Foresee Your Next Patient

Collapsing Focal Segmental Glomerulosclerosis

Akhilesh Rao, MD[1] • Dallin Tonks, DO[2] • David Rabinovich, DO[3]

A 66-year-old African American woman with a history of type 2 diabetes, stage 4 chronic kidney disease (CKD), hypertension, heart failure with reduced ejection fraction (HFrEF), and gout presented with a chief concern of dyspnea and chest pain.

She had been experiencing vomiting and diarrhea every other day for the past 6 weeks. She had noticed abdominal and lower-extremity swelling over the past few weeks. The patient had had diabetes for the past 43 years. Her renal function had rapidly declined over the preceding 4 months. Her recent creatinine levels were as follows: 4 months before presentation, 1.62 mg/dL; 1 month before presentation, 2.66 mg/dL; and the day before presentation, 9.62 mg/dL.

Her family history was notable for a mother and sister with type 2 diabetes and CKD on dialysis. She had a 30 pack-year smoking history but had quit 30 years ago.

Results of a serologic workup were negative for anti–glomerular basement membrane antibodies, antineutrophil cytoplasmic autoantibodies, antinuclear antibodies, and HIV, and the serum C4 level was within normal limits at 33 mg/dL. Echocardiography showed a left ventricular ejection fraction of 30% to 35% with moderate pulmonary hypertension. Physical examination findings were notable for crackles at the lung bases, lower-extremity pitting edema bilaterally, and asterixis.

AFFILIATIONS:
[1]Americare Kidney Institute, Parma Heights, Ohio
[2]University Hospitals Parma Medical Center, Parma Heights, Ohio
[3]Kent Hospital, Warwick, Rhode Island

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CORRESPONDENCE:
Akhilesh Rao, MD, Americare Kidney Institute, 9050 N Church Dr, Parma Heights, OH 44130 (arao@americarekidney.com)

Results of a kidney biopsy showed focal and segmental collapsing lesions in 5 of 5 glomeruli on light microscopy. The biopsy specimen also showed numerous calcium oxalate crystals in the tubules and moderate diffuse and nodular diabetic nephrosclerosis, as well as moderate focal tubular atrophy and interstitial fibrosis (**Figure**). Based on these findings, she was diagnosed with collapsing focal segmental glomerulosclerosis (cFSGS). The patient appeared uremic, so hemodialysis was initiated prior to discharge.

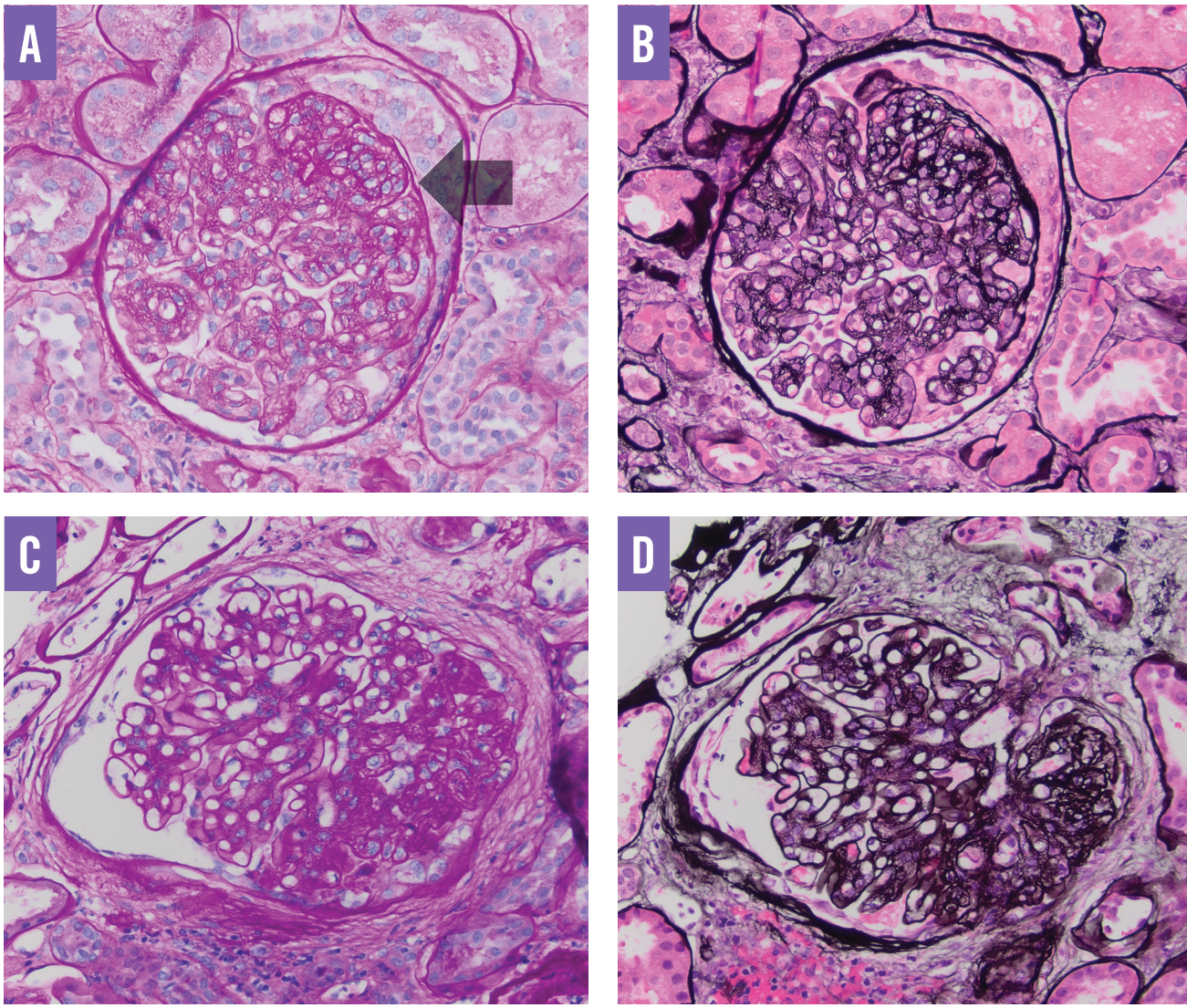
Discussion. FSGS is the most common primary glomerular disorder causing kidney failure in the United States.[1] It has a prevalence of 4% and accounts for approximately 20% of cases of nephrotic syndrome in children and 40% of cases in adults.[1]

The identifying characteristic of FSGS is progressive glomerular scarring. Both FSGS and minimal change disease have been discovered to be diseases of podocytes. However, while minimal change disease can be reversed with glucocorticoid therapy, FSGS is often progressive and irreversible. There are several histologic subtypes of FSGS, including not otherwise specified (NOS) or classic, perihilar, cellular, tip, and collapsing. These subtypes refer to the location of the glomerulus that is damaged, except for NOS, which is used when the histology is unclear. Remission rates are highest for the tip subtype, whereas cFSGS is the most aggressive variant with the worst prognosis.

Also known as collapsing glomerulopathy, cFSGS was first identified in 1986 by Weiss and colleagues.[2] In their study, patients whose histologic findings showed a collapse of glomerular capillary loops experienced nephrotic syndrome with a relatively rapid progression to irreversible kidney failure. Later, cFSGS was detailed as a distinct entity characterized by predominance in African Americans, massive proteinuria, relatively rapid progressive renal insufficiency, and the pathologic findings described above.[3]

While cFSGS currently has no established cause, more recent research has recognized the apolipoprotein L1 gene (*APOL1*) on chromosome 22 as a factor contributing to the higher rates of FSGS and kidney failure in African Americans compared with Americans of European decent.[4] *APOL1* sequence variants that are common in African chromosomes coded for apolipoprotein L1 variants that lysed *Trypanosoma brucei* subsp *rhodesiense,* the protozoan that causes African sleeping sickness. It was speculated that while this promoted survival from such organisms in Africa, these mutations may have contributed to the higher rates of kidney disease in African Americans. Other studies have linked cFSGS to bisphosphonate use (eg, pamidronate),[5] HIV infection,[6] and systemic lupus erythematosus (SLE).[7]

The patient in this case had preexisting stage 4 CKD, along



Kidney biopsy revealed 5 glomeruli that exhibited tuft collapse (arrow, **A**) with extracapillary proliferations (**A and B**). Overall, almost half of the glomeruli were either globally or segmentally sclerosed on a background of moderate nodular diabetic glomerulosclerosis; **C and D** are examples of a segmentally sclerosed glomerulus with adhesion to the Bowman capsule and diabetes-related changes (periodic acid–Schiff [A and C] and Jones silver [B and D] stained paraffin section; original magnification for all images ×200).

with long-standing type 2 diabetes, hypertension, and HFrEF. Over a period of 3 months, her creatinine level worsened from 1.62 to 2.66 mg/dL. One month later, it had worsened to 9.62 mg/dL. This rate of decline in kidney function is much more rapid than that of patients with diabetic nephropathy as the sole cause. Renal biopsy revealed cFSGS, a finding that coincides with the higher rate of the condition in African Americans due to *APOL1* sequence variations. It could explain why the patient's mother and sister also developed kidney failure that required dialysis.

On the other hand, the patient did not have other associated risk factors for cFSGS, such as HIV infection, pamidronate use, or SLE. The cFSGS shown on renal biopsy explains the rapid decline in this patient's kidney function.

Without an identifiable cause of this patient's cFSGS, the pathology was categorized as a primary FSGS. If the patient were to have had secondary cFSGS, it could be addressed by treating the inciting factor, such as antiviral therapy for HIV or ceasing pamidronate. In primary cFSGS, the appropriate therapy includes glucocorticoids, renin-angiotensin system inhibition,

and calcineurin inhibition. However, this patient required renal replacement therapy (dialysis).

With increasing awareness and research, progress has been made in understanding the risk factors contributing to cFSGS, but more needs to be done to find an etiology and develop treatment. ■

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