Case and Review

Collapsing FSGS with Concurrent Class 2 and 3 Lupus Nephritis: A Case Report and Review of the Literature

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Keywords

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Abstract

Lupus nephritis (LN) and the collapsing variant of focal segmental glomerulosclerosis (cFSGS) are separate histologic diagnoses that are generally thought to have separate etiologies. We describe the presentation of a 20-year-old African American female with advanced renal failure (creatinine 7.16 mg/dL), nephrotic-range proteinuria, and a 30-pound weight loss. Renal biopsy demonstrated class 2 and 3 LN as well as cFSGS. A review of the current literature demonstrates that the dual diagnosis of LN and cFSGS may not be as rare as previously understood. Whether the presence of one of these pathophysiologic processes predisposes a patient to the development of the other, or whether genetic variation increases the risk for development of both conditions, remains unclear. Currently there is no standard therapy to manage these patients, and overall renal prognosis is poor.

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Introduction

Lupus nephritis (LN) is a common manifestation of systemic lupus erythematosus (SLE), occurring in 60–70% of African American patients with SLE and 25–30% of European-American patients with SLE [1]. Within the past 10 years, several groups have reported a collapsing focal segmental glomerulosclerosis (cFSGS) variant of LN [2–10]. These findings have been recognized concurrently with the discovery, via genome-wide association studies (GWAS), that certain gene variants are associated with the likelihood of developing LN and FSGS. In this case report, we present a patient with concurrent new diagnoses of SLE and cFSGS. We then review the literature regarding the epidemiology of lupus-associated cFSGS, as well as newer data exploring the genetic connection between these two diagnoses. In addition, we review the potential relationship between cFSGS and thrombotic microangiopathy (TMA), a disorder of microvascular alterations characterized by intravascular hemolysis, and LN, of which TMA is a well-recognized complication.

Case Report

A 20-year-old African American female with no significant past medical history was admitted for lower abdominal pain. Pelvic ultrasound revealed a ruptured ovarian cyst, which was thought to be the cause of her pain. Her serum creatinine was discovered to be 3.55 mg/dL, with spot urine protein to creatinine ratio (PCR) of 1.56 g/g. She denied any history of lower extremity swelling, shortness of breath, or change in urination. Aside from the abdominal pain, she had no complaints, and reported no rash, joint pain, or fatigue. Subsequent serologic workup was positive for anti-nuclear antibodies (titer 1:1,280) and anti-double stranded DNA (titer 1:160, 158 IU/mL). C3 and C4 were both within normal limits. A renal biopsy was recommended, but the patient insisted on discharge before it could be performed and did not present for follow-up. She was readmitted six weeks later with nausea, epigastric pain, and a 30-pound weight loss. Serum creatinine had risen to 7.16 mg/dL, random urine PCR had increased to 5.31 g/g, and C3 was found to be mildly low at 80 mg/dL. A renal biopsy revealed collapsed glomerular loops with segmental sclerosis, consistent with the cFSGS (Fig. 1). Mesangioproliferative LN (class 2) and minor focal proliferative LN (class 3) were also observed (Fig. 2). A moderate degree of interstitial fibrosis and tubular atrophy were present. HIV, Epstein-Barr virus, and cytomegalovirus serologies were negative. The patient was managed with oral prednisone 1 mg/kg/day and mycophenolate mofetil (MMF) 1 g BID. Three months later, her creatinine had improved to 3.27 mg/dL, and urine PCR was 3.69 g/g. She subsequently self-discontinued all of her medications. She was readmitted at the end of the following month with a creatinine of 7.37 mg/dL and volume overload. Repeat renal biopsy demonstrated slight improvement in mesangial and capillary proliferation. The degree of interstitial fibrosis was unchanged. The patient was restarted on MMF and is being followed closely as an outpatient.

Discussion

PubMed was searched in September 2019 using the general key words “collaps*” and “lupus” in order to maximize results. Nine articles describing 45 patients with LN and cFSGS were found [11–19]. Results are summarized in Table 1 and Table 2 for comparison. Additionally, the key words “thrombotic microangiopathy” were then added to this search in order to locate relevant literature describing TMA in the setting of LN and cFSGS.

Age and sex were specified in 19 cases, with an average age of 33.8 years. 84% (16 patients) were female. Race was specified in 42 cases, of which 39 patients were African American. Of the 45 patients, 33 had a previous history of LN, while 12 were diagnosed with LN at the same time they were diagnosed with cFSGS. One carried a concurrent diagnosis of antiphospholipid antibody syndrome (APLA) and had signs of TMA on biopsy [5]. Table 3 specifies how many patients were diagnosed with each class of LN. Management of almost all of these patients involved the initial use of steroids. Additional therapy included MMF in seven patients, cyclophosphamide in two, hydroxychloroquine sulfate in two, and azathioprine in one. Additionally, one patient was started on tacrolimus, which was quickly discontinued due to side effects. Another patient was managed with intravenous immunoglobulin. Response to treatment varied greatly, hampered in part by limited follow-up in some cases (ranging from 1 to 42 months). Four patients achieved partial remission, while two experienced immediate renal failure [5].

Our patient had evidence of proliferative glomerular changes characteristic of lupus-related inflammation, as well as focal glomerulosclerosis and podocytopathy typical of cFSGS. Our literature search demonstrates that the concurrence of these renal diagnoses has been previously recognized. The relation between them, however, remains unclear. One possibility is a shared pathophysiologic process, such as TMA. This is a pathologic state characterized by endothelial damage and the development of vascular microthrombi, which manifests with microangiopathic hemolytic anemia, thrombocytopenia, and end-organ damage. TMA is a known complication of LN, even in the absence of associated complications such as APLA or malignant hypertension [20]. It has been described in the presence of complement pathway activation and may be triggered by infections [11, 12]. The endothelial damage caused by renal TMA has been postulated as a cause of cFSGS in one retrospective study examining 53 patients with TMA on renal biopsy, of which 19 showed evidence of cFSGS [13]. In a case series describing 12 patients with LN and cFSGS, a more limited loss of podocyte differentiation was seen on renal biopsy than in classic cFSGS lesions seen with HIV-associated nephropathy or idiopathic cFSGS [5]. These observations suggest that LN-associated cFSGS may be a reactive response to vascular dysregulation, rather than an immune-mediated phenomenon, and provide a plausible etiologic link between cFSGS, LN, and TMA [14].

In addition to a shared pathophysiologic mechanism, another possible explanation for the link between LN and cFSGS is a shared genetic predisposition to developing either condition. Like most other reported cases of concurrent SLE and cFSGS, our patient was of African American ancestry (two case reports involve Hispanic patients; no cases of Caucasian Americans have been reported). Genetic factors have long been postulated to play a role in both the incidence of LN in SLE patients and the renal outcomes. Certain immunoglobulin alleles have been

shown to be significantly more common in African American patients with LN [15, 16]. The discovery of the association between Apolipoprotein L1 (ApoL1) variants and development of renal disease [17] has led to investigations of whether ApoL1 is associated with the likelihood of developing LN. GWAS analyses have shown a relationship between ApoL1 variants and LN, without regard to WHO class [18]. Kopp et al. [19] showed an increased risk of developing primary FSGS in persons with even one high-risk APOL1 allele; individuals with two high-risk alleles were over 40 times as likely to develop FSGS than individuals with no high-risk alleles. Recently, a retrospective case series assessed whether ApoL1 genotypes are associated with the development of LN-associated cFSGS [6]. All but one case was associated with the presence of one or two ApoL1 risk alleles. It remains unknown whether there is an association between the pathophysiologic development of LN and cFSGS, or whether patients with high-risk APOL1 alleles develop these diseases in parallel but separate processes. Currently, the mechanism by which the APOL1 gene confers increased risk of kidney disease in affected individuals is unknown.

This patient case adds to the growing body of literature linking cFSGS and LN, and also emphasizes the importance of prompt renal biopsy in determining the cause of nephrotic-range proteinuria in patients with suspected LN. More research is needed to determine the optimal treatment regimen for patients with both of these diseases. Further investigation into the mechanism of APOL1-associated renal disease may lead to individualized therapies based on a patient's genetic profile, a major advance into the realm of personalized medicine.

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Statement of Ethics

Written informed consent for publication including images was obtained from the subject. All research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. This article does not contain any studies with human participants performed by any of the authors. All efforts were made to protect the identity of the patient.

Conflict of Interest Statement

The authors declare that there is no conflict of interest to disclose regarding the publication of this article. The authors declare no competing financial interests.

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Author Contributions

Aimen Vanood and Dr. Lisa Cohen took care of the patient and were major contributors in the writing of this manuscript. Dr. Ryan Owen, Dr. Marina Maraskine, Dr. Rajesh Pokharel, and Ariyon Schreiber took care of the patient and revised and approved the manuscript.

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Fig. 1. Light microscopy with periodic acid-Schiff staining demonstrating a collapsed glomerular tuft (arrows), epithelial cell hyperplasia, moderate interstitial fibrosis, and tubular atrophy.

Fig. 2. Electron microscopy revealing mesangial electron-dense deposits (white arrow) and diffuse podocyte foot process effacement (black arrows).

Table 1. Summary of demographics and LN history and class found in literature review

First author [Ref.], year	Age	Sex	Race	LN Hx?	LN class	Renal function	Treatment	Outcome
Gupta [2], 2011	42	F	–	Previous	4	Serum Cr = 1.2 mg/dL PCR = 1,846 mg/g	Steroids Hydroxychloroquine sulfate	6 mo: Serum Cr = 1.1 PCR = 1,600 mg/g
	28	F		Previous	4	Serum Cr = 1.1 mg/dL PCR = 1,230	Tacrolimus (but dis- continued)	3 mo: Serum Cr = 1.0 PCR = 3,500 mg/g
	46	F		Previous	4	Serum Cr = 0.5 mg/dL PCR = 2,429	Steroids	4 mo: PCR = 1,091 mg/g
Melo [3], 2011	18	F	African American	Concurrent	4	Serum Cr = 6.5 mg/dL 24-h protein: 7.5 g/dL	Steroids Cyclophosphamide	4 mo: 24-h protein: 2.0 g 24 mo: Serum Cr = 0.96 24-h protein: 2.2 g
Tungekar [4], 2011	12	F	African American	Previous	5	Serum Cr = 4.6 mg/dL PCR = 2,735 mg/g	Steroids MMF	6 mo: Serum Cr = 1.2 PCR = 42
Salvatore [5], 2012	34	F	African American	Concurrent	2	Serum Cr = 1 24-h protein: 10 g/dL	Steroids	42 mo: <i>Partial remission</i> Serum Cr = 1.2 24-h protein = 0.65 g/dL
	16	F	African American	Concurrent	5	Serum Cr = 1.6	Steroids IVIG	24 mo: <i>Partial remission</i> Serum Cr = 1.77 24-h protein = 0.37 g/dL
	50	M	African American	Previous	3	Serum Cr = 26.5	Steroids MMF Dialysis	Immediate renal failure
	36	F	African American	Concurrent	2	24-h protein: 4.4 g/dL	–	<i>No data available</i>
	29	F	Hispanic	Concurrent	4	Serum Cr = 0.6	–	<i>No data available</i>

LN, lupus nephritis; F, female; M, male; Cr, creatinine; PCR, protein to creatinine ratio; h, hour; mo, months; MMF, mycophenolate mofetil; –, no data available.

Table 2. Summary of demographics and LN history and class found in literature review (continued)

First author [Ref.], year	Age	Sex	Race	LN Hx?	LN class	Renal function	Treatment	Outcome
Salvatore [5], 2012	31	M	Hispanic	Concurrent	2	Serum Cr = 1.4 24-h protein: 11 g/dL	Steroids MMF Hydroxychloroquine sulfate	18 mo: <i>Partial remission</i> Serum Cr = baseline 24-h protein = 1-2 g/dL
	49	F	African American	Concurrent	3	Serum Cr = 1.8 24-h protein: 3.6 g/dL	–	No data available
	65	F	African American	Previous	4	Serum Cr = 3.6 24-h protein: 8 g/dL	Steroids	15 mo: Renal Failure
	26	F	African American	Concurrent	5	Serum Cr = 5.6 24-h protein: 12 g/dL	Steroids MMF	Immediate renal failure
	44	M	African American	Concurrent	2	Serum Cr = 8.75 24-h protein: 8.4 g/dL	Steroids Azathioprine	24 mo: <i>Partial remission</i> Serum Cr = 3.6
Larsen [6], 2013	26 patients; African age and sex unspecified			Previous	Class 1: 2 Class 2: 5 Class 3: 2 Class 4: 3 Class 4/5: 3 Class 5: 9 Class 6: 2	–	–	–
Tariq [7], 2014	36	F	African American	Concurrent	2	Serum Cr = 5.2 24-h protein: 5.2 g/dL	Steroids MMF	1 mo: Serum Cr = 0.7 24-h protein: 3.3 g/dL
Midhun [8], 2016	17	F	Asian	Concurrent	4	Serum Cr = 2.5 24-h protein: 5.4 g/dL	Steroids Cyclophosphamide MMF	6 mo: Serum Cr = 1.4 24-h protein = 1.5 g/dL
Abadeer [9], 2017	36	F	African American	Previous	4	Serum Cr = 2 24-h protein: 8.8 g/dL	Steroids MMF	25 mo: Serum Cr = 1.2 24-h protein = 1.1 g/dL
Chokshi [10], 2019	28	F	African American	Concurrent	2	Serum Cr = 1.3 mg/dL PCR = 1,290 mg/g	Steroids MMF	3 mo: Serum Cr = 0.7 PCR = 282 mg/g

LN, lupus nephritis; F, female; M, male; Cr, creatinine; PCR, protein to creatinine ratio; h, hour; mo, months; MMF, mycophenolate mofetil; –, no data available.

Table 3. Number of patients with cFSGS and LN organized by pathological class

Class 1	Class 2	Class 3	Class 4	Class 5	Class 6	Class 4/5
2	11	4	11	12	2	3

cFSGS, collapsing focal segmental glomerulosclerosis; LN, lupus nephritis.