Collapsing focal segmental glomerulosclerosis due to SARS-CoV-2: A scary diagnosis

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ABSTRACT

Collapsing focal segmental glomerulosclerosis (collapsing FSGS) is a rare morphological variant of focal and segmental glomerulosclerosis characterized by collapse of the glomerular capillaries, podocytes hypertrophy and hyperplasia and severe tubulointerstitial disease. The pathogenesis is still unclear and multiple conditions as viral infections, autoimmune disorders and drugs can be the cause of this entity. One of the most described risk factors is the presence of *APOL1* gene mutation, generally seen in Black race patient with sub-Saharan African descent. Most recently, SARS-CoV-2 has been associated with this entity with a few cases described in the available data. Here we report a case of a 70-year-old patient without any history of kidney disease, who was infected with COVID-19 and admitted to the hospital with non-oliguric acute kidney injury KDIGO stage III. Due to the non-recovery of renal function, laboratory blood tests were performed and tested positively for antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies PR-3. Renal computerized tomography showed normal sized kidneys with normal cortical and parenchymal differentiation. Because of the suspicion of ANCA vasculitis, the patient started immunosuppression with methylprednisolone and cyclophosphamide and a kidney biopsy was performed, which showed a collapsing focal segmental glomerulosclerosis. The patient didn´t recover renal function and started hemodialysis, which maintained until these days. After deliberation by the medical team, following clinical, laboratory and histological findings, the diagnosis of FSGS collapsing was assumed to be more likely due to SARS-CoV-2 infection.
This case report aims to highlight a rare entity which treatment and management remains unknown with poor prognosis. Since the beginning of the COVID-19 pandemic in December of 2019, few cases were described.

Keywords: Glomerular diseases. Collapsing glomerulopathy. Kidney. SARS-CoV-2.

INTRODUCTION

Collapsing focal segmental glomerulosclerosis (collapsing FSGS) is a rare morphological variant of FSGS characterized by segmental and focal collapse of the glomerular capillaries, podocytes hypertrophy and hyperplasia and severe tubulointerstitial disease. Pathogenesis has not yet been clarified and generally the most usual form of clinical presentation is nephrotic syndrome. This entity is commonly observed in patients with human immunodeficiency virus infection. However, it can be idiopathic and, since 2020, it has been described in association with SARS-CoV-2 infection. The treatment of this entity remains unknown. Unfortunately, this glomerulopathy has poor prognosis, with rapid progression to end-stage renal disease requiring definitive renal replacement therapy.

Here, the authors present a case of an adult with a collapsing FSGS due to SARS-CoV-2 infection.

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CASE REPORT

70-year-old female Caucasian patient with a personal history of essential hypertension controlled and treated with lercanidipine 10 mg and valsartan 160 mg, with no other relevant personal history. The patient was admitted to the hospital on January 20 of 2022 for asthenia, diarrhea and dyspnea with five days of duration. Two weeks before hospital admission, on January 5 of 2022, the patient had been diagnosed with mild COVID-19 infection and presented with a dry cough, odynophagia and generalized myalgias which were treated only with paracetamol 1000 mg every 8 hours for two days with complete relief of symptoms. From the personal history, it should be noted that

this patient had not been vaccinated against the SARS-CoV-2 virus. The patient denied fever, weight loss, vomiting, abdominal pain, arthralgias, skin lesions, urinary symptoms. On physical examination, was noted a respiratory frequency of 25 breaths per minute, blood pressure of 188/78 mmHg, heart rate 110 beats per minute and bimalleolar oedema. Laboratory results showed normocytic normochromic anemia with hemoglobin 8.3 g/dL, platelets 239 x 10^3/µL, serum creatinine 7.96 mg/dL (baseline 1.01 mg/dL) and serum urea 301 mg/dL, hyperkalemia 5.9 mmol/L, C-reactive protein 18 mg/dL and sedimentation velocity greater than 120 mm. The urine analysis showed countless erythrocytes, rare leukocytes and proteins of 300mg/dL. Arterial gasometry collected with a FIO_2 of 21% showed metabolic acidemia (pH 7.30, $PaCO_2$ 23 mmHg, PaO_2 103 mmHg, SaO_2 98.3%, HCO_3 11.8 mmol/L). She was admitted for non-oliguric acute kidney injury (AKI) KDIGO stage III of an unclear etiology. From the study carried out during hospitalization, the patient presented a normal peripheral blood smear, hypoalbuminemia, hypercholesterolemia, urinary protein/creatinine ratio 13.89 g/g, positive antinuclear antibodies (ANA) with a title of 1/320 and positive antineutrophil cytoplasmic antibodies PR-3 (ANCA) with a title of 1/160, namely 139.8 U/mL. Anti-glomerular basement membrane antibodies were negative. The serum complement levels were normal. The RT-PCR SARS-CoV-2 test was persistently positive. Viral serology tests for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus (CMV), human herpes virus 8 (HHV-8), Epstein Barr virus (EBV) and Parvovirus B19 (PB19) were all negative. The remaining analytic results and etiological analytical study are presented in table 1 and table 2, respectively. A renal

Table 1. Analytical results

Analytical parameters	Results	Reference value
Hemoglobin (g/dL)	8.3	13.7-17.3
Hematocrit (%)	35	40.0-51.0
White blood cell count (10^3/µL)	9.2	4.8-10.8
Platelets (10^3/µL)	239	144.0-440.0
Sedimentation velocity (mm)	> 120	< 20
Creatinine (mg/dL)	7.96	0.70-1.20
Blood urea nitrogen (mg/dL)	301.0	16.6-48.5
Sodium (mmol/L)	139.0	136.0-145.0
Potassium (mmol/L)	5.90	3.50-5.10
Chloride (mmol/L)	95.0	98.0-107.0
Phosphorus (mmol/L)	5.20	2.50-4.50
Calcium (mmol/L)	8.38	8.90-10.30
Albumin (g/L)	27.5	35.0-62.0
GPT (U/L)	26.2	< 33.0
GOT (U/L)	29.0	< 32.0
Alkaline phosphatase (U/L)	45.0	35.0-104.0
Gamma-glutamyl transferase (U/L)	23.0	5.0-36.0
Total bilirubin (mg/dL)	0.17	< 1.20
Lactate dehydrogenase (U/L)	313.0	< 250.0
Total cholesterol (mg/dL)	244.0	< 200.0
C-Reactive protein (mg/dL)	18.0	< 5.0
Creatine kinase (U/L)	238.0	< 170.0
B-type natriuretic peptide (pg/mL)	5467	< 300
Urine analysis II	Density: 1.008; pH: 8.0; nitrites: negative; proteins: 300 mg/dL; glucose: 70 mg/dL; leukocytes: rare; erythrocytes: countless;	

Table 2. Etiological analytical study

Analytical parameters	Results	Reference value
Complement C3 (mg/dL)	103.0	70.0-176.0
Complement C4 (mg/dL)	30.9	12.0-36.0
Serum protein electrophoresis		
– Total protein (g/L)	55.9	60.0-80.0
– Albumin (g/L)	25.4	38.0-49.0
– Alfa 1 (g/L)	4.4	1.8-3.5
– Alfa 2 (g/L)	8.8	3.4-7.4
– Beta 1 (g/L)	4.9	3.8-6.4
– Beta 2 (g/L)	4.7	1.7-5.0
– Gama (g/L)	7.7	6.8-15.0
– Albumin/globulin ratio	0.83	
General serum immunology		
– IgG (mg/dL)	882.0	700.0-1600.0
– IgA (mg/dL)	370.0	70.0-400.0
– IgM (mg/dL)	78.0	40.0-230.0
– Kappa free light chains	253.0	170.0-370.0
– Lambda free light chains	147.0	90.0-210.0
– Kappa/lambda ratio	1.72	1.35-2.65
Antinuclear antibodies	Positive 1/320	
Anti-DsDNA antibodies	Negative	
Antineutrophil cytoplasmic *antibodies PR-3 (ANCA)*	Positive 1/160 *139,8 U/mL*	
Anti-glomerular basement membrane antibodies (Anti-GBM)	Negative	
HIV ½ antibody/antigen test	Negative	
HCV serology: Anti-HCV	Negative	
HBV serology: HBsAg, Anti-HBs and Anti-HBc	Negative	
IgG and IgM Cytomegalovirus antibodies	Negative	
Parvovirus B19 IgG antibodies	Negative	
Epstein-Barr virus VCA-IgG, VCA-IgM and EBNA-IgG	Negative	
Influenza A and B RT-PCR test	Negative	
Blood cultures (aerobic and anaerobic)	Negative	
Urine culture	Negative	
Stool culture	Negative	

and urinary tract computed tomography showed normal sized kidneys and no evidence of an obstructive cause for the AKI. Initially, the main diagnostic hypothesis was ANCA vasculitis, so the patient started immunosuppressive treatment therapy with methylprednisolone and then cyclophosphamide. Subsequently, for a better understanding of the clinical picture, a renal biopsy (fig. 1 and 2) was carried out, which revealed «19 glomeruli in terminal sclerosis due to glomerulonephritis; in the remaining 17 glomeruli, there were sclerosing lesions of varying size with adhesions to Bowman's capsules and a large part with evident podocyte hyperplasia and hypertrophy with drops of resorption leading to the collapse of the capillary balloons (collapsing form of segmental sclerosis), severe tubulointerstitial disease with intense lymphoplasmocytic infiltrate; the blood vessels didn't show any changes». After this unexpected biopsy result and excluding other etiologies, the medical team considered has the

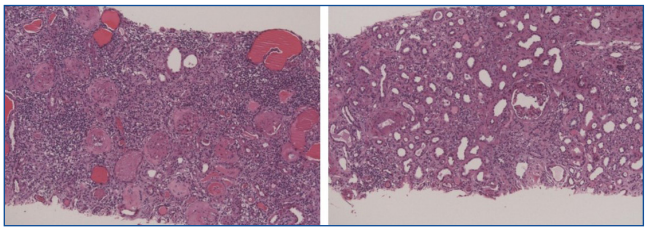

Figure 1. Photomicrographs showing severe tubulointerstitial disease with intense lymphoplasmacytic infiltrate (hematoxylin-eosin, 100×).

most likely diagnosis to be collapsing FSGS associated with SARS-CoV-2 infection. Unfortunately, due to the lack of improvement in renal function and no clinical response to immunosuppressive therapy, the patient started hemodialysis and was discharged on a chronic dialysis program.

DISCUSSION AND CONCLUSIONS

Collapsing FSGS is a rare, complex and serious entity. It is considered a morphological variant of FSGS that has been gaining great interest in the scientific community for a number of reasons. It has a global distribution and in the last few years, incidence has been increasing with a predilection for individuals of the Black race[1]. This disorder is known for a rapidly progress to end-stage renal disease with no therapy available currently[2].

Many etiologies have been described for this entity, which may be idiopathic or have a secondary cause, namely viral infections (PB19, CMV, VHB, VHC, EBV and Influenza virus), autoimmune diseases like systemic lupus erythematosus and Still's disease or the use of high doses of pamidronate or interferon alpha[3]. At the moment, collapsing FSGS is the most common nephropathy associated with human immunodeficiency virus infection. It is interesting to note that the association of ANCA vasculitis with collapsing FSGS is exceedingly rare, with only one case of ANCA vasculitis documented in the available literature[4]. In that clinical case described by Singh et al., a male patient presented with 3 months of intermittent fever, dry cough, arthralgias in small joints and sub-nephrotic proteinuria of 2.4 g. On the other hand, in this clinical case, the patient did not experience any systemic symptoms suggesting vasculitis, in addition to having nephrotic proteinuria, which makes this hypothesis less likely.

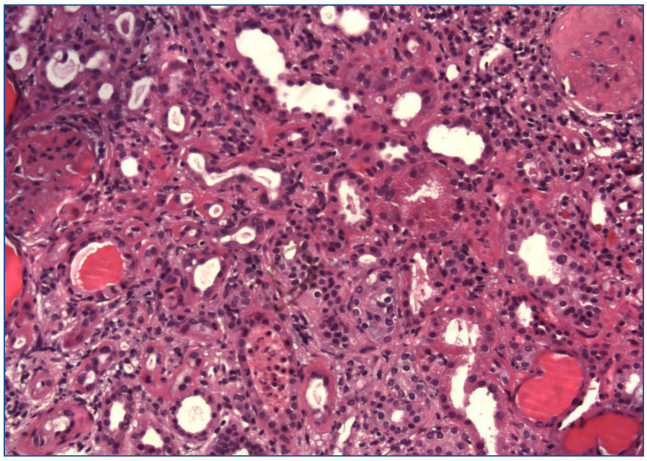

Figure 2. Photomicrograph showing proliferating podocytes and collapsed tuft (hematoxylin-eosin, 200×).

On the other hand, patients with mutations in the *APOL1* gene have been shown to be more prone to the onset of this entity, particularly Black individuals of sub-Saharan African descent. More recently, it is known that SARS-CoV-2 infection is associated with this disorder and few cases are described in the literature since the emergence this virus in December of 2019 in Wuhan, a province from China. Thus, it is believed that this diversity of causes and/or probable associations shows that collapsing FSGS is not a singular pathology, but rather an end product of different insults culminating in an identical histological outcome[5].

The pathogenesis of collapsing FSGS associated with SARS-CoV-2 (COVAN) is not yet fully understood. It is believed that several mechanisms act together and are responsible for kidney damage, namely a cytokine storm caused by the inflammatory response, direct cytopathic damage through the use of angiotensin-converting enzyme two as a substrate and endothelial damage, among others. Several studies carried out on patients infected with SARS-CoV-2 have shown that on hospital admission, around 40% to 60% of patients have proteinuria, 25% have hematuria and 19% have high serum creatinine levels[6].

Generally, from a histological point of view, podocytes undergo phenotypic and immunohistochemical changes with prominent hypertrophy and hyperplasia, collapse of glomerular capillaries tufts with pseudocrescents formation[7,8]. Although characteristic glomerular changes defined this entity, tubulointerstitial involvement can occur like tubular atrophy, interstitial fibrosis, edema, inflammation and the formation of microcysts[9].

According to the cases reported in the literature, this glomerulopathy manifests with nephrotic range proteinuria, arterial hypertension, hypoalbuminemia, hypercholesterolemia and edema[10]. The diagnosis is made throughout the histological evaluation of the renal biopsy where the respective glomerular alterations are found.

According to a longitudinal analysis published in 2022, which included 23 patients with collapsing FSGS, all the patients presented with nephrotic range proteinuria without oliguria[11]. Sixty-one percent (n = 14) of the patients required dialysis on admission and seven of these remained on a chronic dialysis program after hospital discharge. Of the patients who did not require dialysis and the patients who became dialysis-independent, none of them achieved total recovery of renal function to baseline values and all were left with proteinuric chronic kidney disease. This study, although retrospective, highlights the variability of the long-term outcome of this entity.

In short, with this clinical case, the authors aim to demonstrate one of the most serious manifestations of SARS-CoV-2 infection with serious and chronic kidney damage and want to highlight the importance and urgency of conducting prospective studies in the treatment of collapsing FSGS. The rapid progression to end-stage renal disease and the need for renal function replacement therapy is real and deserves to be taken seriously.

Conflict of interest

The authors have no conflict of interest to declare. This case report has not received any contribution, grant or scholarship. The authors declare that they have followed the protocols of their work center on the publication of data from patients. The patient agreed with the submission of this case report.

This case report has never been submitted before.

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