American Society of Nephrology Quiz and Questionnaire 2013: Glomerulonephritis

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Abstract
The Nephrology Quiz and Questionnaire (NQ&Q) remains an extremely popular session for attendees of the Annual Meeting of the American Society of Nephrology. As in past years, the conference hall of the 2013 meeting was overflowing with interested audience members. Topics covered by expert discussants included electrolyte and acid-base disorders, glomerular disease, ESRD/dialysis, and transplantation. Complex cases representing each of these categories, along with single best answer questions, were prepared by a panel of experts. Before the meeting, program directors of United States nephrology training programs answered questions through an Internet-based questionnaire. A new addition to the NQ&Q was participation in the questionnaire by nephrology fellows. To review the process, members of the audience test their knowledge and judgment on a series of case-oriented questions prepared and discussed by experts. Their answers are compared in real time using audience response devices with the answers of nephrology fellows and training program directors. The correct and incorrect answers are then briefly discussed after the audience responses and the results of the questionnaire are displayed. This article recapitulates the session and reproduces its educational value for CJASN readers. Enjoy the clinical cases and expert discussions.

Introduction: Mark A. Perazella and Michael 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. The 2013 NQ&Q in Atlanta, with full-house attendance, was no exception. Each of the discussants prepared vignettes of puzzling cases, each illustrating some topical, challenging, or controversial aspect of the diagnosis or management of various areas of nephrology. These eight interesting cases were presented and eloquently discussed by our four expert ASN faculty. Subsequently, each discussant prepared a manuscript summarizing his or her discussion of the cases, which serves as the main text of this article.

In this NQ&Q, Dr. Fernando Fervenza presents his two challenging cases of glomerular disease and discusses the appropriate diagnosis and management of these cases. The audience responses are reviewed along with the training program director and nephrology fellow responses obtained before the meeting, giving an interesting perspective into the thought processes of nephrologists with varying levels of training and experience. Dr. Fervenza reviews essential clinical, laboratory, and renal pathology data and walks the reader through the diagnosis and appropriate management of two complicated and challenging glomerular disorders. Overall, this event was an educational experience for all who participated. We hope that this “distillate” from Atlanta will serve CJASN readers well and provide some fresh insights into the complexity and vibrancy of clinical nephrology for those who were unable to attend the meeting.

GN Case 1: Fernando C. Fervenza (Discussant)
A 45-year-old man with a history of hypothyroidism, primary sclerosing cholangitis, and ulcerative colitis, and a baseline creatinine of 1.0 mg/dl was evaluated in July 2007 for sudden onset of nephrotic syndrome (NS). A kidney biopsy was performed and showed minimal change disease (MCD) and acute tubular necrosis. After the biopsy, the serum creatinine concentration continued to rise to 5.8 mg/dl, and the patient was started on dialysis. Methylprednisolone (1 g, twice intravenously) was initiated followed by 1 mg/kg per day of prednisone orally. After two dialysis sessions, kidney function started to recover. Prednisone was tapered and discontinued by November 2007. Urine protein excretion fell to <100 mg/24 h. In February 2008, the patient relapsed with proteinuria of 9.7 g/24 h. Remission was induced with oral prednisone and the patient was started on cyclosporine with a plan to wean off steroids. However, he could not tolerate cyclosporine because of a severe headache despite dose reduction, and it was discontinued in April 2009. In May 2009, the patient developed another acute relapse with proteinuria of 12.1 g/24 h and his serum creatinine increased to 3.1 mg/dl. A repeat kidney biopsy showed only MCD and acute tubular necrosis. Renewed treatment with high-dose steroids induced remission but was complicated by the
development of diabetes mellitus. The patient was then started on 150 mg/d oral cyclophosphamide for 3 months with steroid tapering. Cyclophosphamide was discontinued in January 2010, but was followed by a relapse 2 weeks later. The patient was instructed to return to the previous regimen of 150 mg/d oral cyclophosphamide and oral prednisone, resulting in a complete remission. In April 2011, cyclophosphamide was stopped. However, in December 2011, the patient had another relapse with proteinuria 7.8 g/24 h. His serum creatinine was 1.1 mg/dl.

Question 1
Once remission has been induced with high-dose prednisone, which of the following would give this patient the best chance for sustained remission without corticosteroids?

A. Cyclophosphamide 1 mg/kg per day for 3 months
B. Cyclophosphamide 2 mg/kg per day for 6 months
C. Sirolimus 5 mg/d adjusting dose for whole blood trough concentration of 16–24 ng/ml
D. Mycophenolate mofetil (MMF) 1000 mg twice daily, orally
E. Rituximab 1 g intravenously on day 1 and day 15

Discussion of Case 1
The patient in this case has MCD with frequent relapses. Of the options provided, treatment with rituximab provides the greatest likelihood of sustained remission without continued glucocorticoid therapy while minimizing the risks of complication from treatment (choice E is correct) (Figure 1).

MCD accounts for the majority of cases of idiopathic NS in children and up to 20% of cases of idiopathic NS in Caucasian adults (1). Corticosteroid therapy is the treatment of choice, leading to complete remission of proteinuria in >90% of cases (2). However, >50% of patients who respond to corticosteroids will have a relapse, and up to 25%–30% of patients will have frequent relapses or become steroid dependent (3,4). Some patients without significant corticosteroid-related toxicity may be maintained in remission with low-dose prednisone (e.g., 15 mg every other day). For patients who cannot tolerate continued corticosteroid therapy, alternatives include the use of alkylating agents, antimetabolites, and calcineurin inhibitors. Although these agents may be beneficial, some patients respond poorly or not at all. In addition, the use of these agents may be complicated by the development of significant side effects, especially when these agents are used in combination, as discussed below. As such, alternative therapies that can induce long-term remission with a favorable safety profile have been sought.

Rituximab, a chimeric mAb directed against the B lymphocyte–restricted cell-surface protein CD20, has been successfully used in the treatment of a number of autoimmune renal diseases affecting the kidney, including ANCA-associated vasculitis and membranous nephropathy (5). Two case reports—one by Gilbert et al. (6), of a 15-year-old girl with high-dose steroid-dependent MCD and one by Francois et al. (7), of a 22-year-old woman with multirelapsing MCD—showed that rituximab can be effective in steroid-dependent and/or frequent-relapsing MCD.

These initial findings were corroborated by a number of other case reports and retrospective and prospective studies (8–23). Rituximab generally induced sustained remission allowing for a marked reduction or discontinuation of corticosteroids and/or immunosuppressive drugs in patients with MCD who were steroid dependent or frequent relapers (24). Rituximab appears to be more effective when given to patients in complete remission, but a few nephrotic patients also responded (18). It also appears to be beneficial to patients who are steroid resistant (10,11,25).

The beneficial effect of rituximab was confirmed in two recent studies (26,27). Bruchfeld et al. reported the long-term follow-up of 16 patients (9 women, 7 men; aged 19–73 years) with frequent-relapsing, steroid-dependent
patients were nephrotic and yet responses were high during a relapse? Some studies suggest that rituximab is indicated during a relapse. In a study by Bruchfeld et al., the majority of patients were nephrotic or near-nephrotic before rituximab treatment. Thirteen patients (81%) responded to therapy with complete remission. Two patients had a 50% and 70% reduction in proteinuria, respectively. One patient did not respond. Follow-up was 12–70 months (median 44 months) and seven patients relapsed after 9–28 months. Relapses coincided with recovery of circulating B cells, but not all patients relapsed upon B-cell reconstitution. Four patients were retreated with rituximab and went back into remission. In three patients, relapses were minor and responded to a reduction of low-dose corticosteroids. Adverse events were limited and infusion-related. At the latest follow-up, 66% of the patients who responded to rituximab were no longer taking any maintenance immunosuppressive therapy. Ruggenenti et al. evaluated the effect of rituximab followed by withdrawal of maintenance immunosuppression in 10 children and 20 adults with MCD and mesangial proliferative GN (n=22) or FSGS (n=8) who had suffered ≥2 relapses over the previous 12 months and were in steroid-induced remission since 1 month. Participants received one (n=28) or two doses (n=2) of rituximab (375 mg/m² each) (27). At 1 year, all patients were in remission: 18 were treatment free and 15 had never relapsed. The total number of relapses and the per-patient median number of relapses decreased from 88 to 22 and from 2.5 to 0.5 after rituximab treatment, respectively, regardless of age or histologic diagnosis. The per-patient steroid maintenance median dose also decreased from 0.27 mg/kg (range, 0.19–0.60) to 0 mg/kg (range, 0–0.23) and the median cumulative dose to achieve remission decreased from 19.5 mg/kg (range, 13.0–29.2) to 0.5 mg/kg (range, 0–9.4). No adverse events were reported in children but eight serious adverse events occurred in six adults. All events occurred in patients during concomitant therapy with steroids or other immunosuppressive medications and the patients recovered fully.

Taken together, these studies reinforce the role of rituximab as a corticosteroid-sparing agent in patients with challenging frequently relapsing/steroid-dependent MCD. However, a number of questions remain to be answered. (1) Who is a candidate for rituximab? (2) What is the optimal dosing strategy (e.g., the “autoimmune protocol” of 1 g rituximab twice, 2 weeks apart; the “lymphoma protocol” of 375 mg/m² rituximab weekly for 4 weeks; or the B cell–driven approach of 375 mg/m² rituximab once)? In some studies, the duration of B-cell depletion is not different in patients receiving one or two rituximab infusions versus those receiving three or four rituximab infusions (22,25), but others found longer B-cell depletion with larger doses (19). (3) Should the initial rituximab treatment be given after remission is induced or during a relapse? Some studies suggest that rituximab is more effective when given to patients in remission (22); however, in a study by Bruchfeld et al., the majority of patients were nephrotic and yet responses were high (26). (4) Who should be retreated? In some patients, remission is long lasting so scheduled retreatment would be unnecessary. (5) When should a relapse after rituximab treatment be retreated? Should it be treated at the first sign of B-cell recovery? Or should it be scheduled (e.g., every 6 months regardless of B-cell count)? B-cell reconstitution can occur without triggering a clinical relapse but relapses have been documented in patients who are still B-cell depleted (15,22). Although the majority of relapses have concurred with B-cell recovery (9,11,14,18,23), no B-cell threshold for relapse has been identified. B-cell numbers at the time of relapse varied greatly between individuals. In one study, age at diagnosis was the strongest predictor of drug-free remission for 6 and 12 months (19). Ravani et al. reported that each year of age was associated with a 71% greater probability of prednisone-free and 31% of calcineurin inhibitor–free remission for 6 and 12 months, respectively (19), but results differ (27).

How rituximab works in MCD is unknown. A number of clinical observations suggest that MCD is mediated by T-cell abnormalities (28,29). On the other hand, a number of clinical and immunologic findings suggest that B cells are also involved in MCD (30). Patients with SLE, a B cell–related autoimmune disease, may develop MCD, which further supports a role for B cells in MCD. Cyclophosphamide, which will be discussed below, has important effects on B-cell function and suppresses the secretion of Igs. However, a role for T cells cannot be discarded because rituximab may affect T-cell function. Rituximab has been approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, a classic T cell–mediated disease. Furthermore, a small population of T cells do express CD20 (31). Finally, increased expression of CD80 on podocytes has been associated with development of proteinuria (32). CD80 is expressed on antigen-presenting cells, natural killer cells, and B cells and provides a costimulatory signal for T cells by binding to the T-cell receptor CD28. In patients with MCD, there is podocyte induction of CD80, and impaired downregulation of CD80 expression may result in persistent CD80 expression due to an abnormal CTLA-4 response by regulatory T cells, resulting in foot process fusion and proteinuria. B cells are important in the induction of inflammatory cytokines; antigen presentation to T cells, dendritic cells, and macrophages; T-cell activation; and generation of ectopic lymphogenesis (33). Treatment with rituximab may directly or indirectly restore T-cell function in patients with MCD.

Although the side effect profile of rituximab has been remarkably good, a number of potential complications should be considered. Patients treated with rituximab can develop Pneumocystis jiroveci pneumonia (PCP) and the infection has a high mortality rate (about 30%) (34). A recent study from the Mayo Clinic evaluating patients treated with rituximab from 1998 to 2011 reported that 30 of 230 patients developed PCP (35). Green et al. advocate routine prophylaxis in patient populations in which the overall incidence of PCP exceeds 3.5% (36). Although the true incidence of PCP in patients receiving rituximab is unknown, I argue that the risk is real and is associated with a high mortality rate, and physicians should use their judgment while carefully weighing the risk of the prophylaxis regimen against the potential risks of PCP while
these patients remain B-cell depleted. Progressive multifocal leukoencephalopathy (PML), a fatal neurologic condition, has been reported in two patients with SLE treated with rituximab, resulting in an official boxed warning from the FDA. No case of PML has been reported in patients with MCD treated with rituximab, whereas >24 cases of PML are known in patients with SLE and ANCA-associated vasculitis who have never received rituximab (37). Nevertheless, the risk of PML is real and needs to be discussed with the patient before initiating treatment with rituximab. There is also a risk for hepatitis B reactivation that led to a black box warning by the FDA. Hepatitis B status should be checked in every candidate for rituximab (38).

Regarding the use of cyclophosphamide, a number of observational studies suggest that approximately 75% of adults with frequently relapsing steroid-dependent MCD will achieve sustained remission with the use of this medication (3,39–41). The recommended dosage of cyclophosphamide is 2 mg/kg per day orally for 12 weeks because a shorter course has been associated with an increased rate of relapse (40,42). Intravenous cyclophosphamide is less effective in inducing long-term remission (43). Remission should first be induced with corticosteroids followed by cyclophosphamide and a steroid taper. However, cyclophosphamide is associated with significant short- and long-term side effects, including bone marrow suppression, leukopenia, infection, malignancy, and infertility. It is therefore prudent that all patients taking cyclophosphamide have complete blood work performed once per week. The dose of cyclophosphamide should be adjusted to maintain a total white blood cell count >3500/mm³ and an absolute neutrophil count >1500/mm³. In addition, to prevent infection with *P. jiroveci*, all patients should receive prophylaxis with either sulfamethoxazole/trimethoprim or an alternative agent.

The long-term risk of malignancy with cyclophosphamide is substantial and is commensurate with the cumulative cyclophosphamide doses received (36 g). By contrast, in children with MCD (n=293 patients) who were treated with cumulative cyclophosphamide doses <36 g, the incidence of malignancies associated with cyclophosphamide exposure in a cohort of 293 patients with granulomatosis with polyangiitis (44). The risk of malignancy was not increased in patients who never received cyclophosphamide or were treated with cumulative cyclophosphamide doses ≤36 g. Another major concern limiting cyclophosphamide utility is related to its gonadal toxicity. Data indicate that ovarian failure is seen in female patients of any age receiving a cumulative dose of as little as 28 g of cyclophosphamide (45). Although male infertility is harder to assess, studies have demonstrated that doses >7.5 g/m² of cyclophosphamide can result in permanent oligospermia (46). Both female and male patients of child-bearing age should be offered cryopreservation of ova and sperm before treatment with cyclophosphamide. For these reasons, prolonged therapy (>12 weeks) or >2 courses of cyclophosphamide should be avoided.

The calcineurin inhibitors cyclosporine or tacrolimus are alternatives for patients who are steroid dependent, relapse after cyclophosphamide, or have contraindications for cyclophosphamide (39,47–52). Approximately 70%–90% of patients with MCD who are frequent relapsers or are steroid dependent can be maintained in partial or complete remission with calcineurin inhibitors (53). Cyclosporine at a dosage of 3.5–5 mg/kg per day orally (microemulsion preparation of cyclosporine may allow for lower doses) or tacrolimus at a dosage of 0.1 mg/kg per day orally can be considered (49). In the case of tacrolimus, I would like to point out that I never start patients on that dose because of concerns with acute nephrotoxicity. Instead, I give two-thirds of the target dose initially and then adjust the dose to target every 7–14 days while monitoring for side effects, and I recommend the same precautions with cyclosporine (i.e., start at the lower dose with subsequent adjustments). Some authors recommend concomitant use of low-dose prednisone; however, in my opinion, cyclosporine or tacrolimus can be used as monotherapy. Unfortunately, >50% of the patients who respond to cyclosporine or tacrolimus will relapse once the calcineurin inhibitor is discontinued. Relapses are more commonly observed if cyclosporine is used for short intervals (39,48), whereas sustained remission is more likely in patients treated for 1 year or longer (47). Therefore, the recommendation is to maintain cyclosporine or tacrolimus therapy for at least 1 to 2 years followed by a gradual taper. Nevertheless, some patients will relapse and steroid dependence may be replaced by calcineurin inhibitor dependence requiring years of treatment and the associated risk of nephrotoxicity (4). Although the risk of nephrotoxicity can be minimized by lowering the maintenance dose of cyclosporine (47), it still can occur even with the use of low cyclosporine doses (54,55).

MMF may also be beneficial in frequent relapsers or in patients with steroid-dependent MCD (3,56–62). Choi et al. retrospectively reviewed the outcome in seven adults with MCD who were steroid and/or cyclosporine dependent and had been treated with MMF for 6–26 months (56). One patient was resistant to MMF, four patients had sustained remission off steroids, and two patients relapsed. In children, Bagga et al. prospectively examined the efficacy of long-term therapy with MMF as a steroid-sparing agent in children with MCD (n=10) or FSGS (n=3) who were steroid dependent (58). Patients were administered MMF and decreasing doses of alternate-day prednisolone for a mean of 11.8 months. After a mean follow-up of 17 months, relapse rates decreased from 6.6 to 2 episodes per year during MMF treatment. Treatment with MMF resulted in a reduction of the mean prednisolone dose from 0.7 to 0.3 mg/kg per day. Fourteen patients showed a ≥50% reduction in relapse rates and prednisolone therapy could be discontinued for ≥6 months in eight patients. After discontinuation of MMF, 68.4% of patients had an increased frequency of relapses and recurrence of steroid dependence, requiring other medications. The majority of the data originate from studies in children; therefore, extrapolation of the findings to the adult population should be done with caution.

In the present case, the patient had two previous courses of cyclophosphamide and additional courses of...
cyclophosphamide (the dose in choice A is inadequate and the course in choice B is too long) that would likely add to long-term toxicity. Sirolimus (choice C) should not be used in patients with proteinuria due to the risk of nephrotoxicity and AKI in these patients (63,64). MMF (choice D) is the second-line agent in children and can certainly be considered in an adult, although a great number of patients need concomitant low-dose corticosteroid maintenance therapy to remain in remission. Data obtained on >250 patients treated with rituximab demonstrate that this drug represents a new therapeutic option. Recent Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines recommend that rituximab be considered in children who are steroid dependent or frequent relapsers despite optimal maintenance therapy and/or have developed significant immunosuppression side effects (2). However, the KDIGO guidelines do not mention the use of rituximab in the treatment of adults with frequent relapsing or steroid-dependent MCD. Part of the problem is that the KDIGO guidelines were published in June 2012, but the actual document was finalized much earlier (thus, at a time when the majority of the information regarding the use of rituximab in MCD was not available to KDIGO members). The case is similar to the KDIGO recommendations for ANCA-associated vasculitis; the Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis trial and the Randomised Trial of Rituximab versus Cyclophosphamide for ANCA-Associated Renal Vasculitis had not yet been published, and the Kidney Disease Outcomes Quality Initiative (KDOQI) panel comments on the discrepancies of KDIGO recommendations in the face on current knowledge (65). Considering that the patient in the above-described case is an adult, I would argue that the number of adult MCD patients who have been treated with rituximab in the published literature vastly outnumbers those treated with MMF. In fact, the KDOQI discussion of therapy of adults states the following: “MMF in this setting is supported only by limited case reports” (65). This does not void the fact that prospective controlled studies and long-term follow-up are required to confirm the efficacy and safety of rituximab in the treatment of patients with MCD.

GN Case 2: Fernando C. Fervenza (Discussant)

A 66-year-old Caucasian man was referred for 3+ proteinuria and hematuria found by dipstick urinalysis on a routine preoperative evaluation before elective orthopedic surgery. His past medical history included hypertension, hyperlipidemia, and gout. Several members of his family are hypertensive, and at least one brother has impaired kidney function. His medications included 25 mg oral hydrochlorothiazide once a day and 20 mg oral simvastatin once a day. He does not smoke. On physical examination, the patient looks healthy. His BP is 140/80 mmHg and his pulse rate is 70 bpm. The patient’s body mass index is 29 kg/m². The head and neck examination are normal. The patient’s chest is clear to auscultation; a first and second heart sounds are present with normal rate and rhythm. His abdomen shows no hepatosplenomegaly or masses. There is no peripheral edema.

The patient’s laboratory results are as follows: hemoglobin, 14.7 g/dl; leukocytes, 6.0 × 10⁹/L; platelets, 225 × 10⁹/L; serum creatinine, 1.52 mg/dl; eGFR, 47 ml/min per 1.73 m²(calculated by the Chronic Kidney Disease in Epidemiology Collaboration equation); electrolyte panel, normal; glucose, 93 mg/dl; serum albumin, 4.4 g/dl; total cholesterol, 200 mg/dl; LDL cholesterol, 122 mg/dl; serum protein immunofixation, negative for monoclonal proteins, HIV and hepatitis B and C serology, negative; ANCA, negative; and C3 and C4 complement levels, normal. Urinalysis shows protein (3+), with positive blood. Sediment shows 3–10 red blood cells per high-power field (25% dysmorphic) and 1–3 white blood cells per high-power field (with occasional fatty casts). Proteinuria is 6.5 g/24 h. A kidney biopsy is performed and the results are shown in Figures 2 and 3.

Question 2A

Which ONE of the following is the MOST likely lesion accounting for the clinical picture?

A. MCD
B. Membranous nephropathy
C. FSGS
D. C3 GN
E. Mesangial proliferative GN

Figure 2. Light microscopy examination for the patient in case 2. (A) A perihilar segmental scar. (B) Electron microscopy showing focal foot process effacement. Original magnification, ×40 in A; ×8000 in B. Courtesy of Dr. Sanjeev Sethi, Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota.
Discussion of Case 2, Question 2A

The presence of a sclerotic lesion on light microscopy (LM), together with presence of focal foot process effacement on electron microscopy (EM), points to the diagnosis of a FSGS lesion (choice C is correct), whereas the presence of a segmental scar on LM excludes MCD (choice A is incorrect). Immunofluorescence shows negative C3 staining and EM does not show subepithelial deposits so it cannot be MN (choice B is incorrect). IgG staining was not shown but it would be positive in MN. C3 GN is characterized by predominant C3 staining on immunofluorescence with little or no Igs. Negative C3 staining on immunofluorescence rules out this option (choice D is incorrect). The absence of mesangial proliferation, negative immunofluorescence, and no deposits on EM also rules out mesangial proliferative GN (choice E is incorrect) (Figure 4).

Question 2B

In this patient, which of the following therapies would you recommend?

A. Losartan 50 mg/d, orally
B. Prednisone 1 mg/kg per day, orally for >4 months
C. Cyclosporine 3.5–5 mg/kg per day orally, with trough blood levels of 125–175 ng/ml
D. MMF 1g, orally, twice a day
E. Sirolimus 5 mg/d, orally, with trough blood levels 12–20 ng/ml

Discussion of Case 2, Question 2B

In this patient, the absence of NS and focal foot process effacement on EM makes FSGS most likely to be secondary and should be treated conservatively, aiming to control BP and reduce proteinuria using inhibitors of the renin-angiotensin system rather than immunosuppressive therapy. For this reason, treatment with losartan is the most appropriate of the options given (choice A is correct) (Figure 5).

Focal sclerosis is a pattern of glomerular injury defined histologically by the presence of sclerosis in parts (segmental) of some (focal) glomeruli (FSGS). FSGS is a lesion and not a disease; the finding of an FSGS lesion is the start of an exploratory process leading to a diagnosis, and is not an end in itself. Recognizing this fact, FSGS has been traditionally divided into primary and secondary (adaptive) FSGS. Primary FSGS should be considered the result of direct damage to the podocyte due to a putative “permeability factor,” viral infections (e.g., HIV), or drugs (66). As such, primary FSGS is a podocytopathy, akin to MCD, with patients presenting with NS and widespread foot process effacement on EM. This is supported by the fact that in recurrent FSGS, glomerular foot process effacement after kidney transplantation is the first morphologic change (67,68).
On the other hand, secondary FSGS can occur due to a genetic mutation or as a result of functional and structural glomerular adaptation to glomerular hypertension and/or hyperfiltration because of a reduced number of healthy nephrons (e.g., unilateral renal agenesis) or hemodynamic stress on an initially normal nephron population (e.g., morbid obesity, reflux nephropathy) (69). The ability to differentiate primary from secondary FSGS is crucial because patients with primary FSGS may respond to immunosuppressive treatments, whereas those with secondary FSGS should be treated conservatively aiming to control BP and reduce proteinuria. Many patients with an FSGS lesion undergo unnecessary immunosuppression due to failure to recognize secondary FSGS. Part of the problem derives from the lack of realization that nephrotic-range proteinuria (>3.5 g/24 h) and NS (>3.5 g/24 h and serum albumin <3.5 g/dl) are not necessarily synonymous. This issue is particularly relevant in FSGS in which nephrotic-range proteinuria without NS is more likely due to a secondary process, whereas NS will more likely be the clinical presentation of a primary form. The Columbia classification, which is based on LM, classifies FSGS as follows: not otherwise specified (NOS) or perihilar, cellular, tip, or collapsing variants (70,71). Although patients with a tip variant or collapsing FSGS are likely to have NS, the majority of patients have FSGS NOS; in my experience, FSGS NOS can be seen in primary as well as secondary cases. Similarly, although the finding of collapsing FSGS may be enough to decide on immunosuppressive therapy, I believe that in other cases the histologic diagnosis is not enough, and additional clinical information (i.e., presence or absence of NS is needed in order to make this decision). Indeed, there are many patients with massive proteinuria that do not develop hypoalbuminemia (72). This is especially true in patients with secondary FSGS (73). Praga et al. reviewed the clinical data in patients diagnosed with FSGS and proteinuria >3.5 g/24 h and classified them according to the presence or absence of NS (73). Of the 18 patients with nephrotic-range proteinuria but without NS, these authors found that FSGS was due to massive obesity, vesicoureteral reflux, and renal mass reduction in 16 of these patients. Only two patients in this group were considered to have idiopathic FSGS. On the other hand, NS was present in 19 patients and they all had primary FSGS. The authors concluded that patients with secondary FSGS may develop massive proteinuria but not NS. This is particularly important when we consider that the majority of cases of adults with FSGS secondary to a genetic mutation do not have NS. Although in a great number of secondary FSGS foot process effacement is variable and relatively mild, the cause is not obvious with our current investigative tools in many cases. However, as our knowledge expands, more causes of secondary FSGS will be added to the current list (e.g., obesity, renal mass reduction, and genetic mutations).

Another important difference between primary and secondary FSGS is the degree of foot process effacement on EM examination. Tip, cellular, and collapsing FSGS usually have widespread foot process effacement, whereas foot process effacement is variable and relatively mild in the perihilar subtype effacement and focal in FSGS NOS (74). Because of the adaptive origin of the lesion in secondary FSGS, patients are more likely to have mild foot process effacement and present with subnephrotic-range proteinuria, whereas patients with primary (or idiopathic) FSGS are more likely to resemble MCD by the presence of widespread foot process effacement and NS, as discussed above.

In the present case, the absence of NS and partial foot process effacement on EM point to secondary FSGS. As such, the finding of FSGS on a renal biopsy represents only the beginning of the diagnostic process. Establishing the correct etiologic diagnosis avoids unnecessary and potentially harmful immunosuppressive treatments. Secondary FSGS should be considered in all patients with proteinuria, including nephrotic-range proteinuria, that do not have hypoalbuminemia and in which EM examination shows only segmental foot process effacement. In secondary FSGS, the relative preservation of the foot process contrasts
with the findings in a primary podocytopathy such as MCD or primary FSGS, even in patients with nephrotic-range proteinuria. Patients with secondary FSGS should be treated conservatively, aiming to maximize BP control with the use of angiotensin II blockade, a low-salt diet (<4 g/d), a low-protein diet (0.8–1 g/kg per day), lipid control with the use of a statin, smoking cessation, weight control, and avoidance of nephrotic medications. It should not be forgotten that one should try to find the etiology of the secondary FSGS and correct it as well. The correct answer to question 3 is choice A. All other choices (e.g., D and E) include immunosuppressive therapy that may be considered in cases of primary FSGS (except choice E: sirolimus, for reasons discussed above) but not in secondary FSGS.

Disclosures

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