American Society of Nephrology Quiz and Questionnaire 2014: Glomerular Diseases

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


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

In this NQ&Q, Andrew S. Bomback presents his two challenging cases of glomerular disease. The audience responses are reviewed along with the responses of the training program directors and nephrology fellows obtained from an online questionnaire before the meeting. Andrew S. Bomback reviews essential clinical, laboratory, and renal pathology data in the two cases. He then walks the reader through the diagnosis, discusses key points in the workup, and reviews the appropriate management of these challenging glomerular disorders. We hope that this distillate from Philadelphia will serve CJASN readers well and provide fresh insights into the complexity and vibrancy of clinical nephrology for those who were unable to attend the meeting.

Case 1: Andrew S. Bomback (Discussant)
A 68-year-old woman first noticed bilateral lower extremity edema in November of 2013. She reduced her sodium intake and a week later saw her primary care physician who, in working up the edema, sent her for a urinalysis that showed 3+ proteinuria and no hematuria. Previous blood and urine tests, done in June of 2013 as part of a routine yearly visit, had been unremarkable, including no detectable proteinuria.

She was referred to a nephrologist in December of 2013. At that visit, she reported no symptoms other than edema, which persisted in both lower extremities to the ankles. Specifically, she denied fevers, anorexia, weight loss, night sweats, rash, joint pain, or change in urine color. Her past medical history included 50 pack-years of cigarette smoking with ongoing tobacco abuse, osteoarthritis, and hyperlipidemia. The only medications that she was taking at this time were an over the counter fish oil preparation and acetaminophen as needed for pain. Her family history was negative for renal disease, but her mother had died of leukemia and her sister had died of uterine cancer.

Her vital signs (including BP) were in normal range, and her physical examination was notable only for 1-mm pitting edema to the ankles. Laboratory workup revealed 10 g/d proteinuria on 24-hour collection, creatinine of 0.7 mg/dl, total cholesterol of 350 mg/dl, and albumin of...
2.6 g/dl. The following tests were either negative or in the normal range: serum protein electrophoresis, urine protein electrophoresis, antinuclear antibody, C3 and C4, hepatitis B and C, rapid plasma reagin, and myeloperoxidase (MPO) and PR3 ANCA. Renal ultrasound was unremarkable, including no evidence of renal vein thrombosis, and ultrasound of the legs showed no deep venous thrombosis. She was started on lisinopril, atorvastatin, and furosemide. A renal biopsy was performed in January of 2014, and the results (light microscopy, immunofluorescence [IF] microscopy, and electron microscopy) are shown in Figure 1.

Question 1A
What is the lesion noted on light, IF, and electron microscopy?
A. Minimal change disease
B. Membranoproliferative GN
C. Membranous nephropathy (MN)
D. FSGS
E. Amyloidosis

Discussion of Question 1A
The biopsy shows findings of MN (choice C is correct) (Figure 2). On light microscopy, the major abnormality is thickening of the glomerular basement membranes (GBMs) caused by the presence of spike formation between subepithelial immune complex deposits, which is most easily seen on the Jones methenamine silver stain (Figure 1A). IF microscopy shows dominant granular staining for IgG (e.g., 3+) (Figure 1B) with similar staining for κ- and λ-light chains along with granular staining for C3 of lower intensity (e.g., 1+). On electron microscopy (Figure 1C), subepithelial electron dense deposits and intervening spikes of GBM material are the hallmark findings of MN.

Question 1B
What is the most appropriate next step in managing this patient?
A. Request serologic testing for anti–M-type phospholipase A2 receptor (anti-PLA2R) antibodies
B. Request IF staining of the biopsy for anti-PLA2R antibodies
C. Start prophylactic anticoagulation with warfarin
D. Arrange age– and risk factor–appropriate cancer screening
E. Recommend first-line immunosuppressive therapy of steroids+alkylating agent

Discussion of Question 1B
This 68-year-old woman with newly diagnosed MN has a past medical history notable for 50 pack-years of smoking and a family history notable for malignancies in her mother and sister; she should be sent for age– and risk factor–appropriate cancer screening (choice D is correct) (Figure 3), which would include Pap smear, mammogram, colonoscopy, and noncontrast computed tomography scan of the chest. The initial step in managing a patient with newly diagnosed MN is to evaluate for secondary forms of the disease, which account for approximately 25% of patients (1,2). This evaluation is often done in the prebiopsy screening laboratory tests (e.g., positive hepatitis B serologies suggesting a viral-associated MN), and it is a component of the biopsy read (e.g., IF pattern of full-house staining indicating membranous lupus nephritis). Cancer screening is particularly important in evaluating secondary forms of MN in patients over the age of 65 years old, because up to 25% of such patients will have a malignancy...
discovered within 1 year of diagnosis (3). Tobacco abuse is another important risk factor for malignancy-associated MN (1,3).

In primary MN, circulating antibodies permeate the GBM and in the subepithelial space form immune complexes with antigens on podocyte membranes. Recently, the PLA2R was identified as the specific podocyte antigen responsible for eliciting immune complex formation with circulating antibodies. Anti-PLA2R antibodies are detected in approximately 75% of patients with primary (formerly termed idiopathic) MN across many ethnicities but are very rare in lupus-, hepatitis-, and tumor-associated MN, indicating alternative pathogenesis in secondary MN (4,5). Additional podocyte autoantigens—mitochondrial superoxide dismutase 2, aldose reductase, α-enolase, neutral endopeptidase, and most recently, thrombospondin type 1 domain-containing 7A (6–8)—have been described, potentially filling in the missing gaps in PLA2R antibody-negative disease. A genome-wide association study of primary MN conducted in three European case-control cohorts identified impressively strong associations with loci on chromosomes 6p21 (HLA-DQA1) and 2q24 (PLA2R1) (9), suggesting that genetic variants might influence the immunogenicity of the antigen (PLA2R), resulting in production of anti-PLA2R autoantibodies. These breakthroughs have established MN as a disease of autoantibodies and made the term idiopathic essentially defunct (10).

It is, therefore, tempting to use anti-PLA2R testing, available as both a serologic assay (ELISA and/or indirect immunofluorescence) and an indirect IF stain for kidney biopsy tissue (11,12), to differentiate primary from secondary forms of MN (choices A and B). However, although this type of profiling may, indeed, promise where the field is headed (13), the approach has yet to be validated in sufficiently large patient samples with sufficient longitudinal follow-up to replace the more traditional methods of screening for malignant, autoimmune, infectious, and medication-associated causes of MN. Furthermore, the

Figure 2. | Answer for case 1, question 1A: What is the lesion noted on light, immunofluorescence, and electron microscopy? The correct answer is C. TPD, Training Program Directors.

Figure 3. | Answer for case 1, question 1B: What is the most appropriate next step in managing this patient? The correct answer is D.
sensitivity and specificity of this testing for primary MN remain to be defined across all populations. The original report by Beck et al. (4) suggested a sensitivity of approximately 75% and a specificity of 100% using a serologic assay; however, subsequent reports have suggested a higher sensitivity combining serum and biopsy testing for anti-PLA2R antibodies (11), whereas other studies have reported a low rate of detection of anti-PLA2R antibodies in patients with MN with comorbidities typically associated with secondary forms of the disease, including hepatitis C, sarcoidosis, malignancy, and lupus (5,14). Therefore, the most conservative approach is to interpret a positive anti-PLA2R antibody test (whether by serum or biopsy staining) as highly consistent with primary MN; conversely, a negative anti-PLA2R antibody test denotes either a secondary form of MN or the roughly 20%-25% of primary patients who associate with a different autoantibody.

Nephrotic syndrome is a hypercoagulable state caused by a number of etiologic factors, including urinary loss of low molecular weight anticoagulants (antithrombin III and protein S) and fibrinolysis (plasminogen), hepatic overproduction of proteins in response to hypoalbuminemia of procoagulants (such as factor V, factor VIII, and fibrinogen), and increased levels of free arachidonic acid (again, in response to hypoalbuminemia), leading to increased synthesis of platelet proaggregants (e.g., thromboxane A2) (15). Of all of the nephrotic syndrome etiologies, for reasons heretofore unexplained, MN is associated with the greatest risk for clot, with some series citing up to a 35% lifetime risk for clot for patients with MN (16,17). In the largest cohort of patients with MN studied to date combining United States (n=412) and Canadian (n=486) patients, Lionaki et al. (17) showed that the risk of thrombotic events in MN increased significantly when serum albumin levels fall below 2.8 g/dl. Therefore, this patient with MN and a serum albumin of 2.6 g/dl would be considered high risk for a clotting complication, but there is no consensus agreement on whether such patients should be offered prophylactic anticoagulation (choice C). Lee et al. (18), using the same combined cohort of United States and Canadian patients, recently created a Markov decision model to evaluate the potential benefit of prophylactic anticoagulation (venous thromboembolic events prevented) relative to the risk of such therapy (major bleeds) in patients with MN (an online version of this model is available at www.gntools.com). The model is intended as a tool for clinical decision-making about prophylactic anticoagulation and influenced by both the nephrologist’s and the patient’s acceptable benefit-to-risk ratio. Prophylactic anticoagulation may not require warfarin on the basis of a retrospective analysis published by Medjeral-Thomas et al. (19), in which 143 patients with nephrotic syndrome (41% MN, 31% minimal change disease, and 28% FSGS) were treated with an anticoagulation regimen on the basis of serum albumin. Patients with albumin <2.0 g/dl received prophylactic-dose low molecular weight heparin or low-dose warfarin; patients with albumin levels of 2.0-3.0 g/dl received aspirin at 75 mg daily. During the 5 years of study, no clinical thromboembolic events occurred in patients established on prophylaxis for at least 1 week. Hence, aspirin may be a viable alternative to warfarin for this patient.

Finally, although choice E proposes an appropriate first-line immunosuppressive therapy of steroids plus an alkylating agent, at the time of biopsy diagnosis, this patient was only 2 months into the course of her disease (if we date onset at the first appearance of edema). Given the approximately 30% chance of spontaneous remission seen in MN (20), most guidelines recommend a conservative watch-and-wait approach for the first 6 months in patients with MN without renal failure or other complications of nephrotic syndrome (e.g., a thrombotic event) (21,22). Therefore, after ruling out secondary causes of MN, a regimen of steroids and an alkylating agent would potentially be recommended to this patient if her proteinuria remained in nephrotic range without evidence of a decline 5 months after her biopsy (6 months after her initial presentation). In this patient, however, her proteinuria had declined to 2200 mg/dl, and her albumin had risen to 3.2 g/dl by that point, suggesting spontaneous partial remission of disease and no indication for immunosuppression.

Case 2: Andrew S. Bomback (Discussant)

An 83-year-old man, who still works part-time as a realtor and plays doubles tennis twice a week, presented to his primary care physician concerned that he had the flu. He reported chills, poor appetite, and “just not feeling like myself” for the last week. He was ill-appearing, and his examination was notable for lack of fever, hypertension (BP of 155/95 mmHg), and trace lower extremity edema. He was sent for blood work and a chest x-ray; 4 hours later, when the serum creatinine returned at 2.9 mg/dl (by comparison, the level had been 0.9 mg/dl when last checked 3 months earlier), his primary care physician sent him into the emergency room for additional evaluation.

Repeat laboratory tests in the emergency room confirmed AKI (creatinine of 3.1 mg/dl), and urinalysis showed 3+ blood and 2+ protein. His complete blood count was within normal limits. His chest x-ray showed no acute infiltrates. A nephrologist saw him in the emergency room and sent off a panel of diagnostic tests, including serum protein electrophoresis, urine protein electrophoresis, κ-λ-free light chains, anti-GBM antibodies, MPO and PR3 ANCA, antinuclear antibody, C3, C4, hepatitis B and C, HIV, and IgG/IgA/IgM levels. Empirical fluid resuscitation was recommended with normal saline in a 1-L bolus followed by 1 ml/kg per hour. Laboratory tests repeated the following morning showed creatinine of 3.2 mg/dl with persistent hematuria and proteinuria. With the serologic workup still pending, the patient was sent for a renal biopsy in the afternoon.

Question 2A

What is the most likely diagnosis on this biopsy?

A. Anti-GBM GN
B. Myeloma cast nephropathy
C. Pauci-immune necrotizing and crescentic GN, ANCA-associated
D. Crescentic IgA nephropathy
E. Proliferative lupus nephritis
Discussion of Question 2A

The patient’s clinical picture suggests a rapidly progressive GN (RPGN), with an acute and steep rise in creatinine accompanied by hematuria and proteinuria. The differential diagnosis for RPGN is classically divided into three potential IF findings: pauci-immune staining (e.g., ANCA-mediated GN), linear staining (e.g., anti-GBM nephritis), and granular staining (e.g., lupus nephritis). Pauci-immune, ANCA-associated GN is the most likely RPGN diagnosis in all adults, and the likelihood of this diagnosis rises significantly with age (choice C is correct) (Figure 4). In a series of 235 patients ages ≥80 years old who underwent kidney biopsy over a 44-month period, pauci-immune GN was the most common diagnosis (detected in 19% of patients). This percentage rose to 33% in the subgroup biopsied specifically for the indication of AKI (23). A multicenter review of elderly patients (defined as age ≥60 years old; n=1064) and very elderly patients (defined as age ≥80 years old; n=185) biopsied for AKI reported similar prevalence rates for pauci-immune GN of 33% and 31%, respectively (24).

In this patient, as expected, the biopsy showed a pauci-immune necrotizing and crescentic GN (Figure 5). His serologic workup subsequently returned positive for MPO ANCA (titer >100 arbitrary unit/ml) and negative for PR3 ANCA antibodies. Pulmonary consult deemed bronchoscopy workup for alveolar hemorrhage unnecessary given no history of dyspnea or hemoptysis, appropriate oxygenation on pulse oximetry and arterial blood gas, unremarkable chest x-ray, and no elevations in diffusing capacity for carbon monoxide.

Question 2B

Which of the following is the most appropriate treatment plan?

A. Pulse steroids followed by oral steroids with no additional immunosuppression
B. Pulse steroids followed by oral steroids and initiation of intravenous cyclophosphamide
C. Pulse steroids followed by oral steroids and plasmapheresis
D. Pulse steroids followed by oral steroids, plasmapheresis, and initiation of intravenous cyclophosphamide
E. Supportive care alone without immunosuppression given the patient’s advanced age

Discussion of Question 2B

Of the four treatment choices offered, the regimen of pulse steroids followed by oral steroids and initiation of cyclophosphamide is the regimen supported by both Kidney Disease Outcomes Quality Initiative and Kidney Disease Improving Global Outcomes in practice guidelines for treating ANCA-associated GN (21,22) (choice B is correct) (Figure 6). The guidelines do not specifically endorse intravenous versus oral cyclophosphamide. A randomized clinical trial conducted in 42 centers in 12 European countries showed similar efficacy between these regimens, with reduced cumulative doses and lower rates of neutropenia using an intravenous regimen (25). However, a subsequent report with the long-term follow-up data from this trial cited significantly higher relapse rates in subjects treated with intravenous cyclophosphamide (39.5%) than in those treated with oral cyclophosphamide (20.8%) (26). The dose of cyclophosphamide (whether administered by the oral or intravenous route) would need to be significantly reduced in this setting given this patient’s advanced age and impaired renal function.

Plasmapheresis (choices C and D) would not be indicated in this patient given the absence of pulmonary hemorrhage and/or severe renal failure, which is defined as serum creatinine >500 μmol/L (5.8 mg/dl) or need for hemodialysis. In small, retrospective case series without controls, plasmapheresis has been shown to reduce mortality in patients with ANCA-associated GN and diffuse alveolar hemorrhage (27,28). Although these data are not particularly robust, the paucity of additional treatment options and the consequences of not treating in a disease with high mortality have overshadowed the shortcomings of the supportive evidence. In contrast, the data supporting...
the use of plasmapheresis for severe kidney failure caused by ANCA-associated GN stem from a randomized, multi-center trial of 137 patients (29). The Plasma Exchange for Renal Vasculitis (MEPEX) Trial, performed by the European Vasculitis Study Group, found that patients who received plasmapheresis had a significantly greater chance of being alive and dialysis independent at 3 (primary end point) and 12 (secondary end point) months compared with patients who did not receive plasmapheresis. Notably, this effect was essentially mediated by reduced rates of ESRD at 1 year (19% with plasmapheresis versus 43% without plasmapheresis), because overall survival between the groups was similar (73% versus 76%, respectively). A report on the long-term follow-up (approximately 4 years) of the patients from the MEPEX Study (30) likewise showed that rates of ESRD were lower in patients who received plasmapheresis (33% versus 49%, respectively), but overall mortality was similarly high (51% for both groups) over the follow-up period.

Finally, previous reports examining the course of ANCA-associated pauci-immune GN in the elderly (usually defined as 65 years of age and older) have highlighted a particularly poor prognosis for older patients, with significantly higher rates of death, ESRD, and treatment-related complications than their younger counterparts (31–33). Very elderly patients (age ≥80 years old), such as this patient, would be expected to experience even worse outcomes. However, in a retrospective cohort study of patients ≥80 years of age with ANCA-associated pauci-immune GN, the use of immunosuppressive therapy significantly reduced the risk for ESRD, death, and the combined outcome of ESRD or death. The benefit of immunosuppressive therapy was experienced early (within the first 6 months of diagnosis) in the form of reduced risk for ESRD and later (after 1 year) in the form of prolonged survival and in particular, prolonged dialysis-free survival. Receiver operating characteristic curve analysis suggested that this benefit could be expected most in very elderly patients who presented with a creatinine of 4.5 mg/dl or lower (34). Hence, this patient should be offered immunosuppression, particularly in light of his excellent functional status and his presenting creatinine well below 4.5 mg/dl.

Disclosures
None.