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Successful treatment of collapsing focal segmental glomerulosclerosis in a patient

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ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is a recognized cause of renal disease worldwide. The collapsing variant is distinct from the others, characterized clinically by a more severe nephrotic syndrome generally resistant to immunosuppressive therapy. It is known that a great number of patients progress to end-stage renal disease. Recognizing this lesion in biopsy is frequently challenging owing to the focal nature of the process which highlights the need for keeping a high index of suspicion for the diagnosis. We report and discuss a case of a non-HIV collapsing FSGS, followed by a complete (unexpected) renal recovery after an oral corticosteroid course.

Implication for health policy/practice/research/medical education:

This report highlights a focal glomerulosclerosis collapsing variant diagnosis and treatment, which is of special interest considering its unexpected complete response after an oral corticosteroid course, during 19 months of follow up.

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Introduction

Focal segmental glomerulosclerosis (FSGS) is marked by a characteristic histologic presentation that embraces segmental scarring involving some but not all glomeruli.

Typically affecting young adults, it is the most common pattern of idiopathic nephrotic syndrome in African Americans, although with a recognized increasing incidence in other races (1,2).

It is described a median age of 30 to 40 years, nonetheless, a broad range has been reported, with patients between 1.5 years and 82 years old (3).

The collapsing form of FSGS (cFSGS) is a distinct morphologic variant, branded by segmental or global collapse of the glomerular capillary, swelling and hyperplasia of podocytes, tubulocystic changes and interstitial inflammation (4,5).

This condition has been described in non-HIV patients,

even though it was first recognized as associated with HIV infection (4,6,7). Numerous etiologies have been reported including viral/bacterial infections, autoimmune diseases, hematologic conditions and medications (8-10).

Comparing with the typical form of FSGS, characterized by segmental scars, cFSGS stands out by a more severe nephrotic syndrome, greater resistance to immunosuppressive treatment, and a rapid progression to end-stage renal disease (ESRD), having the worst prognosis among the different variants (1).

Several observational studies described decreased complete and partial remission rates, regarding different immunosuppressive treatments including corticosteroids, calcineurin inhibitors and cyclophosphamide (7).

Otherwise, we report a case of a non-HIV collapsing FSGS, followed by complete renal recovery after an oral corticosteroid course.

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Case Report

A 74-year-old Caucasian woman was admitted to the hospital for periorbital and lower limb edema, orthopnea, anorexia and foamy urine for two weeks. She also mentioned an episode of respiratory tract infection one month before presenting, treated with a 3-day course of clarithromycin. She denied fever, cough, hemoptysis, chest pain, sick contacts, vomiting, diarrhea, arthralgia, skin lesions, oral ulcers, dysuria and macroscopic hematuria.

The patient medical past comprised hypertension, treated for five years. She hadn't been submitted to any surgeries and had no reported allergies. She also denied alcohol intake, smoking or drug abuse. Her home medication consisted of losartan 100 mg plus hydrochlorothiazide 25 mg, once a day.

The physical examination was unremarkable, except for peripheral edema and bilateral crackles in the pulmonary auscultation. Her vital signs were within the normal range. Heart sounds were regular on cardiac auscultation with no murmur, rubs, or gallop. The abdomen was soft and non-tender and bowel sounds were audible in all four quadrants.

Laboratory tests revealed mild anemia (hemoglobin 9.4 g/L), a serum creatinine of 2 mg/dL [baseline 0.85 mg/dL], hypoalbuminemia (1.52 g/dL), hypercholesterolemia (total cholesterol 242 mg/dL, LDL 158 mg/dL) and moderate proteinuria (3.5 g/24-h), with no leukocytosis, thrombocytopenia or hematuria.

She started diuretics and albumin replacement. Serological evaluation for HIV, hepatitis B virus, hepatitis C, rapid plasma reagin (RPR), cytomegalovirus, antibodies to nuclear antigens (ANA), anti-neutrophil cytoplasmic antibody (anti-PR3 and anti-MPO), antiglomerular basement membrane antibodies, rheumatoid factor, anti-cardiolipin, and anti-beta 2 glycoprotein 1 were negative. Serum complement values (total, C3 and C4), free light chain (kappa and lambda), protein electrophoresis, immunofixation, beta 2 microglobulin and immunoglobulin (A, G and M) were within the normal range. Spikes weren't detected by urine and serum protein electrophoresis.

Renal ultrasound showed normal-sized kidneys and no hydronephrosis. A kidney biopsy was conducted and specimens were sent for light and immunofluorescent microscopy. There were 9 glomeruli in the biopsy fragment, one globally sclerosed and two of them with focal sclerosis, podocyte hyperplasia and prominent protein droplets in visceral epithelial cells (Figure 1).

One of the glomeruli presented with severe podocyte hyperplasia conditioning capillary tuft collapse (Figure 1 – panel A and B). Additionally, there was severe acute tubular injury, evidence of mild mononuclear interstitial infiltrate and about 50% of diffuse edema of the cortical

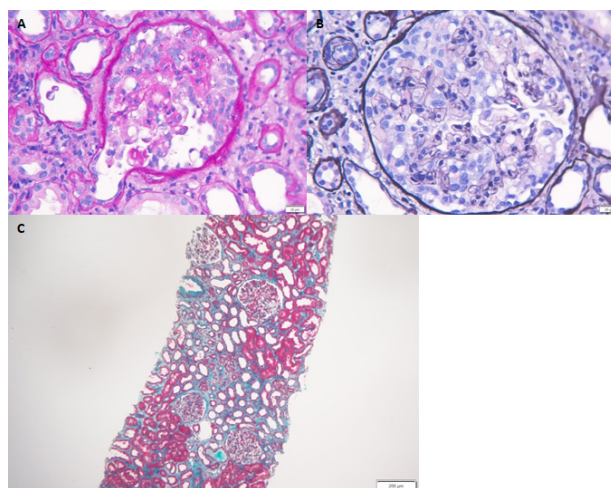


Figure 1. Renal biopsy showing collapsing FSGS with microtubular dilatation: (A) A globally “collapsed” glomerulus with prominent epithelial cell hyperplasia. Periodic acid-Schiff staining; (B) The same globally “collapsed” glomerulus on Silver stain; (C) Trichrome stain showing severe acute tubular injury, mild mononuclear interstitial infiltrate and diffuse edema of the cortical.

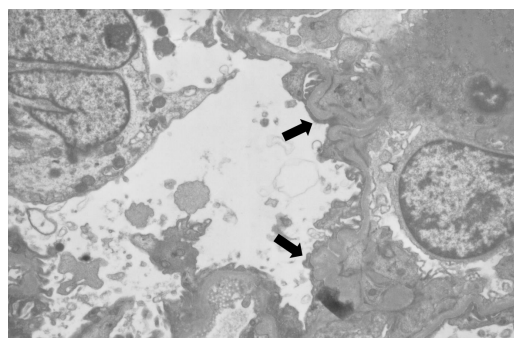


Figure 2. Evaluation of the kidney biopsy specimen by electron microscopy showed capillary loop with prominent foot process effacement (arrows). Electron photomicrograph (×9000).

(Figure 1– panel C). Arterioles showed mild to moderate intimal hypertrophy. Immunofluorescence studies showed no significant glomerular staining for IgM, IgG, IgA, C3, C1q, fibrinogen, albumin and kappa or lambda light chains. Electron microscopy revealed podocyte foot process effacement without immune complex deposits (Figure 2).

A cFSGS diagnosis was made and prednisone was started at 60 mg daily (1 mg/kg/d). There was a favorable clinical evolution, with progressive improvement of peripheral edema although kidney function did not return to her baseline. The patient was discharged 5 days later with a corticosteroid (prednisone 60 mg), angiotensin-converting enzyme inhibition (losartan 50 mg/d), a statin and a loop diuretic (furosemide 40 mg/d). In the fourth month of follow-up, during prednisone tapering, serum creatinine dropped to the baseline value (0.9 mg/dL), 24-hour urine protein was 1.1g, serum albumin 3.7 g/dL,

without any symptoms.

The patient has now been followed up for 19 months and remains asymptomatic. On her last follow-up, her 24-hour urine protein was 365 mg, serum creatinine 0.9 mg/dL and serum albumin 4.1 g/dL. Figure 3 shows the evolution of her clinical and laboratory parameters during the course of the treatment.

Discussion

This case refers to an adult-onset collapsing FSGS, which was successfully treated after a corticosteroid course, maintaining total remission after a 19-month follow-up, without requiring additional immunosuppressant drugs.

Collapsing FSGS constitutes 11-23.7% of FSGS cases, most of them idiopathic or associated with HIV, although it has been reported to occur in association with a growing list of disorders. The collapsing form of FSGS assumes a particularly deprived prognosis regarding renal survival. Irrespective of the etiology, the clinical course is remarkably uniform and most cases rapidly progress to ESRD (11).

Collapsing glomerulopathy consists of a morphologic variant of FSGS, being characterized by a global or segmental implosion of capillary loops and string prominence of visceral epithelial cells. As in classical FSGS, patients present with a nephrotic syndrome that usually becomes steroid-resistant.

It is important to reinforce that the kidney biopsy diagnosis of cFSGS is not the end-diagnosis, since the lesion is not a single entity and requires an extensive differential diagnosis. The list of etiologic agents/associated conditions includes primary (idiopathic) FSGS, SV40 infection (Simian virus 40 infection), parvovirus B19 infection, acute cytomegalovirus infection, interferon therapy, pamidronate toxicity, acute vaso-occlusive injury and occasional familial forms.

Therefore, the detection of a cFSGS in kidney biopsy led us to search for these etiological factors, none present

in our patient. Therefore, lacking the usual associations, namely age group, African-American race or history of intravenous drug abuse, infection would be the only known risk factor in this case, despite no agent was identified. This may provide support to the theory that immune dysregulation due to infection per se, rather than infection by specific viral agents, may lead to collapsing glomerulopathy in susceptible individuals.

The pathogenesis of cFSGS is an area of intensive research, but the picture is still far from clear. It has been hypothesized that, unlike other podocytopathies, the podocyte suffers a dedifferentiation process resulting in a dysregulated phenotype. Pathologic podocytes display a differentiation loss and proliferation gain. Podocytes have been described to “transdifferentiate” towards a macrophage-like cell (12).

The main challenge remains the recognition of this lesion in the biopsy specimen, considering the focal nature of the process. This is a highlighting case, stressing the need for high index suspicion for the diagnosis since we found the characteristic collapsing glomerular lesion in one solitary glomerulus included in the biopsy that could have easily been missed if not meticulously and carefully sought by the examining pathologist.

The prognosis of cFSGS in non-HIV patients has been uniformly dismal. According to several observational studies regarding response to treatment of cFSGS, the rates of durable complete and partial remission were 9.6 and 15.2%, respectively (7).

Nowadays therapeutic strategies are anecdotal and equivalent to those used for non-collapsing FSGS, based on steroids or immunosuppressive agents. There is plenty of variation between studies regarding therapeutic agents, their dosages, duration and even the definition of response, which contributes to irregular results between series (3). Renin-angiotensin-aldosterone system antagonism therapy is central to all progressive chronic kidney disease, directly addressing the hemodynamic

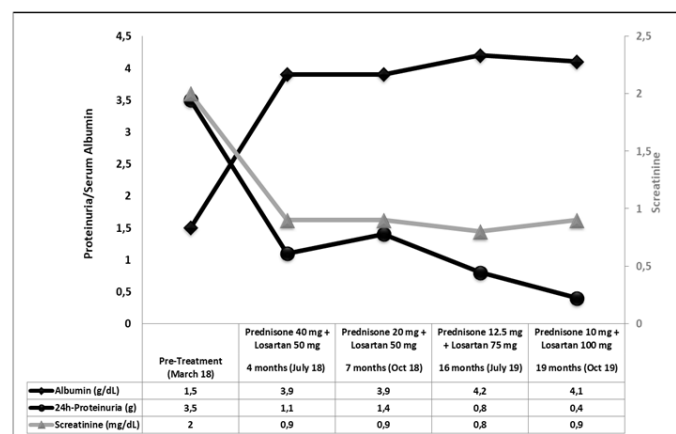


Figure 3. Temporal evolution of the laboratory parameters during the course of the treatment.

changes in adaptive FSGS. It may not only reduce blood pressure but also proteinuria in primary FSGS adjunctive to immunosuppressive therapies (13). Plus, antiplatelet agents/anticoagulants, and lipid abnormality-ameliorating agents are used as adjuvant therapy (14).

Response to steroid therapy is probably one of the best predictors of long-term prognosis in FSGS (5). Furthermore, even though disease definition relies on glomerular lesions, it is known that it's the extent and severity of acute and chronic changes in the tubulointerstitial compartment that determine the prognosis of the disorder (2).

Conclusion

In summary, this case reports a rare subtype of FSGS called collapsing FSGS. FSGS encompasses a complex set of syndromes, most with multiple causes. Hence, FSGS represents a diagnostic challenge that requires close and thoughtful team collaboration to gather the necessary data (patient, family, nephrologist and pathologist). Information from clinical history, laboratory testing, renal biopsy, and in some patients, genetic testing can be used to identify which syndrome is present, guide therapy, and provide prognostic information.

We believe that in some patients there might be an infectious trigger for cases of collapsing FSGS initially considered to be idiopathic, although some of them remain unraveled. Despite this possible association, the implications of this infection on the prognosis and treatment of the disease remain unclear. It is important to identify patients who present with nephrotic-range proteinuria secondary to FSGS, since early treatment may alter the course of the disease and prevent relentless progression to terminal renal failure.

Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical considerations

The patient gave her written informed consent for publication of this report.

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