Kidney Case Conference: How I Treat

How I Treat Focal Segmental Glomerulosclerosis

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Introduction

There has been much confusion regarding the terminology of FSGS, with consequent variability in the diagnosis and management of differing clinical presentation. This is a result of ascribing a histopathologic pattern of injury onto a disease entity, where there are no discerning features on the kidney biopsy specific to different clinical situations. The Kidney Disease Improving Global Outcomes (KDIGO) guideline update in 2021 made a significant effort in standardizing the clinical definition of people presenting with an FSGS lesion (1) to allow for consistency in clinical studies and management approaches, especially in identifying appropriate individuals suitable for immunosuppression therapy.

Patient 1

TBK, a 50-year-old gentleman with a history of hypertension, had a proteinuria of 3.8 g/day and a normal serum albumin of 4.5 g/dl during an annual health screening. His BP is 130/80 mm Hg with no pedal edema. A kidney biopsy was reported as FSGS-NOS with about 70% foot process effacement. The nephrology fellow was wondering whether to start him on a course of corticosteroids.

Discussion

Defining the Patient Population

Corticosteroids remain the mainstay of treatment in people with primary FSGS, a condition currently thought to be caused by a yet identified circulating permeability factor that is toxic to the podocytes (2). In other forms of FSGS, however, corticosteroids are ineffective, and indiscreet use results in unnecessary side effects without achieving clinical benefits. Importantly, histopathologic features, including the percentage of foot process effacement, are not pathognomonic of primary FSGS. Diffuse foot process effacement on electron microscopy is an unreliable diagnostic marker nor is it unique to primary FSGS. There is wide variability in the percentage of foot process effacement in secondary FSGS, with diffuse effacement being reported only in certain series (3,4). Moreover, the presence of diffuse foot process effacement has been seen in genetic forms of FSGS, and conversely, absence of diffuse effacement has been reported in primary FSGS, with an incidence as high as 75% in one series (5). Therefore, the presence of diffuse foot process effacement should not be an impetus to diagnose primary FSGS or to initiate corticosteroid treatment.

Although patients with primary FSGS often have nephrotic-range proteinuria, the absence of nephrotic syndrome (defined as the presence of nephrotic-range proteinuria and hypoalbuminemia with or without edema) is discordant with the diagnosis, and corticosteroids should be avoided in such situations. In one study, when secondary forms of FSGS have been excluded, nephrotic syndrome was consistently seen in all patients with primary FSGS (6). In the absence of a convincing diagnosis of primary FSGS, we ensure that efforts are made to look for an underlying cause of the FSGS lesion and to treat such a condition, if so detected, rather than starting corticosteroids at the outset (Figure 1).

When a secondary cause is not apparent, as in this case, the patient is considered to have FSGS of undetermined cause in accordance with the new classification proposed by KDIGO. We suggest that the management for this group of patients should follow general supportive care for proteinuric kidney diseases, including maximizing renin-angiotensin system (RAS) blockade and control of hypertension for at least 6 months. Recently, the use of SGLT2 inhibitors has become a popular therapeutic option in patients with CKD, although its efficacy in patients with primary or secondary FSGS remains unsubstantiated. In a subgroup analysis of patients with FSGS in the DAPA-CKD trial, individuals randomized to receive dapagliflozin showed a greater reduction of albuminuria up to 12 months, but thereafter, albuminuria levels were similar to the placebo group (7). However, the causes of FSGS were heterogeneous in the study, and there was no statistical significance in the rate of eGFR decline. Therefore, SGLT2 inhibitors should not be considered as the standard of care for supportive therapy in patients with FSGS; nonetheless, we will consider adding an SGLT2 inhibitor in patients with persistent proteinuria >0.75 g/d

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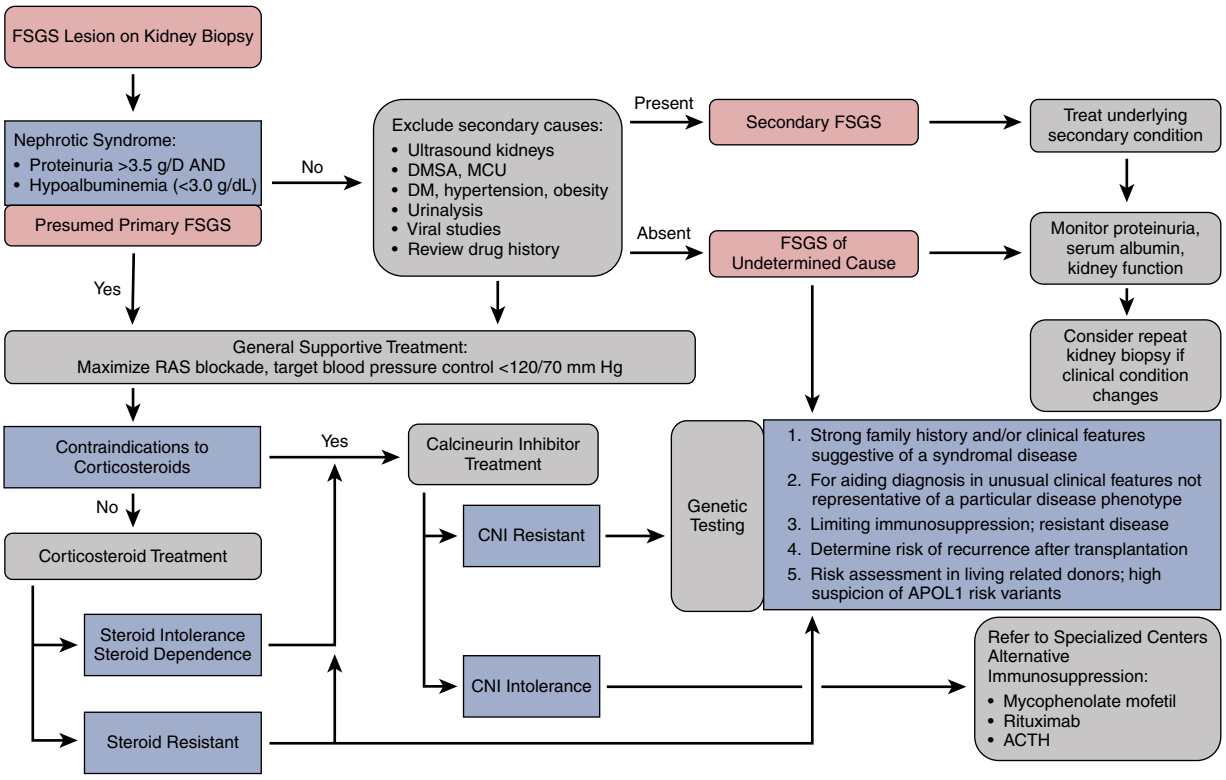

Figure 1. | **Approach to a patient with an FSGS lesion on the kidney biopsy.** ACTH, adrenocorticotropic hormone; CNI, calcineurin inhibitor; DM, diabetes mellitus; DMSA, dimercaptosuccinic acid scan; MCU, micturating cysto-urethrogram; RAS, renin-angiotensin system.

despite maximally tolerated doses of RAS blockade. We will consider a repeat kidney biopsy in situations of worsening proteinuria, deteriorating kidney function, or new-onset nephrotic syndrome.

Immunosuppression in Primary Focal Segmental Glomerulosclerosis

Although corticosteroid therapy is accepted universally as the first-line therapy for primary FSGS, calcineurin inhibitors (CNIs) should be considered as the initial treatment in patients with medical conditions where corticosteroid use may be detrimental (1). The KDIGO guideline offers a dosing approach to both corticosteroid and CNI therapy (1). CNI remains the only alternative therapeutic option with acceptable efficacy from clinical studies on primary FSGS and is indicated in those with intolerance, dependence, or resistance to corticosteroids. Treatment choices after exhausting the option of corticosteroids and CNIs remain poorly evaluated, with conflicting outcomes from clinical studies. These patients should be referred to specialized centers for consideration of alternative immunosuppression, such as mycophenolate mofetil and rituximab (Figure 1).

Patient 2

KHJ is an obese 16-year-old boy with hypertension, a proteinuria of 1.8 g/d, a normal serum albumin, and eGFR of 45 ml/min per 1.73 m^2. His mother has FSGS requiring long-term dialysis. Kidney biopsy revealed moderate tubular atrophy/interstitial fibrosis and segmental glomerulosclerosis in an NOS pattern. Genetic studies revealed a hemizygous nonsense variant in the COL4A5 gene. The decision was made to avoid steroids and start RAS blockade.

Role of Genetic Testing

Genetic testing is not recommended universally for all patients with FSGS as it is not cost effective, but it may be beneficial for a selected population (Figure 1). Conventional algorithms target children under the age of 1 year or with syndromic presentations. Studies have shown that disease-causing mutations can be found in almost 100% of patients with congenital nephrotic syndrome, but the likelihood of finding a genetic pathology falls significantly with older age of onset of FSGS (8). However, such as in our patient, the chance of finding a monogenic etiology in patients with FSGS is higher in familial (52%–67%) cases than in sporadic cases (8,9).

In addition to providing new clinical insight into the underlying cause of FSGS, identification of pathogenic mutations is associated with corticosteroid resistance and may therefore influence one's choice of therapy. In an exome sequencing analysis of >3300 ethnically diverse patients over the age of 21 years with CKD, over 10% had an identifiable pathogenic mutation. Of those with COL4A mutations, over 60% were misdiagnosed with other conditions (10). For our patient, this information increased confidence in the decision to avoid a trial of corticosteroid, move directly to therapies with the best data to support

kidney function preservation, and provide the family with valuable information that may help other affected members seek care earlier in their disease process. Genetic testing in FSGS should also be considered in patients being evaluated for a kidney transplant as it is valuable in informing the unlikely risk of recurrence of nephrotic syndrome due to a genetic cause, where in contrast, the risk of recurrent disease after transplantation is high in primary FSGS. Conversely, detection of at-risk mutations, in particular the APOL1 risk variant (11), in potential donors in the family may preclude kidney donation.

Finally, genetic testing should be handled in specialized centers with sufficient expertise and should include a multidisciplinary team involving a nephrologist, a clinical geneticist, a pathologist, and a medical social worker.

Conclusion

A histopathologic diagnosis of FSGS, although valuable, provides incomplete data for clinicians in deciding treatment. As the nephrology community works to establish more precise biomarkers, using available clinical data to define subpopulations and using tools like genetic testing can be beneficial.

Disclosures

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Author Contributions

K.L. Gibson and A. Liew conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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