American Society of Nephrology Quiz and Questionnaire 2015: 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 kidney 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, training program directors of United States nephrology fellowship programs and nephrology fellows answered the questions through an Internet-based questionnaire. During the live session, members of the audience tested their knowledge and judgment on a series of case-oriented questions prepared and discussed by the experts. They compared their answers in real time using their cell phones with a special app with the answers of the nephrology fellows and training program directors. The correct and incorrect answers were then discussed after 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 clinical nephrology readers. Enjoy the clinical cases and expert discussions.

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

For most attendees at the American Society of Nephrology’s (ASN’s) Kidney Week meeting, case-based clinical nephrology talks are one of the most exciting venues of the meeting. The Nephrology Quiz and Questionnaire (NQ&Q) is the essence of clinical nephrology and represents what drew all of us into the field of nephrology. This year’s NQ&Q in beautiful San Diego, California, with full-house attendance, was no exception. The expert discussants prepared vignettes of puzzling cases, which illustrated some topical, challenging, or controversial aspect of the diagnosis or management of key clinical 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 case discussions, which serves as the main text for this article.

In this NQ&Q, Dr. Andrew S. Bomback presents his two challenging cases of glomerular disease and eloquently synthesizes the available data to make the correct diagnosis. The audience responses are reviewed, along with the responses of the training program director and nephrology fellow responses obtained from an online questionnaire administered before the meeting. This provides an interesting perspective into the thought processes of nephrologists with various levels of training and experience. Dr. 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 San Diego will serve the Clinical Journal of the American Society of Nephrology 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: Dr. Andrew S. Bomback (Discussant)

A 23-year-old man with no significant medical history presented to an emergency department with a rash of 2 weeks’ duration. Three weeks earlier, he developed subjective fevers and night sweats that lasted for 4 days. As his fever abated, he noticed gum irritation and bleeding, along with chest pain and throat irritation. He saw his primary care physician, who prescribed doxycycline and acyclovir. Shortly thereafter, he noticed a rash on both of his ankles. He initially thought it was “bug bites.” The rash progressed up his legs and looked “like blisters.” By the second week of this spreading rash, he developed pain and swelling in his ankle, knee, and elbow joints, prompting him to go to the emergency department.

He was admitted; empirical ceftriaxone therapy was started and doxycycline was continued. He also began receiving intravenous methylprednisolone, 60 mg every 8 hours. Despite these therapies, his rash continued to progress, covering his legs, arms, superior trunk, and scrotum but sparing the face, palms,
and soles. His initial laboratory results were notable for a platelet count of 135,000/microliter but otherwise normal complete blood count, normal liver function test results, and normal basic metabolic panel, with serum creatinine level of 0.9 mg/dl. Other laboratory results obtained during the first week of his hospital course included a negative sexually transmitted diseases workup (including for HIV), elevated C-reactive protein level of 100 mg/L, normal C3 and C4 complement levels, negative results for ANCAs, negative blood and urine cultures, and urinalysis showing 3+ protein and 3+ blood. He received prednisone, 60 mg daily, after 5 days of pulse methylprednisolone, with no apparent improvement in his rash.

**Question 1A**
What would you recommend for this patient?

A. Skin biopsy alone  
B. Renal biopsy alone  
C. Skin biopsy and renal biopsy  
D. Plasmapheresis  
E. High-dose intravenous immunoglobulin (IVIG)

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**Figure 1.** | Answer for Case 1, Question 1A: What would you recommend for this patient? The correct answer is A. IVIG, intravenous immunoglobulin; TPD, training program director.

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**Figure 2.** | Answer for Case 1, Question 1B: What would you recommend for this patient? The correct answer is B. IV, intravenous; TPD, training program director.
Discussion of Question 1A

This patient’s presentation suggests a diagnosis of Henoch-Schönlein purpura (HSP), also known as IgA vasculitis (IgAV). The classic tetrad of IgAV (HSP) is rash, arthralgias, abdominal pain, and kidney disease, and he presents with three of these findings. However, the diagnosis should be confirmed with tissue biopsy at this point, given the lack of response to empirical therapy with steroids, because his presentation could also fit with a non-IgA form of vasculitis. Renal biopsy or skin biopsy can confirm the diagnosis of IgAV in this patient. Skin biopsies are usually adequate to diagnose IgAV, particularly when lesions that appeared less than 24 hours earlier are sampled. With no clear clinical evidence of severe GN, it is reasonable to start with the less invasive skin biopsy in this patient (choice A is correct; Figure 1). At this point, proteinuria had not been quantified other than 3+ proteinuria on urinalysis; a quantification of proteinuria, particularly if the value had been in the nephrotic range, would have altered diagnostic decisions for this patient.

In this case, skin biopsy was performed and showed leukocytic vasculitis. Given a clinical suspicion for IgAV, immunofluorescence was requested on the skin biopsy specimen. This test demonstrated IgA and C3 in the blood vessel walls, confirming the diagnosis. Oral corticosteroids were continued at 60 mg daily, with plans for taper beginning at week 4, and the patient was discharged home. Three days after the skin biopsy, the patient had an episode of gross hematuria, prompting him to return to the emergency department. Laboratory tests showed a creatinine of 1.2 mg/dl (0.9 mg/dl at discharge), urinalysis with 3+ protein and 3+ blood, and a serum albumin of 2.4 g/dl. He was admitted, and an initial 24-hour urine protein collection showed 7000 mg protein.

Question 1B

What would you recommend for this patient?

A. Discontinue oral prednisone and start intravenous pulse steroids
B. Renal biopsy
C. Continue oral steroids and add plasmapheresis
D. Discontinue oral prednisone, start intravenous pulse steroids, and add plasmapheresis
E. Continue oral steroids and add intravenous cyclophosphamide

Discussion of Question 1B

IgAV had previously been diagnosed by skin biopsy, and the patient is already receiving corticosteroid therapy. Despite appropriate therapy, he has evidence of progressive renal involvement, with a rising creatinine level and nephrotic-range proteinuria. Renal involvement in IgAV typically is more severe in adults than in children, with higher rates of AKI and nephrotic syndrome (1). In these instances, escalation of immunosuppression may be warranted, and a renal biopsy is recommended to guide such treatment decisions (choice B is correct; Figure 2).

The renal biopsy specimen for this patient showed diffuse endocapillary proliferative and focal crescentic GN; seven of 17 glomeruli (41%) had segmental cellular crescents on light microscopy (Figure 3). As expected, immunofluorescence showed dominant IgA staining (3+) with trace to 1+ staining for IgG and C3, equal staining for κ and λ, and 2+ staining for fibrinogen. The results were consistent with IgA nephropathy (HSP nephritis), with moderate to severe activity and no significant chronicity.

Question 1C

What is the most appropriate next step in managing this patient?

A. Discontinue oral prednisone and start intravenous pulse steroids
B. Continue oral steroids and add rituximab
C. Continue oral steroids and add plasmapheresis
D. Discontinue oral prednisone, start intravenous pulse steroids, and add IVIG
E. Continue oral steroids and add intravenous cyclophosphamide

Discussion of Question 1C

The evidence base for treating this patient is limited and rooted almost exclusively in case series. The Kidney Disease

Figure 3. | Kidney biopsy specimen for patient in case 1. Light microscopy reveals a crescentic GN; shown here are two of the seven glomeruli with cellular crescents, accounting for 41% of the total 17 glomeruli sampled. Immunofluorescence microscopy (not shown) revealed dominant IgA staining. Magnification, ×400 in (A), ×400 in (B). Courtesy of Dr. Glen Markowitz, Department of Pathology and Cell Biology, Columbia University College of Physicians and Surgeons, New York, NY.
Improving Global Outcomes (KDIGO) practice guideline on GN defines crescentic IgA nephropathy as crescents in >50% of glomeruli with rapidly progressive renal deterioration and, in this setting, suggests a regimen of steroids and cyclophosphamide. This patient does not fit those criteria precisely, but this case highlights the importance of using guidelines as a launching point for clinical decisions rather than a strict treatment algorithm (2). Indeed, the >50% crescent threshold to define IgA as crescentic is based on small, retrospective studies, and this definition is explicitly ungraded in the KDIGO practice guideline. Many centers consider lower percentages of crescentic glomeruli (e.g., 25% or 33%) as a better indicator of advanced disease activity.

The biopsy, performed to see whether histologic indicators of enhanced immunosuppression were present, shows moderate to severe activity of disease with a significant crescentic burden in a patient who has been receiving corticosteroids for approximately 2 weeks, including 5 days of pulse methylprednisolone. Addition of cyclophosphamide to his regimen is warranted (choice E is correct; Figure 4) because the patient’s presentation is consistent with a crescentic form of rapidly progressive GN. Plasmapheresis and IVIG have been tried in small samples of patients with noncrescentic HSP nephritis (3,4), and rituximab is being evaluated in a study of progressive IgA nephropathy (clinical trial identifier: NCT00498368). The patient in this case is not reflected by the patient populations evaluated with these therapies.

Case 2: Dr. Andrew S. Bomback (Discussant)
A 79-year-old woman, whose medical history includes hypertension and breast cancer (treated 11 years ago with mastectomy and chemotherapy), presented to her primary care physician with new onset of edema that began about 4 weeks ago. The edema initially began in both feet and now...
has spread to her ankles. She reports no symptoms other than edema.

Her examination is notable for elevated BP and 3-mm pitting bilateral edema to the midshins. After laboratory tests show an elevated creatinine (1.31 mg/dl; eGFR, 39 ml/min per 1.73 m²) and 3+ proteinuria with no hematuria on dipstick, she is referred to a nephrologist. Repeat laboratory testing confirms the elevated creatinine and shows 24-hour urine protein excretion of 8.6 g/d and serum albumin of 2.4 g/dl. In addition, the following serologic test results are negative or within normal range: C3, C4, anti-nuclear antibody, ANCA, hepatitis B and C virus, serum protein electrophoresis, and urine protein electrophoresis. A renal biopsy is performed; the findings on light microscopy are displayed in Figure 5.

**Question 2A**
What lesion is seen on this biopsy specimen?

A. FSGS, collapsing variant
B. Membranous nephropathy  
C. FSGS, tip-lesion variant  
D. Amyloidosis  
E. Minimal-change disease

Discussion of Question 2A
The biopsy specimen shows FSGS, tip-variant, also known as glomerular tip lesion (GTL) (choice C is correct; Figure 6). This variant is marked by a segmental lesion at the tubular pole, adjacent to the origin of the proximal tubule. The biopsy specimen in this case fits the original description of the GTL, which reported that the remaining glomeruli show no alterations except for diffuse podocyte effacement on electron microscopy, akin to the findings of minimal-change disease (5). The Columbia classification of FSGS uses less restrictive criteria and defines the tip variant as having the presence of at least one tip lesion in the absence of collapsing lesions or perihilar sclerosis (6). Hence, the tip variant may still contain other glomeruli with segmentally sclerotic lesions.

FSGS is rarely found on biopsy specimens from elderly (usually defined as ≥65 years of age) and very elderly (usually defined as ≥80 years of age) patients; when detected, the lesion is usually felt to be a secondary process (7). The clinical history of this case—a very elderly patient presenting with nephrotic syndrome and AKI—rather suggests minimal-change disease, the most common biopsy finding when patients in this age range undergo biopsy for nephrotic syndrome (8). However, the clinical presentation of GTL mimics minimal-change disease with usually acute onset or short duration of full nephrotic syndrome. As with minimal-change disease, particularly in older patients, GTL can present with AKI that resolves with remission of nephrotic syndrome (9), presumably due to a hemodynamic insult in the setting of hypoalbuminemia.

Question 2B
Which of the following is the most appropriate treatment plan in this 79-year-old patient?

A. Conservative therapy (angiotensin-converting enzyme inhibitor or angiotensin receptor blocker) alone
B. High-dose oral prednisone (1 mg/kg daily or 2 mg/kg every other day) for 8–12 weeks, then taper
C. Low-dose oral prednisone (0.5 mg/kg daily or 1 mg/kg every other day) for 8–12 weeks, then taper
D. Cyclosporine, 3.5 mg/kg per day, or tacrolimus, 0.1 mg/kg per day, divided into two daily doses, to avoid steroids
E. Rituximab, 375 mg/m², once weekly for four doses

Discussion of Question 2B
Immunosuppressive therapy is indicated for treatment of FSGS in the presence of nephrotic syndrome. The GTL variant of FSGS is almost always associated with nephrotic-range proteinuria and hence obviates the question of distinguishing primary from secondary forms of FSGS (the latter of which would not be treated with immunosuppression). Tip variant is the most treatment-responsive FSGS lesion, with remission rates approaching 80%. In contrast, remission rates for the collapsing variant of FSGS are typically 10%–15%, and rates for the not otherwise specified FSGS lesion fall in the 30%–40% range (10,11). The concomitant AKI makes treatment even more imperative in this case. First-line therapy would be prednisone at a dose of 1 mg/kg per day (or 2 mg/kg every other day) for 8–12 weeks, followed by a taper (choice B is correct; Figure 7). Data on the safety of a high-dose prednisone regimen in the elderly and very elderly population are lacking, and a lower dose of prednisone might reduce the risk of steroid-associated adverse effects in this population. However, a low-dose oral steroid regimen has been consistently shown to have a lower remission rate than treatment with high-dose prednisone (Figure 8) (12–22). Cyclosporine and rituximab are generally reserved for steroid-resistant or steroid-dependent cases of FSGS and, excepting a clear contraindication to steroids, should not be used as first-line therapy.

Disclosures
None.

Figure 8. | Remission rates with steroid therapy for FSGS. A high-dose prednisone regimen (A) has consistently shown about twice the rate of response compared with a low-dose prednisone regimen (B) when treating adults with FSGS and nephrotic syndrome.
References


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