP of complement in C3GN is important not only to dissect the pathologic process, but also because it has implications for treatment. A proposed evaluation sequence for complement-mediated MPGN includes checking C3 and C4 serum complement levels, soluble membrane attack complex levels, alternative pathway functional assays, and hemolytic assays (or CH50). If abnormalities are found, then patients should be evaluated for genetic mutations and the presence of autoantibodies to complement cascade proteins (such as C3Nef or anti-CfH). A patient with positive autoantibodies may benefit from immunosuppressive therapy, whereas those cases due to genetic mutations in the complement cascade may benefit from treatment with drugs that inhibit formation of membrane attack complex, e.g., eculizumab. Eculizumab could also be used in patients with autoantibody-mediated disease. In the present case, evaluation of the AP cascade showed the presence of an antibody against factor H. Treatment with high-dose corticosteroids resulted in both improvement of serum creatinine and proteinuria 6 months after the start of therapy (serum creatinine 1.6 mg/dl; proteinuria 728 mg/dl).

The differential diagnosis of MPGN includes cases due to monoclonal gammopathy (option A), hepatitis B and C (option B), postinfectious glomerulonephritis (due to the presence of subepithelial humps; option D), and autoimmune disease, e.g., lupus nephritis (due to subepithelial, lupus nephritis, and low CH50.

**Figure 12.** In vivo, the alternative pathway (AP) is constantly being activated at low levels. The AP is tightly regulated by a number of factors including factors B, H, and I. Amplification of soluble C3bBb occurs with low efficiency because free C3b is rapidly inactivated by factors H and I. Antibodies to C3bBb, also known as C3 nephritic factor (C3Nef), protects the C3Bb from inactivation resulting in constant amplification of the AP. Similarly, mutations or autoantibodies to factors H (or I) can result in failure to control levels of C3b in the fluid phase, leading to constant amplification of AP complement proteins. (From Smith et al. [27])
subendothelial, and mesangial deposits); option E). However, in cases of MPGN due to a monoclonal protein, IF studies will show Ig and light-chain restrictions on renal biopsies (e.g., IgG and kappa light chains) (21). Similarly, chronic viral infections such as hepatitis C and B, with or without circulating cryoglobulins, are an important and common cause of MPGN (31,32). In these cases, however, the classic pathway is preferentially activated (normal or low C3, low C4). IF demonstrates deposition of IgM, IgG, and C3, kappa and lambda in the mesangium and capillary walls, and on EM, subendothelial immune complexes are usually seen and may have a fibrillar or immunotactoid pattern suggestive of cryoglobulin deposits. In regards to differentiating between C3 glomerulonephritis and a postinfectious glomerulonephritis (option D) or autoimmune proliferative glomerulonephritis (option E) are the histologic features showing the lack of immunoglobulins on kidney biopsy IF studies in the former (the diagnosis of SLE is suggested by a “full-house” pattern on IF). In the present case, the histologic pattern consisted of C3 deposition in the absence of Ig deposition, and the absence of highly electron-dense intramembranous deposits that thickened and transformed the lamina densa on EM (34) makes C3 GN the correct diagnosis. As discussed above, these cases of MPGN with C3 deposition, just like DDD, result from dysregulation of the alternate pathway of complement due to mutations or antibodies to the complement-regulating proteins, making evaluation of the complement cascade (option C) the correct answer (33).

Recent advances in the understanding of the pathophysiologic processes involved in the development of MPGN suggest that the traditional EM-based classification of MPGN as type I, II, or III may result in overlap between the types, often leading to poor understanding and evaluation of the patients, as well as inadequacies in treatment. Labeling a patient as having MPGN type I or III does not help in distinguishing between an immune complex mediated versus a complement-mediated process as cause of the disease. A classification of MPGN that is based on the pathogenic process by analysis of IF, complemented by EM, has recently been proposed (33). Based on this new classification, MPGN can be divided as: a) immune complex-mediated, or b) complement-mediated. In the opinion of the author, this new approach is more valuable for the practicing clinician because it helps direct the correct clinical evaluation and design potential disease-specific treatments.

Disclosures
None.

References


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