Focal Segmental Glomerulosclerosis in a Patient with Ambiguous Genitalia: A Diagnostic Dilemma

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ABSTRACT

Introduction: The renal condition referred to as focal segmental glomerulosclerosis (FSGS) presents a diagnostic dilemma for the clinician. It encompasses and displays a nonspecific histologic appearance on a kidney biopsy specimen, rather than a unique disease entity. This characteristic of FSGS often makes treatment decisions and prognostication difficult. A 34-year-old man, who was born with ambiguous genitalia, had received a diagnosis of FSGS in young adulthood and now had advanced kidney disease. He underwent genetic testing to determine whether a genetic disorder was underlying his kidney disease and to ascertain his risk of FSGS recurrence if he were to receive a kidney transplant. The literature pertaining to genetic causes of FSGS is reviewed. We present here a diagnostic dilemma that clinicians face when confronted by a case of FSGS for which the underlying cause is unclear.

INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a term to describe findings in the kidney biopsy or a separate disease entity of its own. On light microscopy, FSGS is characterized by segments of solidification caused by accumulation of extracellular matrix affecting portions of the renal glomeruli, amorphous glassy material beneath the glomerular basement membrane, endocapillary foam cells, wrinkling of the glomerular basement membrane, and adhesions of the glomerular tuft to the Bowman capsule.[1] Podocytes are cells in the Bowman capsule that maintain selective filtration from the glomeruli of the kidney—damage to these cells lead to proteinuria and progressive kidney disease. It is hypothesized that idiopathic (primary) FSGS is caused by a yet-unidentified circulating permeability factor that damages podocytes. Secondary FSGS is caused by podocyte damage from various causes, including certain genetic mutations, viral infections, medications, and as adaptation to glomerular hypertension or injury resulting from various pathologic states.[2] Causes of secondary FSGS are summarized in Table 1.

Idiopathic FSGS has a high response rate to immunotherapy but also has a high rate of recurrence in the transplanted kidney, sometimes manifesting within days after transplantation.[3] In contrast, FSGS due to secondary causes (including genetic causes) is resistant to immunotherapy and thought to have a low recurrence rate in the transplanted kidney.[4] Thus, detection of a known genetic mutation in a patient with FSGS is important not only from a treatment standpoint but also from a prognostic standpoint after kidney transplantation.

We present here a diagnostic dilemma that clinicians face when confronted by a case of FSGS for which the underlying cause is unclear, and highlights the importance of having familiarity with discoveries being made in the field of genetic medicine.

THE DILEMMA

Presenting Concerns

A 34-year-old man of mixed Hispanic and African American heritage sought care for advanced kidney disease and soon thereafter began dialysis because of uremic symptoms. He stated that his initial diagnosis of kidney disease was made more than 10 years earlier after results of routine laboratory studies showed a mildly elevated creatinine and proteinuria. A kidney biopsy was performed around that time, and the result showed FSGS. He reported that he was treated for 6 months with prednisone therapy without response; he experienced gradual worsening of kidney disease as well as developing hypertension. His medical history was remarkable for ambiguous genitalia at birth. He underwent reconstructive surgery as an infant to make him phenotypically male and reported the presence of a residual urethral-cutaneous fistula on the ventral surface of his penis. In addition, he underwent bilateral orchiectomy because of cryptorchidism as an infant. Pathology reports from the orchiectomies were unable to be obtained. He reported receiving intramuscular testosterone therapy since childhood. His family history was unremarkable, and the patient had no siblings. Physical examination findings revealed a well-built

Table 1. Secondary causes of focal segmental glomerulosclerosis

Cause	Description
Genetic	Mutations in genes for nephrin, podocin, and Wilms tumor 1, among others
Medications and drugs	Heroin, anabolic steroid, interferon therapy, bisphosphonate, sirolimus, calcineurin inhibitor
Viral infections	Human immunodeficiency virus, parvovirus B19, cytomegalovirus, Epstein-Barr virus
Adaptation to reduced renal mass or increased glomerular pressure/injury	Solitary kidney, reflux nephropathy, advanced chronic kidney disease, primary glomerular disease, systemic hypertension, obesity

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man of average height with male-pattern baldness, male-pattern body hair, a penis with a small fistula on the ventral surface, and the absence of testicles.

In light of his being born with ambiguous genitalia and developing FSGS in young adulthood, a *WT1* (Wilms tumor 1) mutation underlying a genetic form of FSGS was strongly suspected. Genetic testing was offered to the patient: the justification for testing stemmed from the patient's desire to have an established diagnosis and to determine the risk of FSGS recurrence if he were to receive a kidney transplant.

The patient underwent genetic testing. Coding regions and splicing junctions of *WT1* were sequenced, and no known clinically significant mutations were detected. In addition, 13 other genes were sequenced as part of a steroid-resistant nephrotic syndrome panel (Fulgent Diagnostics, Temple City, CA); these results showed no clinically significant abnormalities. Whole-genome array-based comparative genomic hybridization and genotype analysis (GeneDx, Gaithersburg, MD) was performed, which showed a deletion in 13q12.11. However, the clinical significance of this deletion is unknown. The patient was also found to have a 46, XX karyotype.

Follow-up and Outcomes

The male phenotypic appearance despite having a 46, XX karyotype was likely the result of his lifelong testosterone therapy. The cause of his FSGS is unknown and is presumed to be idiopathic.

DISCUSSION

Underlying Genetic Mutations

Multiple genetic mutations involving genes that encode proteins involved in the structure and function of podocytes, such as organization of the slit diaphragm and actin cytoskeleton, have been identified as underlying FSGS and other steroid-resistant nephrotic syndromes. Identified mutations include *NPHS1* (nephrin), *NPHS2* (podocin), and *PLCE1* (phospholipase Cε 1) leading to childhood-onset, steroid-resistant nephrotic syndrome, as well as *ACTN4* (actinin-α 4), *INF2* (formin), and *TRPC6* (transient receptor potential cation channel C6) leading to adult-onset, steroid-resistant nephrotic syndrome.[5,6] In general, mutations characterized by an autosomal recessive manner of inheritance tend to present in childhood, whereas those characterized by an autosomal dominant manner of inheritance present in adulthood, but incomplete penetrance of the genotype may lead to mutation carriers being unaffected by clinical disease.[6] Given the overall low-reported prevalence of underlying single-gene mutations in adult-onset FSGS, the most recent guidelines from *Kidney Disease: Improving Global Outcomes* (KDIGO) do not recommend routine genetic testing in adult patients with a diagnosis of FSGS, even in cases of steroid resistance.[7] Interestingly, one study involving patients with adult-onset nephrotic syndrome referred for *NPHS2* mutation testing found that 18 of 119 patients (mostly of European and South American descent) had a single pathogenic mutation in *NPHS2* and p.R229Q, suggesting that compound heterozygosity with p.R229Q may underlie a substantial proportion of cases of adult-onset, steroid-resistant nephrotic syndrome.[8] Of note, the aforementioned study was not limited to patients with FSGS on histologic analysis, as some patients were known to have minimal change disease and diffuse mesangial proliferation. African Americans have a disproportionately higher prevalence of FSGS compared with other ethnic groups in the US, possibly related to the higher prevalence of risk alleles in the genome, such as certain variants of the *APOL1* gene. Possessing certain variants of the *APOL1* gene has been associated with 17-fold higher odds of having FSGS and 29-fold higher odds of having human immunodeficiency virus-associated nephropathy.[9]

In addition to causing isolated FSGS and other steroid-resistant nephrotic syndromes, point mutations in various genes may underlie syndromic forms of FSGS associated with extrarenal manifestations of disease. An example of such a gene is *WT1,* which encodes a zinc finger transcription factor that plays an important yet poorly understood role in urogenital development and maintenance of mature podocytes.[10]

WT1 Mutation Syndromes: Denys-Drash and Frasier Syndromes

The *WT1* gene was identified after investigations in children with WAGR syndrome (Wilms tumor, aniridia, genitourinary malformations, and mental retardation) and sporadic Wilms tumor (nephroblastoma) revealed large segments of deletion on chromosome 11p13.[11] Denys-Drash syndrome and Frasier syndrome, 2 known syndromes involving genitourinary malformations and neoplasms as well as nephrotic syndrome, were subsequently identified as being associated with mutations in the *WT1* gene.[12,13] A study investigating the characteristics of *WT1*-related nephrotic syndromes reported a 6% prevalence of *WT1* gene mutations among 746 patients of all ages with steroid-resistant nephrotic syndrome.[14]

Most cases of Denys-Drash syndrome are attributed to missense or nonsense mutations in Exon 8 or 9 of *WT1* (a sequence of DNA coding for protein). Frasier syndrome occurs with mutations in the donor splice-site of Intron 9 of *WT1* (a sequence of DNA *not* coding for protein), leading to a lower proportion of *WT1* protein isoforms containing a specific lysine-threonine-serine residue in between zinc fingers 3 and 4.

The classic presentation of Denys-Drash syndrome occurs with 46, XY karyotype and is characterized by male pseudohermaphroditism with gonadal dysgenesis presenting with female external genitalia or ambiguous genitalia, a high risk of Wilms tumor, and nephrotic syndrome developing in young childhood with histologic findings showing diffuse mesangial sclerosis. The classic presentation of Frasier syndrome occurs with 46, XY karyotype and is characterized by male pseudohermaphroditism with gonadal dysgenesis presenting with female external genitalia or ambiguous genitalia, and nephrotic syndrome developing in young adulthood with histologic findings often showing FSGS.[11] The gonadal dysgenesis occurring in both Denys-Drash syndrome and Frasier syndrome in 46, XY individuals present a major risk of gonadoblastoma, often necessitating prophylactic resection. Individuals with 46, XX karyotype carrying missense or nonsense mutations in Exon 8 or 9 or a donor splice-site

mutation in Intron 9 generally have normal female development but may present with isolated (nonsyndromic) nephrotic syndrome.[15] The development of Wilms tumor in young childhood is most commonly associated with exonic mutations in *WT1*, but a couple of cases of Wilms tumor occurring with intronic mutation have been reported in the literature.[14]

Patients with diagnosed *WT1* mutations associated with nephrotic syndrome inherently have poor clinical response to corticosteroids, and the lack of response to corticosteroids is often the impetus for genetic testing. Denys-Drash syndrome and Frasier syndrome are associated with nonresponsiveness to corticosteroids. There are reports of substantial improvement of proteinuria with cyclosporine administration in a few children with nephrotic syndrome associated with *WT1* mutations. However, it is difficult to gauge the overall effectiveness of this therapy given the possibility of publication bias.[16] A case of posttransplant recurrence of nephrotic syndrome in a patient with Frasier syndrome has been reported in the literature, suggesting that *WT1*-related FSGS may not be completely immune from recurrence after kidney transplant.[17] ❖

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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Diagnosis

The diagnosis of a disease is often easy, often difficult, and often impossible.

— Peter Mere Latham, 1789-1875, English physician and medical educator