

Clinical and pathological findings of SARS-CoV-2 infection and concurrent IgA nephropathy: A case report

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Case Report

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Abstract

Background: Since the Coronavirus Disease 2019 (COVID-19) outbreak, there is limited data on the clinical characteristics, treatment strategies and prognosis of COVID-19 in patients with concurrent renal disease. The kidney is believed to have a predisposition for COVID-19 due to its abundant angiotensin-converting enzyme 2 (ACE2) expression, which acts as a cell entry receptor for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Recent postmortem investigations reveal renal involvement in COVID-19, and case reports describe collapsing glomerulopathy in African American patients with COVID-19. However, there is limited data regarding IgA nephropathy in the setting of COVID-19.

Case presentation: In the present case, we report a 65-year old Chinese woman who presented with macroscopic hematuria, worsening proteinuria and decreased renal function after COVID-19 infection. She received a renal biopsy during COVID-19 infection. The renal biopsy revealed IgA nephropathy without any evidence for SARS-Cov-2. The findings suggest that the renal abnormalities were a consequence of exacerbation of this patient's underlying glomerular disease after COVID-19 infection. After a regimen of 3-day course of glucocorticoid and angiotensin II receptor blocker therapy, the patient recovered and remained stable upon follow-up.

Conclusions: It is important to consider the underlying glomerular disease exacerbation rather than virus induced injury when dealing with renal abnormalities in patients with COVID-19.

Background

The Coronavirus Disease 2019 (COVID-19) is an emerging infectious disease attributed to the infection by a novel coronavirus termed severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2)(1). Chronic kidney disease (CKD) that accounts for 0.7%-2.9% of the investigated population is not a frequent underlying condition in patients with COVID-19 (2-4). Patients in older age and with comorbidities such as hypertension are at a higher risk to progress. Currently, there is no robust evidence to indicate that patients with CKD are at an increased risk compared with other comorbidities. To date, publications linking COVID-19 with renal comorbidities are mostly focused on patients with end-stage renal disease (5, 6). IgA nephropathy is the most common primary glomerular disease(7), and the impact of COVID-19 on patients with glomerular diseases has not been studied. In the current report, we present the clinical and histological findings in a patient with IgA nephropathy after SARS-CoV-2 infection.

Case Presentation

The patient is a 65-year-old Chinese woman with a 4-year history of hypertension, and a 14 months history of proteinuria and microscopic hematuria. The patient had been in her baseline renal condition until January 9, 2020. As shown in Table 1, her baseline estimated glomerular filtration rate (eGFR) in the past year range from 64.2 ml/min/1.73m² to 72.6 ml/min/1.73m². Baseline urine sediment examination showed 36.61 cells/ml -74.43 cells/ml in erythrocyte count and baseline proteinuria excretion was up to 510 mg/day. Three days prior to her admission, she got flu-like symptoms including headache, myalgia and fatigue, which were resolved in 1 to 2 days. However, she developed dark-colored urine and flank pain a day later and presented to the out-patient clinic. Urine sediment investigation showed significant worsening in urine erythrocyte count (2518.03/mL) and she was admitted to the hospital on January 10, 2020. On admission, vital signs were normal with a body temperature of 36.8°C, blood pressure of 149/104 mm Hg, heart rate of 80 beats per minute, and a respiratory rate of 16 breaths per minute. Both lungs were clear to auscultation. The rest of the physical examination was also unremarkable.

Table 1 Laboratory characteristics of the patient

Date	2019.1.25	2019.3.18	2019.5.22	2019.9.23	2020.1.9	2020.1.10	2020.1.20	2020.1.25	2020.4.20	Reference range
RBC	70.4	NA	NA	36.6	2518.0	98.9	NA	NA	28.3	0-30
Proteinuria excretion, grams/24 hours	0.51	0.45	0.27	0.43	NA	1.07	NA	NA	NA	£140
Creatinine, mmol/L	83	75	80	75	84	96	74	79	73	45-84
eGFR, ml/min/1.73m ²	64.2	72.6	67.1	72.1	62.8	53.6	73.5	67.9	74.7	>90
UACR, mg/g	43.6	NA	NA	36.1	NA	288.8	NA	NA	33.61	0-30
WBC, x 10 ⁹ /L	NA	NA	NA	NA	NA	4.57	4.58	7.45	5.72	3.5-9.5
Lymphocyte count, 10 ⁹ /L	NA	NA	NA	NA	NA	0.86	0.81	1.05	1.34	1.1-3.2
Lymphocyte percentage, %	NA	NA	NA	NA	NA	18.8	17.8	14.1	23.4	20-50
hs-CRP, mg/L	NA	NA	NA	NA	NA	19.6	36.6	4.6	NA	NA

RBC: urine red blood cell count; WBC: blood white blood cell; eGFR: estimated glomerular filtration rate; hs-CRP: hyper-sensitive C reaction protein; UACR: urine albumin to creatinine ratio; NA: not applied.

Laboratory results from the time of admission are summarized in Table 1. She got decreased eGFR (53.6 ml/min/1.73m²) and deteriorated proteinuria (1.07 g/day) when compared to her baseline level. Notably, the patient had mild lymphopenia and increased C reaction protein level. Serologic examinations for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) were negative. Anti-nuclear antibody, anti-extractable nuclear antigen antibodies, anti-neutrophil cytoplasm antibodies and anti-glomerular basement membrane antibody were negative. Serum immunoglobulin (Ig) A level was slightly increased at 4.71 g/L (reference range: 0.82 g/L-4.53 g/L), whereas IgG, IgM, complement C3 and C4 levels were within the normal range. An ultrasound and a Computed tomography (CT) examinations for the urinary system were unremarkable. A chest CT scan revealed scattered ground glass opacity (GGO) (Fig. 1A and 1B).

On admission day 5, a renal biopsy was performed. A total of 16 glomeruli were identified in the tissue submitted for evaluation, 5 of which were completely sclerosed. One glomerulus showed segmental sclerosis and one showed a fibrocellular crescent (Fig. 2A). Focal mild mesangial hypercellularity is identified in rare glomeruli. There is no evidence of significant glomerular inflammation or necrosis. The tubular parenchyma showed moderate interstitial fibrosis associated with nonspecific mononuclear cell inflammatory. Intact tubules showed focal acute tubular injurious changes characterized by attenuation of the brush borders and cytoplasmic vacuolization as well as luminal cellular debris (Fig. 2A and 2B). By immunofluorescence microscopy, the glomeruli showed 2+ granular mesangial staining for IgA (Fig. 2C), C3, kappa and lambda light chains. IgG, IgM and C1q were negative. Electron microscopy (EM) examination revealed mesangial electron dense immune-type deposits. There is no evidence of definitive viral particles (Fig. 2D). A diagnosis of IgA nephropathy with an Oxford score of M₀E₀S₁T₁C₁ was rendered.

With the diagnosis of IgA nephropathy, she received valsartan, an angiotensin II receptor blocker (ARB), with an initial dosage of 20 mg per day. She experienced dry cough without fever, dyspnea, diarrhea, myalgia or sore throat on admission day 12. Consequently, we repeated a chest CT scan for her out of caution due to COVID-19. The CT images showed a significant interval progression with a viral pneumonia pattern (Fig. 1C and 1D). A panel of infectious disease screening was initiated including IgM antibodies against nine respiratory pathogens: influenza virus A, influenza virus B, parainfluenza virus, adenovirus, respiratory syncytial virus, pneumonophagous legionella, Q fever rickettsia, mycoplasma pneumoniae and chlamydia pneumoniae, which were all negative. A throat swab specimen tested positive for SARS-CoV-2 later. The frozen renal tissue from biopsy specimens was submitted for reverse transcription-polymerase chain reaction, however, which was tested negative for SARS-CoV-2. Immunohistochemical (IHC) evaluation for the spike protein (40150-R007, Sino Biological, Beijing, China) of SARS-CoV-2 in the kidney was negative as well (Fig. 2E). According to the guideline for COVID-19 issued by the National Health Commission of China (8), she received methylprednisolone (40 mg per day for 3 days) and empirical anti-virus medication (oseltamivir at 75mg, twice a day for 5 days).

On admission day 17, a follow-up chest CT scan showed a significant improvement (Fig. 1E and 1F). Laboratory investigations showed stable renal function and restored lymphocyte count (Table.1). A repeated throat swab specimen tested negative for SARS-CoV-2. The patient was discharged.

Three months later, the patient remains asymptomatic clinically. A follow-up investigation revealed positive IgG and the IgM antibody against SARS-CoV-2. Her eGFR and UACR were 74.69 ml/min/1.73m² and 33.61mg/g respectively; her urine erythrocyte was 28.3 cells/ml (her baseline level). The valsartan dosage was titrated to 40 mg OD for optimizing her blood pressure control.

Discussion And Conclusions

The spike protein of SARS-CoV-2 uses ACE2 as a receptor to targeted cells(1). ACE2 is broadly expressed in human organs especially in the apical brush borders of the proximal tubules and to a less extent in the podocytes in kidneys(9). This finding raised interest over the relationship between ACE2 and COVID-19. Histological findings from postmortem specimens confirmed the deposition of viral components (e.g. spike protein) in renal tissue and virus-like particles within epithelial cells(10). Moreover, Pan et al. suggests that kidney has a predisposition to COVID-19 due to ACE2 expression(11). A recent study from our group reveals that up to 43.9% of patients exhibited renal impairment including abnormal urinalysis and acute kidney injury (AKI)(12). However, whether these abnormalities are directly caused by the virus infection remains unclear.

The flu-like symptoms, lymphopenia and chest CT image with GGO of the current patient presented prior to the biopsy, although she did not have fever or dyspnea and denied exposure to the Huanan Sea Food Market (the presumptive epidemic origin of the Wuhan City(13)). As a result, that the patient got SARS-CoV-2 infection before renal biopsy is highly suggestive. Here, the renal biopsy shows patchy acute tubular injury. It is important to identify whether these changes are directly related to COVID-19. IHC examination for SARS-CoV-2 antigen was negative; viral particles were not identified from EM and nucleic testing in renal tissue was negative as well. As a result, we favor that the acute tubular injury is unlikely to be a direct consequence from COVID-19. However, we cannot completely exclude the possibility that the viral load was too low to be detectable as the biopsy was performed only 8 days from symptoms onset.

IgA nephropathy is the most common primary glomerular disease in the world. It is accountable for up to 54.3% of biopsy-proven primary glomerulonephritis in China(14). Our patient has the usual presentation of IgA nephropathy with macroscopic hematuria and associated reversible AKI, which is frequently seen in patients after bacterial or viral upper respiratory infection(14). Hematuria-related AKI is common in patients with IgA nephropathy who are older than 65 years(15), and it has been increasingly observed that macroscopic hematuria-associated AKI is reversible when hematuria resolves(16, 17).

Viral infections may exacerbate glomerular disease, such as immune-complex-mediated glomerulopathies related to HCV infection and collapsing glomerulopathy (CG) related to HIV infection(18). Importantly, recent studies show that African American patients with COVID-19 who carried the APOL1 gene risk variant developed CG, which raise the possibility that COVID-19 can induce glomerular disease(19, 20). To date, these morphological changes have not been reported in Chinese patients. However, a longer follow-up period for all patients who have recovered from COVID-19 as well as renal biopsy for patients with persistent proteinuria and/or renal injury may be warranted.

In summary, we reported a patient with COVID-19 with IgA nephropathy. Although the evidence for early viral entry into the kidney is absent, COVID-19 can act as a trigger for exacerbating IgA nephropathy. Renal abnormalities in patients with COVID-19 could be the first presentation of their underlying glomerular disease, which may be unnecessarily attributed to the SARS-CoV-2 infection as one of the complications. Further studies are needed for a better understanding of COVID-19, including its effects in kidney. And it is important to consider the underlying glomerular disease when dealing with renal abnormalities in patients with COVID-19.

Abbreviations

COVID-19 Coronavirus Disease 2019

SARS-Cov-2 Severe acute respiratory syndrome coronavirus 2

CKD Chronic kidney disease

eGFR Estimated glomerular filtration rate

HBV Hepatitis B virus

HCV Hepatitis C virus

HIV Human immunodeficiency virus

Ig Immunoglobulin

CT Computed tomography

GGO Ground glass opacity

ARB Angiotensin II receptor blocker

AKI Acute kidney injury

CG Collapsing glomerulopathy

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for Publication

The patient approved of publishing this manuscript and signed a written informed consent. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and materials

If required, the relevant material can be provided by corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflicts of interest to disclose.

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Authors' Contribution

LL, XJL, GX and YH were involved in diagnosis, management and follow-up for this patient. Data acquisition and manuscript writing were done by LL; YL and WD were responsible for performing the histological examinations. TS and MH interpreted the biopsy results. GX designed the study; WYL performed the nucleic testing; TS and GX significantly revised the manuscript. All authors have read and approved the manuscript, and ensure that this is the case.

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Figures

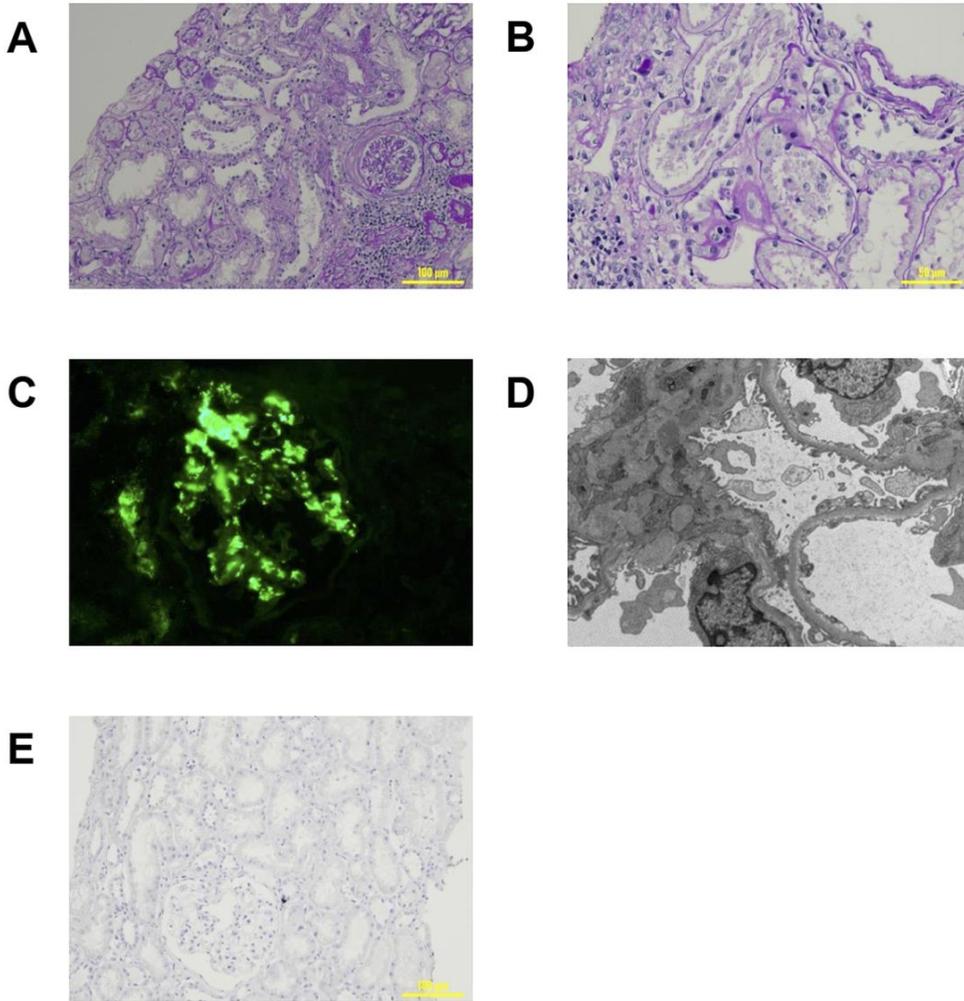


Figure 1
Renal biopsy findings. (A) Glomerulus with a fibrocellular crescent, adjacent acute tubular injury, as well as associated tubular atrophy/interstitial inflammation (PAS stain; original magnification x200); (B) Cells debris within the proximal tubular lumen (PAS stain; original magnification x400); (C) direct immunofluorescence staining with IgA (original magnification x400); (D) Ultrastructure examination reveals mesangial electron-dense deposits (transmission electron microscopy; original magnification x2500); (E) Negative immunohistochemistry staining for the S1 spike protein of SARS-CoV-2 (original magnification x200). PAS: Periodic Acid-Schiff; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.

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