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CASE REPORT

Double glomerulopathies or two-faced janus? A challenging case in the COVID-19 era

Giuliana Papalia[1] · Simona Barbuto[1] · Anita Campus[1] · Gisella Vischini[1]

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Abstract

SARS-CoV-2 very often causes kidney involvement through various mechanisms including: acute tubular injury, virus cell invasion, vascular damage due to hypercoagulability and finally dysregulation of the immune system. Even though there are no pathognomonic morphologic features that can rule out or confirm direct damage by SARS-CoV-2, the latest literature suggests that there may be some association. SARS-CoV-2 infection represents a poor prognostic factor, regardless of pulmonary involvement. We report a challenging case with complex renal biopsy findings suggestive of collapsing glomerulopathy and focal proliferative IgA-dominant glomerulonephritis in a patient affected by active hepatitis C virus (HCV), SARS-CoV-2 infection and personal history of cocaine abuse.

Keywords Glomerulopathy · Collapsing · SARS-CoV-2 · HCV

Introduction

SARS-CoV-2 infection most frequently affects the lungs, but other organs can be affected [1]. Renal involvement is common and it may be revealed by various laboratory findings; Li et al. showed that on the day of admission, 59% of patients with SARS-CoV-2 infection had proteinuria, 44% hematuria, 14% increased blood urea nitrogen levels and 10% increased serum creatinine levels [2].

The exact pathophysiology of renal insult is still unclear, but it is widely accepted that it could result from several types of injury. Data emerging from kidney biopsies and autopsies provide more detailed information about etiology. Glomeruli are the most often affected nephron compartment, especially in the form of focal segmental glomerulosclerosis (FSGS) collapsing variant [3].

Similarities between SARS-CoV-2 kidney lesions and those observed in HIV-associated nephropathy (HIVAN) have led to the use of the term COVAN for SARS-CoV-2-associated nephropathy which presents with a histological pattern of collapsing glomerulopathy [4].

Other types of glomerular diseases have been reported with varying frequency, but it is not possible to rule out that they are incidental findings; among these, only few cases of IgA nephropathy have been observed.

We describe the case of a patient with cocaine abuse, worsening renal function associated with nephrotic proteinuria during HCV and SARS-CoV-2 infection, in the absence of other symptoms or pulmonary involvement.

Case report

In September 2020, a 49-year-old Tunisian male with a past medical history of multifactorial liver cirrhosis (i.e. alcoholic and 1b genotype HCV infection) and active cocaine use was admitted to our Emergency Department for new onset ascites, bilateral lower extremity edema and oliguria.

On arrival he was afebrile, hemodynamically stable with blood pressure 155/90 mmHg, heart rate 75/min and oxygen saturation 99% on room air. PCR throat swab testing for SARS-CoV-2 was performed and resulted negative.

Laboratory investigations revealed reduced estimated glomerular filtration rate (eGFR 59 mL/min/1.73 m2) and increased serum creatinine (sCr 1.64 mg/dL), normal sodium (Na+ 138 mmol/L) and potassium (K+ 5.1 mmol/L) serum

✉ Anita Campus
anita.campus@studio.unibo.it

[1] Nephrology, Dialysis and Renal Transplant Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Alma Mater Studiorum University of Bologna, Via Massarenti 9, 40138 Bologna, Italy

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levels, increased b2-microglobulin (B2M 6.6 mg/L) and cystatin C (CysC 2.44 mg/L) serum levels.

Urinalysis revealed non selective glomerular nephrotic-range proteinuria (UP 22 g over 12-h urine collection), microscopic hematuria (MH 1000 red blood cells/microL), microalbuminuria (UMAlb 250 mg/dL) and active cocaine metabolites. Other laboratory characteristics are reported in Table 1.

During hospitalization the patient became febrile (38.6 °C); blood cultures were collected twice resulting negative both times, as did PCR (0.08 mg/dL) and PCT (0.2 ng/mL). No signs of volume overload or evidence consistent with microbial infection were detected on chest X-ray. Abdominal ultrasonography revealed normal volume hyperechoic kidneys with increased cortical echogenicity and loss of corticomedullary differentiation.

Diuretic therapy was started leading to resolution of ascites. The patient was discharged and referred to our Nephrology department to undergo renal biopsy.

On 28th October, 2020 he underwent a PCR throat swab test for SARS-CoV-2 which resulted positive and was therefore admitted to a COVID-Unit. He did not require any specific treatment for SARS-CoV-2 infection.

Table 1 Laboratory characteristics at admission

Anti-thyroglobulin antibodies (TgAb)	17 UI/mL
Anti-thyroperoxidase antibodies (TPOAb)	118 UI/mL
Free triiodothyronine (FT3)	2,3 pg/mL
Thyrotropin (TSH)	1,4 UI/L
Total cholesterol (TC)	260 mg/dL
Triglycerides	170 mg/dL
Complement C3 (C3)	86 mg/dL
Complement C4 (C4)	14 mg/dL
Immunoglobulin A (IgA)	417 mg/dL
Hepatitis C virus ribonucleic acid (HCV-RNA)	202,613 UI/mL
Antinuclear antibodies (ANA)	1:80 speckled pattern 1:160 "rods and ring" pattern
Anti-neutrophil cytoplasm antibodies (ANCA)	Negative
Anti-phospholipase A2 receptor antibodies (anti-PLA2R Ab)	Negative
Extractable nuclear antigen (ENA)	Negative
Anti-glomerular basement membrane antibodies (anti-GBM Ab)	Negative
Serum amyloid A (SAA)	Negative
Free light chain ratio (FLC ratio)	1.1
Serum protein electrophoresis (SPEP)	Negative
Urine immunofixation electrophoresis (UIFE)	Negative
Cocaine metabolite in urine	Positive

After 10 days his throat swab for SARS-CoV-2 turned negative, therefore he was admitted to our Nephrology Department where an ultrasound-guided percutaneous kidney biopsy was performed. Light microscopy demonstrated 8 glomeruli, none of which were globally sclerotic. Four glomeruli showed segmental sclerosis, one of which was a collapsing variant. In addition, one glomerulus presented with segmental endocapillary hypercellularity and double contours (Fig. 1). There was disproportional interstitial fibrosis and tubular atrophy in about 50% of the sample with focal microtubular dilatation (Fig. 2). Immunofluorescence study was positive for IgA (3+) (Fig. 3) and C3 (2+) in the mesangium and along the capillary wall. Taken together all these histological features were suggestive of focal proliferative IgA-dominant glomerulonephritis. Moreover, there was focal acute tubular necrosis and moderate acute

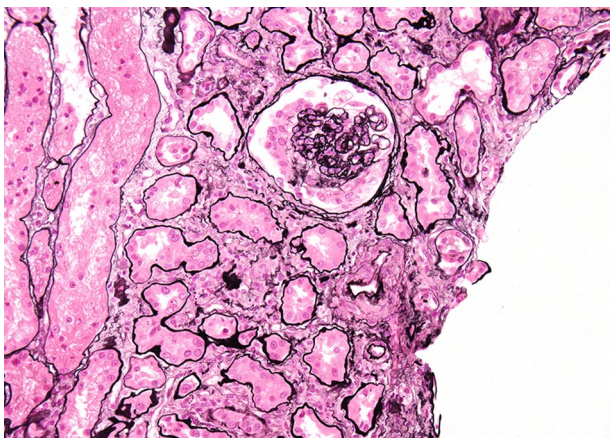

Fig. 1 Kidney biopsy findings. Jones silver stain. Original magnification ×200. Glomerulus presenting segmental sclerosis collapsing variant, characterized by the collapse of the capillary loops and segmental endocapillary hypercellularity

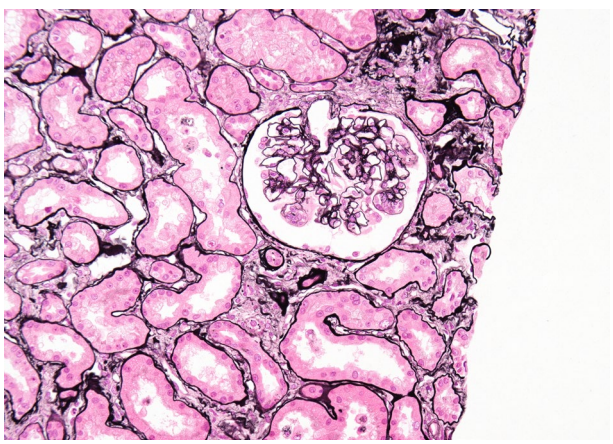

Fig. 2 Kidney biopsy findings. Jones silver stain. Original magnification ×200. Glomerulus hypercellularity. Tubular atrophy

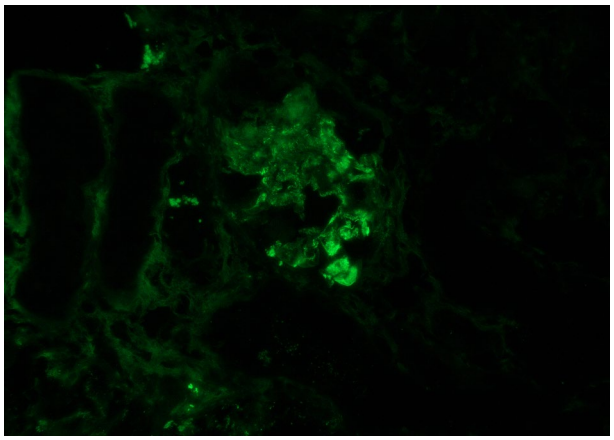

Fig. 3 Kidney biopsy findings. Immunofluorescence study. Deposition in the mesangium and along the capillary wall for IgA

tubular injury characterized by cellular swelling and loss of brush border. Electron microscopy was not performed nor were immunohistochemical studies for SARS-CoV-2 on paraffin-embedded tissue.

The final diagnosis was consistent with a dual glomerulopathy pattern of injury: FSGS collapsing variant and IgA-dominant glomerulonephritis.

The patient was discharged dialysis independent but with worsened renal function (sCr 2.27 mg/dL, eGFR 33 mL/min). Oral steroid administration (0.6 mg/Kg/die) was administered which was then rapidly withdrawn due to new onset, imbalanced iatrogenic diabetes. Antiviral therapy with Sofosbuvir and Velpatasvir was started. Two months later, at follow-up, his serum creatinine had worsened (3.1 mg/dL) and proteinuria had dropped to 4 g/24 h. There was complete clearance of HCV replication (HCV-RNA < 12 UI/mL) and serum IgA was in the normal range (IgA 252 mg/dL). Cocaine metabolites still remained detectable in the urine.

Discussion

Renal involvement is common in SARS-CoV-2 infection, and it is recognized as a poor prognostic factor. The incidence is variable, depending on the population and the setting. In patients requiring hospitalization, it is estimated to be 5.1% [5].

Several theories have been proposed to explain the pathogenesis. Acute renal injury (AKI), may be secondary to acute tubular injury (ATI), as a result of ischemic damage due to persistent volume depletion. The virus might induce dysregulation of the immune system resulting in a cytokine storm, a state of hypercoagulability and endothelial cell dysfunction that could favor the formation of thrombi in the renal vessels [6]. Furthermore, some authors have suggested the possibility of direct viral injury, but immunohistochemistry for SARS-CoV-2 resulted positive only in < 1% of tubular epithelial cells and in situ hybridization resulted negative; virus-like particles have been described in vacuoles or cisternae at electron microscopy, but they seem to be clathrin-coated vesicles [7]. Due to the absence of traces of the virus in the renal parenchyma it is difficult to identify a causality link between SARS-CoV-2 infection and histological lesions.

In the largest multi-center retrospective study conducted to date by May et al., encompassing 284 kidney biopsies performed in patients with ongoing kidney failure up to three months after SARS-CoV-2 infection, collapsing glomerulopathy represents the most common type of glomerular disease observed in native kidneys [3].

In the case we report, biopsy revealed the presence of two coexisting types of glomerulonephritis: collapsing glomerulopathy, according to epidemiological data, and IgA-dominant glomerulonephritis.

Collapsing glomerulopathy is a rare histological pattern of injury which is associated with viral infections such as HIV, malignancies, autoimmune conditions and drug toxicity or abuse. The activation of interferon (INF) is the common denominator for most of these etiologies, as is demonstrated by the presence of endothelial tubuloreticular inclusions at electronic microscopy [8].

Even though the chronic use of cocaine by our patient could not be definitively excluded as a possible etiologic agent, the temporal correlation between new onset nephrotic-range proteinuria and SARS-CoV-2 infection (i.e. less than three months) suggests the predominant role of the virus rather than of the drug in the pathogenesis. In addition, biopsy revealed the presence of microcystic dilatation in some tubular profiles which are very similar to those observed in patients affected by HIVAN. This aspect allows us to speculate that the same type of lesions might be associated with SARS-CoV-2.

Moreover, although the patient kept using cocaine, proteinuria markedly dropped after virus clearance without any significant immunosuppressive therapy,which had to be discontinued early due to the iatrogenic side effects.

Nevertheless, we could not completely exclude the presence of histological signs related to chronic cocaine use, especially with regard to interstitial fibrosis and non collapsing segmental sclerosis in three of the four glomeruli involved, as previously reported by Jaffe et al. [9].

An interesting feature of collapsing glomerulopathy is that it prevails in African-American subjects: 60.7% of people affected by SARS-CoV-2 infection undergoing kidney biopsy carry the APOL1 high risk variant, which confers a selective advantage against trypanosomiasis but it increases the probability of developing collapsing glomerulopathy as per the double hit model. Considering the ethnicity of our patient, we speculate a possible APOL1 variant [10].

Kidney data from the study by May et al. described other nephropathies in patients with SARS-CoV-2

infection: minimal change disease, non-collapsing FSGF, pauci-immune crescentic glomerulonephritis, membranous nephropathy, myoglobin cast nephropathy, thrombotic microangiopathy, etc. There was a lower frequency of chronic diseases such as diabetic nephropathy, arterionephrosclerosis, and IgA nephropathy regarding the general population as the biopsies were performed during acute kidney injury [3].

We found superimposed IgA-dominant proliferative glomerulonephritis in our patient.

IgA renal deposits are typical features in cirrhotic patients even though their pathogenetic role is still unclear; reduced IgA clearance due to liver dysfunction may lead to IgA deposition in the glomeruli mimicking IgA nephropathy. Both IgA nephropathy and alcoholic cirrhosis abnormally glycosylate IgA1 and soluble CD89-IgA and IgG-IgA complexes, all of which are common mechanisms for distinct diseases [11].

In our patient, serum IgA levels were increased during HCV replication and they decreased after reducing the viral load.

Post-infectious glomerulonephritis related to SARS-CoV-2 has been described in the literature: the virus may act as a super antigen, similarly to Staphylococcus Aureus, activating B cells that subsequently produce polyclonal IgA and IgG, with glomerular deposition [12]. Therefore, in our patient IgA clearance after specific therapy for HCV suggests that IgA deposition is more likely associated with liver dysfunction than with SARS-CoV-2 infection. An interesting finding is that in IgA glomerulonephritis related to HCV, immunofluorescence usually shows a less intense complement deposition than what we found, and mesangial proliferation is less represented [13].

We did not perform electron microscopy therefore we could not definitively identify the real etiology.

Conclusions

Considering the pathogenic mechanisms that we describe, it is not possible to exclude that some glomerular diseases reported in the literature are unrelated to SARS-CoV-2 infection and may represent incidental findings or are related to other conditions. Interestingly, patients with glomerular involvement show fewer SARS-CoV-2-related symptoms than patients without, and perhaps interferon plays a role, but despite this, paucisymptomatic patients' general conditions could worsen. Our patient had no fever or other respiratory symptoms, however he showed progressive decline, resulting in hospital admission, in line with data reported in the literature confirming that SARS-CoV-2 infection is associated with poor general outcome [14].

This case shows how SARS-CoV-2 pandemy made clinicians face all the complex and kaleidoscopic aspects of renal pathology.

Declarations

Conflict of interest All the authors confirmed they have contributed to the intellectual content of this paper and they declared no competing interests.

Ethical approval This study was approved by the local Ethics Committee and was performed according to the Declaration of Helsinki. Participant received an explanatory statement and gave his written informed consent to participate in the study.

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