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FSGS: Forme Pleine or Forme Fruste

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EDITORIAL

FSGS: Forme Pleine or Forme Fruste

Several years ago, I was asked by a physician-colleague to conduct a consultation on her spouse who had enjoyed robust health. Apparently, proteinuria was present, and the couple was worried. He was a young, adult, white man: no hypertension, no edema, normal serum creatinine, an absence of erythrocyturia and lipiduria, and a urine protein-to-creatinine ratio between 0.6 and 1.0 g of total protein per gram of creatinine were reported. The ratio of the urine albumin-to-creatinine ratio to the urine protein-to-creatinine ratio was nearly 0.7 g albumin-to-total protein (normal range <0.4), indicating that the bulk of proteinuria was albuminuria. All the usual serologic assays and hepatitis antibody assays were unrevealing. The patient was 35 years old and "needed to know" what the diagnosis was. So, an ultrasound-guided kidney biopsy was conducted. The glomerular histology was established: focal and segmental glomerulosclerosis (FSGS), with a tip lesion.[1] Minimal tubulointerstitial disease favored longevity for the patient's parenchyma. However, the patient was informed that kidney failure was in his horizon. Recalling that FSGS, first described in 1957, is a lesion with variations and not a disease, it was important to establish a diagnosis in this patient who had manifested a rather nonclassical presentation.

In retrospect, it would have been unlikely that the histology would have been FSGS had the PCR been less than 0.5—an important guide to the clinical evaluation.[2] However, this criterion was established in children and not in adults. Interestingly, with aging, adults incur an increase in albumin-to-creatinine ratio, and this has been attributed to a diminution of the denominator of this ratio, but what if the numerator was increasing instead with aging. Interestingly, in Munich-Wistar-Fromter rats, loss of the vascular endothelial glycocalyx in nonkidney and kidney vessels occurs in association with aging and accounts for a 10-fold increase in albuminuria. This observation was subtotally mitigated by feeding of Munich-Wistar-Fromter rats with wheat germ agglutinin lectin and consequent re-establishment of the endothelial glycocalyx.[3] In older, bodyweight-matched Wistar rats, there was not a statistically significant increase in albuminuria with aging, although urinary total protein tripled. Although the rat may not represent an ideal model for human disease, glycocalyx restoration therapy in man is potentially tenable for certain glomerulopathic states characterized by glycocalyx disruption, such as diabetes.

The patient was HIV negative and was not African-American. He did not fit the phenotype of Alonzo Mourning or Sean Elliott whose illustrious, professional basketball careers were interrupted by full-blown nephrotic syndrome from FSGS (*forme pleine*). Remarkably, both played competitively, despite significant illness, up until the point of kidney transplantation. After allograft implantation, neither individual had immediate recurrence of their disorder as Hoyer described 3 decades ago.[4] However, the absence of disease recurrence does not imply that either of these individuals were absent of any circulating glomeruloproteinuric factor. Two have been identified: soluble urokinase-plasminogen activating receptor that engages the podocyte beta-3 integrin receptor and induces podocytes to become flat-footed with proteinuria[5] and the interleukin-6 family member, cardiotrophin-like cytokine-1 (CLC-1, Savin-Sharma factor), that exponentially increases glomerular albumin permeability.[6] In fact, the majority of such cases of FSGS do not recur in the kidney allograft, although when relapse ensues, it may manifest itself quite sharply and immediately.

My patient had something else. His presentation was subtle, almost unstructured (*forme fruste*). He had never used heroin, and this agent among others has been implicated in the 1960s and 1970s as causative of FSGS.[7] Drug purity appears important in so-called heroin-associated nephropathy, but adulterants more than the putative agent represent a viable causative alternative.[6] Although the patient was muscular, he was not a competitive bodybuilder. Nonetheless, the question of anabolic steroid use arose. Recently, proteinuria and bodybuilding have been linked, with anabolic steroids as pathogenic for FSGS.[8] Ten bodybuilders, 6 white and 4 Hispanic, with proteinuria and a long history of anabolic steroid use, had kidney biopsy-proven FSGS: 3 with collapsing FSGS and 4 with perihilar lesions. Glomerulomegaly appeared in 4 biopsy specimens; in 1 patient, this was the sole lesion. Withdrawal

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of the offending agent led to a partial clinical resolution in most cases. Relapsing disease on voluntary but ill-advised drug readministration occurred in 1 patient.

The exact etiopathogenic sequence of anabolic steroid-induced kidney injury has not been delineated, but the combination of excessive lean body mass plus anabolic steroid use may be causative in this mesomorphic proteinuric disorder. Whether hyperfiltration is attendant to this disorder, as it is in obesity-related glomerulosclerosis, has not been discerned to date. Importantly, the concept that proteinuria could only induce kidney damage through hyperfiltration had been overturned much earlier. It had already been documented by Tapp and colleagues[9] in 1989 that calories, not protein intake, induced equal amounts of kidney parenchymal damage in an animal model of hyperfiltration. In summary, anabolic steroid-related FSGS should be considered in muscular athletes who demonstrate significant proteinuria, namely beyond that of exercise-induced proteinuria.

Note that the 2 basketball players mentioned before are black, and although they differed greatly in muscle mass (Mourning, highly muscular; Elliott, slim), they had the same disorder. Plausibly, these 2 individuals were similarly predisposed to FSGS by inheritance of one of the kidney risk alleles of the apolipoprotein L1 gene (*APOL1*)—a recently evolved member of the *APOL* gene family with 2 allelic variants, G1 and G2, that confer protective trypanolytic activity at the expense of enhanced risk for glomerular damage.[10,11] The increased risk of CKD in susceptible individuals is estimated at 7- to 30-fold for a subset of black individuals with G1 or G2 haplotypes. The risk is disproportionately greater in those afflicted with FSGS and HIV-associated nephropathy and hypertensive nephrosclerosis. In 2 trials of CKD, AASK (African American Study of Kidney Disease), and CRIC (Chronic Renal Insufficiency Cohort), Parsa and his coinvestigators determined greater rates of end-stage kidney disease and progression of CKD in black patients, with kidney risk variants of *APOL1*, compared with white patients (hazard ratio 1.88).[12] This is concordant with the results of genetic studies that estimate that 50% of African Americans harbor either 1 or 2 risk alleles and that 10% to 15% have 2 alleles.[11] In brief, although not a classical Mendelian disorder, *APOL1* gene mutations functionally act as such. Several world class, African American bodybuilders had developed FSGS with kidney failure, previously. Steroids were blamed. Quite possibly, multiple stressors were at play. These individuals may have harbored the *APOL1* risk alleles, self-imposed hyperfiltration from protein ingestion of 300 g daily, and added the injurious effects of anabolic steroids.

The clinical diagnosis of the patient was possibly primary FSGS. Depending on the classification scheme, primary could mean a congenital cause of FSGS. Per National Kidney Foundation Kidney Disease Outcomes Quality Initiative,[13] this would include such causes, but not so by KDIGO (Kidney Disease: Improving Global Outcomes).[14] As a middle-aged adult, it was unlikely that he had concealed for decades of one of the pediatric, steroid-resistant, gene mutation-induced podocytopathies that produce an FSGS lesion. These podocytopathies include derangements of multiple, structural proteins[15]: slit diaphragm protein, nephrin[16]; the stomatin protein family member, podocin, which is generally associated with congenital and childhood nephrosis[17] and is a raft-associated component of the slit diaphragm that interacts with nephrin and CD2-associated protein (*CD2AP*), a scaffolding protein that regulates the actin cytoskeleton[18]; Wilm tumor-1[19]; and ras-activating phospholipase C, epsilon-1 (*PCLE1*).[20-22]

In contrast, he may have been harboring one of the autosomal dominant gene mutations: laminin beta-2 (*LAMB2*),[23] alpha-actinin-4 (*ACTN2*),[24] transient receptor potential cation channel 6 (*TRPC6*),[25] or the actin-regulating, inverted formin gene 2 (*INF2*).[26] LAMB2 nephropathy was unlikely as it and nephrin-, podocin-, and WT1-related FSGS generally manifest in the first year of life. ACTN2 and TRPC6 disorders stem from extremely rare gene mutations that produce disease in adults. INF2 disease covers a broad range of ages, however, from the teenage to the elderly population in those of European ancestry. To distinguish among these possibilities, molecular biology tools would be required.

Secondary FSGS seemed unlikely, and the patient was neither diabetic nor in the age category of those who develop a monoclonal gammopathy with nodular glomerulosclerosis. There was no history of chronic bisphosphonate administration or an HIV infection: no collapsing glomeruli, proliferating parietal cells,[27] or reticular inclusion bodies detected in the biopsy specimen. The history was absent prior and remote glomerular tuft insult with residua of remnant scarring and proteinuria, attributable to incomplete restoration of the vascular endothelium, glomerular basement membrane, or investing glomerular visceral epithelial cells—podocytes that are subjected to multiple traumatic stressors and reticent to repopulate themselves.

Recently, support for the clinical observation that FSGS as a secondary lesion may follow a prior kidney injury, such as vesicoureteral reflux, has been experimentally verified. Glomerular deposition of "natural" immunoglobulin M (IgM) with consequent activation of cognate C3 ligand was demonstrated in 3 different animal models of glomerular injury induced by adriamycin-induced toxicity.[28] Previously, the presence of C1q and C3 deposition, usually in the mesangial compartment, had been thought somewhat "incidental." Attenuation of albuminuria followed B-cell depletion after anti-murine CD20 antibody, peritoneal B-cell depletion after hypotonic shock, and in a strain of genetically B-cell-depleted mice (Jh). IgM deposition was reduced in all 3 models. These observations reconcile in part the somewhat enigmatic entity of IgM nephropathy and its variable responsivity to glucocorticoid steroids.[15]

In the end, the cause of the patient's FSGS was uncovered. The patient's diagnostic evaluation had required genetic analysis, under the auspices of The Nephrotic Syndrome Study Network [NEPTUNE], led by Matthias Kretzler at the University of Michigan. The comprehensive system-based approach used in the Kretzler laboratory is enriched and empowered by multiple collaborators in diverse biologic and computational fields and has determined other disease variants of minimal change

disease and FSGS. There was a compound heterozygous mutation of the podocin gene (R229Q), a *forme fruste* of FSGS. Clinical expression of autosomal recessive podocin mutations is contingent on the specific mutation in each of the parental copies of the gene. In other words, podocin-induced FSGS is subject to multiple allelism.[29] Compound heterozygosity for R229Q in conjunction with a podocin mutation is now a cause of steroid-resistant nephrotic syndrome of young adults. Today, the patient remains normotensive and albuminuria is mild. The estimated glomerular filtration rate remains >60 mL/min/1.73 m^2, and he is relieved that he does not have classical FSGS. Impassioned and inspired by the science behind his kidney problem, the patient developed an enthusiastic, enduring relationship with the NephCure Foundation,[30] the sole, nonprofit public charity devoted to supporting research of nephrotic syndrome and FSGS. To support the NephCure community, the patient shares his story to help others (and their families) who had FSGS or nephrotic syndrome.

FSGS has been running into me for many years. Certainly, the clinical course of FSGS is not always that which has been written into the classical texts since its initial description in 1957 by Rich,[31] and that is the progress. "The more I learn, the more I realize how much I don't know."—A.E. Truly. FSGS has been an abiding part of my life as a nephrologist, and it will continue to be so. "That's just the way it is, it is, it is, it is."—B.H.

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