

Paraneoplastic Focal Segmental Glomerulosclerosis Associated With Acute Lymphocytic Leukemia



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INTRODUCTION

Proteinuria and nephrotic syndrome that develop among patients with malignancies are typically categorized as paraneoplastic syndromes or chemotherapy-associated toxicities.¹ Focal segmental glomerulosclerosis (FSGS) is a rare histology found on kidney biopsy in patients with paraneoplastic glomerular disease.² Membranous nephropathy and minimal change disease (MCD) are the most common histology described, and other rarer lesions include membranoproliferative glomerulonephritis and IgA nephropathy. Among hematologic malignancies, acute lymphoblastic leukemia (ALL)-associated glomerular disease is rare, and ALL-associated FSGS has only been described in children. Here, we describe the first known reported case of collapsing FSGS associated with B-cell ALL in an adult who also presented with FSGS and ALL as a child.

CASE PRESENTATION

An 11-year-old African American boy with no significant past medical history developed acute onset facial and lower-extremity edema. Lab work revealed a serum creatinine (SCr) level of 0.7 mg/dl (estimated glomerular filtration rate [Bedside Schwartz Formula] 88.5 ml/min per 1.73 m²), and a serum albumin level of 2.1 g/dl (normal: 3.5–5.5 g/dl); urinalysis showed 4+ protein, negative blood, and no cells on urine microscopy. A random urine protein-to-creatinine ratio was 9.7 g/g. He was diagnosed with nephrotic syndrome

and empirically treated with prednisone (~2 mg/kg per day). His edema improved, but he did not achieve a remission in his proteinuria. He also developed hypertension and was treated with lisinopril. Six weeks after steroid initiation, he underwent a percutaneous kidney biopsy. The biopsy demonstrated collapsing FSGS (Figure 1). Segmental sclerosis involved 2 out of 8 glomeruli, with capsular adhesion and epithelial cell hyperplasia. Other glomeruli showed variable mesangial expansion. There was mild to moderate interstitial fibrosis. Immunofluorescence was nonspecific or negative for IgG, IgA, IgM, C3, and C1q. Electron microscopy showed extensive podocyte foot process effacement and no immune-type electron-dense deposits. The histopathologic diagnosis was reported as FSGS.

His prednisone was tapered, and he was started on tacrolimus. He achieved complete remission of nephrotic syndrome after 5 months of treatment with improvement in urine protein-to-creatinine ratio to 0.8 g/g, and serum albumin level to 3.8 g/dl; he maintained a SCr level of around 0.7 to 1.0 mg/dl (eGFR [Bedside Schwartz Formula] 62–89 ml/min per 1.73 m²). Six months after kidney biopsy, he developed neutropenia with an absolute neutrophil count of 0.2 × 10³/μl (normal range: 1.80–7.50 × 10³/μl). A bone marrow and aspirate showed a hypercellular bone marrow almost completely replaced by lymphoblasts, and he was diagnosed with B-cell ALL. Tacrolimus was stopped, and he was treated with the Children’s Oncology Group Protocol AALL0232, which included cytarabine,

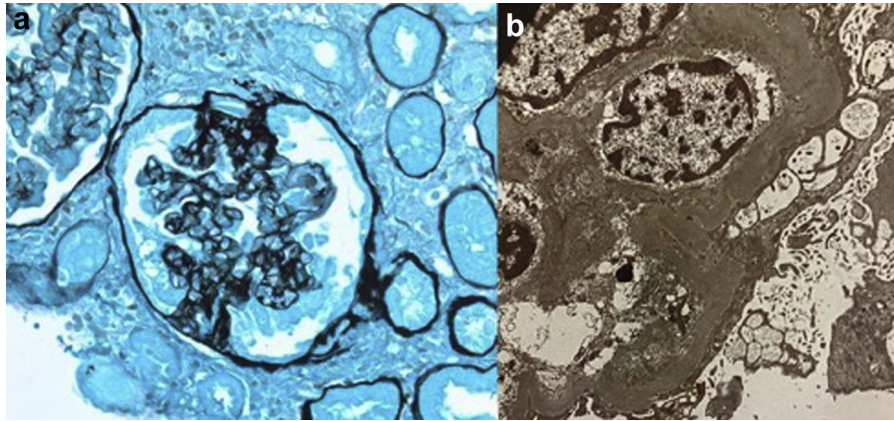


Figure 1. The first biopsy shows a glomerulus (a) with capsular adhesion, tuft retraction, and epithelial hypertrophy (Jones silver stain, original magnification $\times 400$) and electron microscopy (b) demonstrating podocyte foot process effacement and microvillous transformation (transmission electron micrograph, original magnification $\times 8000$).

vincristine, daunorubicin, dexamethasone, methotrexate, pegaspargase, cyclophosphamide, mercaptopurine, doxorubicin, and thioguanine. His therapy was complicated by severe typhlitis requiring a prolonged hospitalization. He achieved complete remission in both nephrotic syndrome and ALL, and he received maintenance chemotherapy until age 17 years.

At the age of 22 years, he presented to the emergency department with chest pain, shortness of breath, nausea, and vomiting. His physical examination was notable for severe bilateral lower-extremity edema. Lab work revealed severe acute kidney injury (SCr level of 14.7 mg/dl; SCr level was 1.9 mg/dl 1 month prior) with a low serum albumin level of 1.1 g/dl. A urinalysis showed >500 mg protein, 150 mg glucose, negative blood, 3–5 white blood cell count, and 0 red blood cells, with a urine protein-to-creatinine ratio of 29.7 g/g. A complete blood count showed pancytopenia (white blood cell count of $2.4 \times 10^3/\mu\text{l}$ (normal $4.0\text{--}11.0 \times 10^3/\mu\text{l}$), a hemoglobin level of 12.0 g/dl ($13.5\text{--}17.5$ g/dl), and a platelet count of $110 \times 10^3/\mu\text{l}$ ($150\text{--}400 \times 10^3/\mu\text{l}$). A retroperitoneal ultrasound did not show evidence of hydronephrosis. He was then initiated on hemodialysis. Serum antibodies to parvovirus B19 and human immunodeficiency virus 1 and 2 were negative.

A percutaneous kidney biopsy was performed (Figure 2) which showed 18 glomeruli per section on light microscopy, 8 of which were globally sclerotic. There were global collapsing changes with podocyte hypertrophy and hyperplasia (“pseudocrescents”) involving 4 glomeruli. A few additional glomeruli showed early segmental sclerosis. There was also mild acute tubular injury and mild interstitial fibrosis. Immunostain for parvovirus B19 was negative. Immunofluorescence showed 1+ staining for IgG, IgM, and kappa and lambda. Electron microscopy showed

diffuse podocyte foot process effacement and no electron-dense deposits.

He was treated with prednisone at 60 mg/day. Dialysis was discontinued after 4 sessions, and he experienced partial recovery of kidney function (SCr level of 2.1 g/dl). A bone marrow aspirate and biopsy were performed for workup of pancytopenia that revealed 92% blast cells, consistent with recurrent ALL. He was treated with R-CVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone), as well as intrathecal methotrexate and cytarabine. He achieved complete remission with minimal residual disease of ALL after 3 weeks of treatment and is currently undergoing maintenance therapy comprising of 6-mercaptopurine, vincristine, methotrexate, and prednisone. At last follow-up, 14 months since initiation of chemotherapy, his SCr level is 1.5 mg/dl, his serum albumin level is

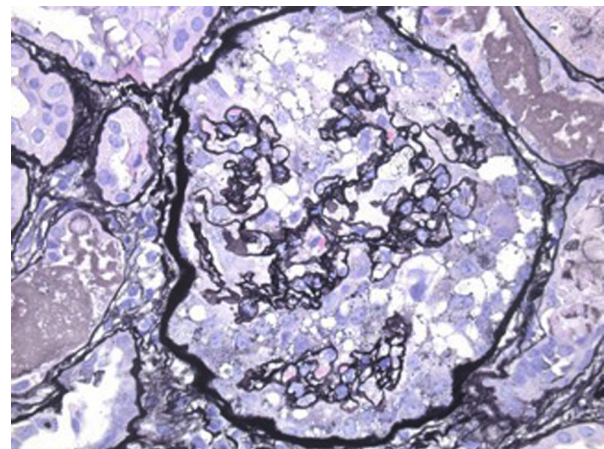


Figure 2. Glomerulus demonstrating a collapsing lesion, with a collapsed capillary tuft and epithelial hypertrophy and hyperplasia (Jones silver stain, original magnification $\times 400$).

3.7 g/dl, and his urine protein-to-creatinine ratio is 3.2 g/g.

DISCUSSION

A variety of paraneoplastic kidney diseases have been described in the literature, with perhaps the most common example being light chain cast nephropathy in the setting of multiple myeloma. However, establishing a pathophysiologic link between malignancy and kidney disease is challenging in many cases. Ronco³ has proposed criteria for establishing the diagnosis of a paraneoplastic glomerulopathy: (i) remission in renal disease occurs after complete surgical removal of the tumor, or with medical anti-neoplastic therapy; (ii) relapse of kidney disease is accompanied by relapse in the cancer; and (iii) a biologic link is established between cancer and kidney disease. Here, we present the case of a patient who developed nephrotic syndrome and was found to have FSGS on kidney biopsy prior to his initial presentation with B-cell ALL, who achieved remission of both ALL and nephrotic syndrome with chemotherapy, and who again presented with nephrotic syndrome and FSGS on kidney biopsy during relapse of ALL. With treatment for ALL, at

the time of publication, his ALL was in complete remission, and his nephrotic syndrome and acute kidney injury were improving. Our case fulfills Ronco's³ criteria 1 and 2, and the temporal association of both of his presentations with nephrotic syndrome and ALL is highly suggestive of a biologic link between cancer and kidney disease.

Nephrotic syndrome in the setting of ALL is rare. We conducted a search of the literature by using Medline/PubMed and Embase (up until December 2018), including the terms "focal segmental glomerulosclerosis," "collapsing," "leukemia," and "nephrotic." We also conducted online resource searches, through Google Scholar for full-text searches, and of reference lists of nephrology textbooks, review articles, and relevant studies. We also searched for relevant abstracts in the American Society of Nephrology Kidney Week abstract books for years 2010 to 2018. Our search was limited to articles in English or English translation. Table 1^{S1-S8} summarizes the published cases of nephrotic syndrome associated with ALL based on our literature search. All of these cases show the nephrotic syndrome preceding a diagnosis of ALL by anywhere from 4 months to 7 years, except for one patient reported by Prestidge *et al.*^{S8} a child who developed

Table 1. Reported cases of nephrotic syndrome and acute lymphoblastic leukemia

Case	Age (yr)	Sex	Race	Kidney function	Proteinuria	SAlb (g/dl)	Kidney biopsy histology	Treatment for NS	Time from NS diagnosis to ALL diagnosis (months)	Renal outcome	Hematologic outcome
1 ^{S1}	1.5	M	NR	NR	NR	NR	First biopsy: FSGS Second biopsy (4 yr after first biopsy): MCD	Prednisone cyclophosphamide ARA-C chlorambucil	84	Persistent NS during ALL treatment—long-term outcome NR	Remission
2 ^{S2}	2.5	M	NR	NR	NR	NR	None (steroid-responsive NS)	Prednisone Levamisole	16	No further relapses of NS while in hematologic remission	Complete remission
3 ^{S3}	3	M	I	NR	UA 4+ protein (>1000 mg/dl)	1.4	FSGS	Prednisone Cyclosporine	14	Deceased	Deceased
4 ^{S4}	3.5	F	NR	CrCl 182 ml/min per 1.73 m ²	NR	NR	First biopsy: MCD Second biopsy (11 mo after first biopsy): FSGS	Prednisone cyclophosphamide	5	Persistent proteinuria	Remission
5 ^{S5}	5	M	AA	NR	UA 4+ protein	1.4	FSGS	Prednisone Cyclosporine Tacrolimus	7	Persistent proteinuria, normal SCr	Remission
6 ^{S6}	12	M	AA	SCr 0.4 mg/dl	24-h urine protein 4290 mg	1.7	First biopsy: FSGS Second biopsy: FSGS	Prednisone	4	ESKD	Remission
7 ^{S7}	10	M	NR	NR	NR	NR	MCD	Prednisone	84	Remission prior to ALL	Remission
8 ^{S8}	3	M	W	"Normal"	UPCR 5.4 g/g	1.6	MCD	Prednisone	-0.3 ^a	Remission	Remission
9 (our case)	11	M	AA	SCr 0.7 mg/dl	UPCR 9.7 g/g	2.1	First biopsy: FSGS Second biopsy (11 yr after first biopsy): collapsing FSGS	Prednisone Tacrolimus	6	Remission followed by relapse after 10 yr	Remission followed by relapse after 10 yr

AA, African American; ALL, acute lymphoblastic leukemia; ARA-C, cytarabine; CrCl, creatinine clearance; ESKD, end-stage kidney disease; F, female; FSGS, focal segmental glomerulosclerosis; I, Indian; M, male; MCD, minimal change disease; NR, not reported; NS, nephrotic syndrome; SAlb, serum albumin; SCr, serum creatinine; UA, urinalysis; UPCR, urine protein-to-creatinine ratio; W, White.

^aMCD was diagnosed 9 d after ALL diagnosis.

nephrotic syndrome 9 days after diagnosis of ALL, which was also believed to be paraneoplastic. There were 2 cases reported by Sathiapalan *et al.*^{S9} (not included in Table 1) that described 2 African American children who both developed FSGS, at 32 and 15 months, respectively, after diagnosis of ALL. The authors concluded in their report that given the interval post-Adriamycin chemotherapy and the onset of nephrotic syndrome, the FSGS may have been induced by anthracycline exposure. There have also been 2 case reports of IgA nephropathy associated with ALL,^{S10,S11} both occurring in Japanese patients, and both cases were believed to be coincidental, given the high prevalence of IgA nephropathy in Japan.

Our case is unique for a few reasons. First, it is the first to describe a patient who achieved complete remission in proteinuria but then relapsed with nephrotic syndrome and ALL with a second biopsy that again showed FSGS. Other patients who underwent a second kidney biopsy did so for persistent proteinuria. Second, our patient's relapse episode is the first case of nephrotic syndrome and ALL described in an adult. Third, our patient is the first described to have FSGS with collapsing features, which may reflect severe, direct podocyte injury.

Patients who underwent kidney biopsy were found to have minimal change disease or FSGS, suggesting that the pathogenesis could be related to direct podocyte injury. Hodgkin lymphoma remains the most commonly reported hematologic malignancy associated with minimal change disease.^{3,4} A pathophysiologic link between hematologic malignancies and podocytopathies remains elusive. Circulating factors such as soluble urokinase receptor (suPAR)⁵ and cardiotrophin-like cytokine-1 (CLC-1)⁶ have been hypothesized to cause increased glomerular permeability, but none have been clinically validated.

In our case, we hypothesize a 2-hit mechanism for the patient's collapsing FSGS. Recent literature shows that mutations in *COL4A4*, podocyte, or *CAKUT* (congenital anomalies of kidney and urinary tract) genes are commonly found in patients with FSGS, particularly those with a family history of kidney disease or nephrotic syndrome.⁷ Additionally, given that our patient is African American, a contributing risk could be the presence of high-risk alleles in *APOL1*. Particularly given the collapsing FSGS features observed on both kidney biopsies in our case, one hypothesis is that the leukemic B cells produced a factor that is directly toxic to podocytes, and that our patient had a predisposition to this injury. Interferon has been shown to be an inducer

Table 2. Teaching points

FSGS is a potential herald of an underlying hematologic malignancy.

In the pediatric or young adult population with FSGS, it is important to be aware of paraneoplastic glomerular diseases and to obtain a careful clinical history and review of possible underlying hematologic malignancy.

Renal outcomes are favorable when hematologic remission is achieved in the setting of paraneoplastic FSGS.

Collapsing FSGS appears to be a form of paraneoplastic glomerular disease that correlates with hematologic status of remission or relapse.

FSGS, focal segmental glomerulosclerosis.

of *APOL1*-associated kidney injury in preclinical models^{S12} and in patients with collapsing FSGS on kidney biopsy,^{S13} and some studies have shown increased circulating interferon levels in patients with ALL.^{S14,S15} Our case description is limited by the lack of genetic testing for this patient.

Additional clinical evidence for the potential role of B cells in the pathogenesis of podocytopathies is demonstrated by accumulating literature supporting the use of rituximab for patients with steroid-sensitive and steroid-dependent nephrotic syndrome, most of whom have minimal change disease on kidney biopsy.⁸ This signal has not been as well established in steroid-resistant nephrotic syndrome and/or when FSGS is found on kidney biopsy. The literature describes ALL-associated paraneoplastic syndromes manifesting as neuropathies, myopathy, arthritis pericardial effusions, and cutaneous disease. These cases have not revealed the biologic link between tumor and paraneoplastic manifestation.

In conclusion, we present a patient who developed nephrotic syndrome and FSGS that was temporally associated with his initial and relapsed presentations of B-cell ALL. The treatment of the ALL resulted in improvement of renal disease (Table 2). Patients with paraneoplastic glomerular disease could also serve as important discovery cohorts in studies to uncover the pathogenesis of their idiopathic counterparts.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

[Supplementary References.](#)

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