Journal of the
Bahrain Medical Society

Elsayed et al., J Bahrain Med Soc. 2022;34(4):38-43

CASE REPORT

IgA Crescentic Nephropathy Post COVID-19 Infection: A Case Report

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Received date: September 15, 2022; **Accepted date:** October 20, 2022; **Published date:** December 31, 2022

Abstract

Background: Since the Coronavirus Disease 2019 (COVID-19) outbreak, individuals affected by COVID19 may be at risk of acquiring certain forms of glomerular disease. Several biopsy researches reveal that acute tubular injury, as well as glomerular nephropathy were common histological findings. However, to our knowledge, there is limited data regarding de novo diagnosis of IgA vasculitis in an adult following a COVID-19 infection.

Case presentation: In the present case report, we document a 24-year-old Bahraini woman with new onset hypertension, microhematuria, proteinuria and decreased renal function after she recovered from COVID-19 infection. Renal biopsy after COVID-19 infection was performed and revealed IgA nephropathy without any evidence of COVID-19 infection. After a regimen of immunosuppression and angiotensin converting enzyme inhibitor therapy, the patient recovered and remained stable upon follow-up.

Conclusions: When dealing with patient with COVID-19 infection and kidney involvement, it is vital to evaluate the underlying glomerular disease aggravation as well as virus-induced consequences. A kidney biopsy may be necessary to roll out rapidly progressive glomerular disease (RPGN).

Keywords: COVID-19, microscopic hematuria, IgA nephropathy, acute kidney injury, case report.

Introduction

Coronavirus disease-2019 (COVID-19) caused by the newly recognized coronavirus-2019, has affected millions of individuals worldwide, with considerable morbidity and mortality since December 2019.

Despite initial reports of low incidence, acute kidney injury (AKI) in patients hospitalized with COVID-19 has now been recognized as an important disease complication. So far, evidence is predominantly sourced from large US series, elderly, and patients with comorbidities such as hypertension are at a higher risk to progress. [1-5]

IgA nephropathy is the most common primary glomerular disease[7], and the impact of COVID-19 on patients with glomerular diseases has not been well studied yet.

The current report presents the clinical course and histological findings in a patient with IgA vasculitis nephropathy after COVID-19 infection.

Table 1. Laboratory characteristics of the patient

	Hospital		Discharge		Clinic		Follow Up	Reference Range
Date	17.11.21	25.11.21	28.11.21	9.12.21	23.12.21	9.01.22	4.02.22	-
RBC, Cells/MI	21-50	100	51-100	3-5	NA	3-5	11-20	0-30
Creatinine mmol/L	81	71	95	78	89	90	96	44-80
eGFR,ml/min/1.73 m^2	69	81	58	73	63	62	57	>90
UACR, mg/mmol	NA	199	201	NA	NA	66	66	0-30
UPCR	0.625	2.2	2.2	1.6	0.62	0.67	0.67	>= 0.2-2

RBC, urine red blood cell count; WBC, white blood cell; eGFR, estimated glomerular filtration rate; UACR, urine albumin to creatinine ratio; UPCR, urine protein to creatinine ratio; NA, not applied

Case presentation

The patient was a 24-year-old Bahraini woman with no past medical history of any chronic illness, presented with high blood pressure, proteinuria, and microscopic hematuria.

Four months prior to her admission, she got flu-like symptoms including headache, myalgia, and fatigue, and was diagnosed as COVID- 19 positive.

After 1 month of recovery, she started complaining about headaches and new onset hypertension with multiple visits to Healthcare Center and Emergency Department. The case was diagnosed to be that of anxiety and was treated as post COVID symptoms.

However, in the last visit the recurrent high blood pressure readings were noted and work up for hypertension was recommended. Upon performance of kidney ultrasound, the urologist found small renal stone (3 mm) and the case was referred to the Nephrology Outpatient Clinic.

Investigation of urine sediment showed significant urine erythrocyte count (21-50/μL), proteinuria, and uncontrolled blood pressure and the patient was admitted to the hospital in November 2021 for the detection of nephritic syndrome.

On admission, vital signs showed high blood pressure with a body temperature of 36.8 °C, blood pressure of 155/104 mmHg, heart rate of 80 beats/min and a respiratory rate of 16 breaths/min. Both lungs were clear to auscultation. The rest of the physical examination was also unremarkable.

The following blood tests were normal, the patient had normal C reactive protein (CRP) level of 1.6 mg/L.

- Serologic tests for hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) were negative.
- The tests for antinuclear antibody, anti-extractable nuclear antigen antibodies, anti-neutrophil cytoplasm antibodies were negative.
- Serum immunoglobulin (Ig A) level was normal at 2.01 g/L (reference range: 0.82 g/L- 4 g/L), whereas complement C3 and C4 levels were within the normal range.

Laboratory results from the time of admission are summarized in Table 1.

The patient demonstrated decreased eGFR (68 mL/min/1.73m2) and urine proteinuria to creatinine ratio (0.625), of which, urine albuminuria was (601 mg/day), urine albumin to creatinine ratio 199 mg/mmol.

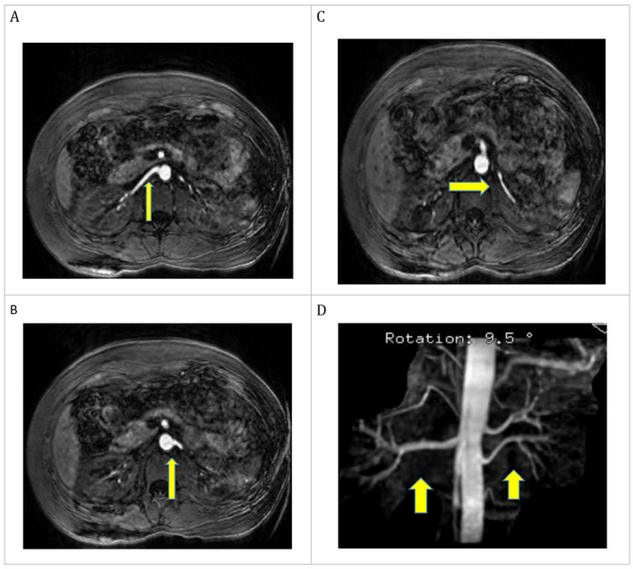


Figure 1: MRA renal arteries without IV contrast. **A**: Showing normal caliber of right renal artery; **B**: Normal origin of left renal artery; **C**: Normal course and caliber of the rest of left renal artery; **D**: Showing normal study of both right and left renal arteries.

A new abdominal ultrasound and a magnetic nuclear resonance (MRA) examination for the urinary system and renal artery were unremarkable (Fig. 1 A, B, C and D).

Renal biopsy was performed without complications. A total of 25 glomeruli were identified in the tissue submitted for evaluation, 4 of which were completely sclerosed. Three glomeruli showed segmental sclerosis and one showed a fibro cellular crescent (Fig. 2A). Focal mild mesangial hypercellularity was identified in rare glomeruli.

There was no evidence of significant glomerular inflammation or necrosis. The tubular parenchyma showed moderate interstitial fibrosis associated with nonspecific mononuclear cell inflammation.

By immunofluorescence microscopy, the glomeruli showed 2+ granular mesangial staining for IgA (Fig. 1A), There is mesangial positivity for IgA (3+), C1q (trace), C3 (2+), C4d (3+), Kappa (trace) & lambda light chains (1+).

Electron microscope (EM) examination revealed the cytoplasmic vacuolation of the podocytes. Less than 5% of the podocyte foot processes were effaced. Rare lysosomal lamellated inclusions were noted. Numerous bulky electron densities were seen in mesangial and Para mesangial areas with increase in mesangial matrix. Endothelial cells were unremarkable. Intra lysosomal, osmiophilic, lamellar and concentric inclusions in podocytes resembling "zebra bodies" were observed.

The findings are compatible with both Fabry's disease and drug-induced phospholipidosis and further investigation was recommended. (Fig. 1C).

The diagnosis of IgA nephropathy with active crescents and FSGS, and an Oxford (MODIFIED): score of M1E1S1T0-C1 was rendered.

The diagnosis of drug-induced phospholipidosis (that was less likely from history) and Fabry's disease (which was excluded by a negative genetic testing) was also reported.

The patient received pulse of steroid for 3 days followed by oral prednisolone (60 mg tapering doses) plus perindopril, an angiotensin converting enzyme inhibitor (ACEI), with an initial dosage of 5 mg/day.

Other immunosuppressive medications were explained and mycophenolate mofetil (MMF) () chosen.6

After 6 months of follow up, the patient was on full remission with negative proteinuria, no RBC in urine test, well controlled blood pressure and serum creatinine of 87 mmol.

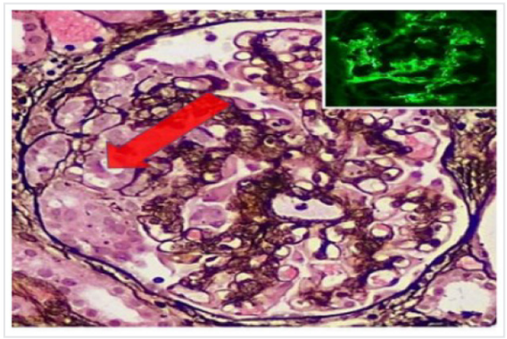
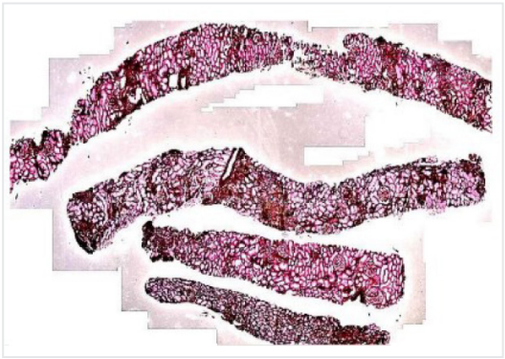
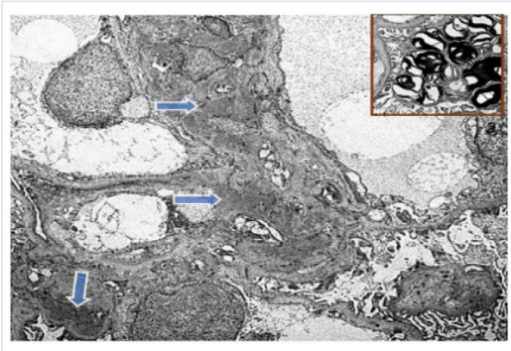


Figure 2: Renal biopsy findings.
A: Glomerulus with a fibrocelluar crescent, adjacent acute tubular injury, as well as associated tubular atrophy/ interstitial inflammation (PAS stain; original magnification × 200); immunofluorescence microscopy: direct immunofluorescence staining with IgA (original magnification × 400)



B: IFTA



C: Electron Microscopy: There is mesangial positivity for IgA (3+), C1q (trace), C3 (2+), C4d (3+), Kappa (trace) & lambda light chains (1+). PAS: Periodic Acid-Schiff; IFTA (interstitial fibrosis and tubular atrophy)

Discussion

Different publications highlighted the link between COVID-19 infection and kidney involvement. ACE2 is broadly expressed in human organs especially in the apical brush borders of the proximal tubules and to a lesser extent in the podocytes in kidneys.[7] This finding increases the interest in 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.[8] Moreover, Pan et al. suggests that kidney has a predisposition to COVID-19 due to ACE2 expression.[9]

The sequence of events in the patient strongly suggests the relation between the COVID-19 infection and her kidney disease. The renal biopsy showed multiple damage in the kidney.

Publications related to recent renal biopsy investigations in patients (who suffer of acute kidney injury and proteinuria in a COVID-19 positive status) have identified that acute tubular injury was a common histological finding and the absence of viral particles did not exclude kidney involvement in COVID-19.[10-12] The possibility that the acute tubular injury is a direct consequence from COVID-19 cannot be completely excluded, because it could be that the viral load was too low to be detectable as the biopsy was performed 4 months from onset of symptoms.

Fabry's disease is an inherited disorder of alpha galactosidase A deficiency was suspected from electron microscopy (due to presence of zebra bodies) but unfortunately was unable to be confirmed by genetic testing.

Also, certain drugs, such as hydroxychloroquine, can produce renal deposits that mimic morphological findings seen in FD, characterizing a type of drug-induced renal phospholipidosis. The patient was sure about no intake of any extra medications during her covid-19 infection despite paracetamol and vitamin C. Unfortunately, we do not have enough evidence to support that zebra bodies could be related to COVID-19 infection.

Finally, the main diagnosis of IgAN explains many of clinical symptoms and laboratory results.

IgAN is the most common primary glomerular disease in the world. The usual presentation is microscopic hematuria, proteinuria and in some cases associated with reversible acute kidney injury (AKI,) which is frequently seen in patients after bacterial or viral upper respiratory infection.[13]

Hematuria-related AKI is common in patients with IgAN,[14] viral infections may exacerbate glomerular disease, such as immune-complex-mediated glomerulopathies related to HCV infection and collapsing glomerulopathy (CG) related to HIV infection.[15]

Importantly, recent studies showed that patients with COVID-19 (who carried the APOL1 gene risk variant) developed CG, which raised the possibility that COVID-19 can induce glomerular disease.

Kidney involvement in patients with COVID-19 could be the first presentation of their underlying glomerular disease and or relapse of known

condition. Patient who develops a deterioration of kidney disease during COVID-19, a kidney biopsy may be indicated to exclude rapidly progressive glomerular nephropathies.

Although, the evidence for early viral entry into the kidney is absent, COVID-19 can act as a trigger for exacerbating primary or secondary glomerulonephritis, we strongly believe that the past infection of COVID-19 played a relevant role as trigger in our case.

IgAN treatment is always a challenge in nephrology daily practice. Lately, an update of KDIGO guidelines in 2021 recommended IgAN treatment as supportive care for at least 3 months. This includes lifestyle modifications, blood pressure management and maximally ACEi/ARB doses.

However, this is not applicable in special situations as IgA vasculitis with associated nephritis, IgAN with acute kidney injury or rapidly progressive glomerulonephritis, IgAN associated to segmental and focal glomeruloesclerosis or minimal changes, IgA secondary to autoimmune diseases or patient who are at high risk of progressive CKD.

The risk/ benefits ratio of glucocorticoids and immusuppressive drugs treatment should be individually discussed with a dynamic approach over time. The presence of crescents in the kidney biopsy is not in itself an automatic indication for commencement of immunosuppression.

Furthermore, the immunosuppressor therapy for these special cases according to KDIGO guidelines include:

1. Cyclophosphamide with steroid.
2. MMF with steroid
3. Rituximab with steroid
4. Plasma exchange. However, there is insufficient data to determine the efficacy of plasma exchange in IgAN with RPGN.

A detailed discussion of the risks and benefits of each drug was conducted with the patient.

The patient had concerns about fertility issues so treatment with MMF, steroid and ACEI was prescribed. Preconception counselling was given and supplements of vitamin D, gastric protection and prophylaxis for pneumocystis were started.

Close follow up was recommended to assess the patient therapy and early detection of complications / side effects.

Conclusion

More studies are needed for a better understanding of the COVID19 virus, including the effects in the kidney.

Patients with underlying primary or secondary glomerular disease must be closely monitored during and post COVID-19 infection and new kidney biopsy may be indicated in some cases with rapid deterioration of kidney function.

Abbreviations

COVID-19: Coronavirus Disease 2019; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; Ig: Immunoglobulin; MRA: Magnetic Resonance; Angiography; ACEI: Angiotensin converting enzyme inhibitor; AKI: Acute kidney injury; FD, Fabry Disease; KDIGO: Kidney Disease Improving Global Outcome

Authors' contributions

AE, HA, and NR were involved in diagnosis, management, and follow-up for this patient. Data acquisition and manuscript writing were done by AE and HA.

NR interpreted the biopsy results. AE, HA, and NR significantly revised the manuscript. All authors have read and approved the manuscript and ensure that this is the case.

Funding

None

Availability of data and materials

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

Ethics approval and consent were taken.

Consent for publication

The patient approved 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.

Competing interests

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

Acknowledgments

We thank Dr. Fahad al-Khalifa, Chief of medical stuff, nurses, and staff in Department of Nephrology for their hard work and support for this and other patients during the pandemic despite enormous challenges.

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