CASE REPORT

Covid-19 and acute kidney injury: A new perspective

Hayder Mutter Al-Kuraishy, Ali Ismail Al-Gareeb

Abstract

The novel coronavirus disease 19 (nCoV19) is universally known as Covid-19, which is caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), and affects diverse range of organs, presenting with pulmonary manifestations as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), and extra-pulmonary manifestations like acute kidney injury (AKI). AKI is regarded as a poor prognostic factor in patients with severe Covid-19, thus early detection and management of this critical status may reduce the risk of complications and mortality. We present the case of a 30 years old man with moderate Covid-19 presenting with haematuria and eventually diagnosed as AKI. The patient was managed compared with a Covid-19 patient as control. The patient recovered within three weeks of supportive and standard care therapy. Reversible AKI and associated haematuria can be the presenting features of Covid-19 and are linked with mild-moderate SARS-CoV-2 infection.

Keywords: Covid-19, Acute kidney injury, SARS-C

Introduction

The novel coronavirus disease 19 (nCoV19), universally known as Covid-19, is caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), leading to acute pro-inflammatory activation, hypercytokinaemia, cytokine storm and multi-organ damage.[1] Covid-19 affects diverse range of organs mainly the respiratory system, and presents with pulmonary manifestations like acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), Extra-pulmonary manifestations include acute cardiac injury, neurological disorders, pancreatic injury and acute kidney injury (AKI).[2] The systemic effect of Covid-19 is due to the wide distribution of angiotensin converting enzyme 2 (AEC2), a receptor and entry-point for SARS-CoV-2.[3] ACE2 receptor is chiefly expressed in the lung alveolar cells type II and proximal renal tubules. Binding of SARS-CoV-2 to ACE2 leads to down-regulation of this protective receptors with consequent increase in the level of vasoconstrictors angiotensin II (Ang II) and reduction of vasodilator angiotensin (Ang 1-7), (Ang 1-9) with induction release of pro-inflammatory cytokines.[4]

Since the declaration of World Health Organization (WHO) of this disease as a pandemic and until late January 2021, the total confirmed cases number 104,250,977 with 2,258,789 deaths. The mortality rate ranged between 0.9% to 10.5% in Covid-19 patients without comorbidities and Covid-19 patients with comorbidities respectively.[5]

AKI is a sudden deterioration of kidney function within a short interval due to acute kidney damage by various nephrotoxic agents, directly or indirectly through immunological and inflammatory disturbances. AKI is usually reversible requiring intensive management to prevent electrolyte disorder-mediated complications.[6] It is frequently encountered among critically ill patients with severe Covid-19, and found in 20-40% of patients in the intensive care unit (ICU). In particular, more than 40% of patients with Covid-19 have abnormal kidney function and proteinuria suggesting kidney involvement in the pathogenesis of SARS-CoV-2 infection.[7] AKI is regarded as a poor prognostic factor in patients with severe Covid-19, thus early detection and management of this critical status may reduce risk of complications and mortality.[8] The underlying causes of AKI in Covid-19 are multi-factorial and related to direct kidney involvement by SARS-CoV-2, cytokine storm, hypervolaemia and heart failure.[9]

Keeping in view, the relevant public health impact of Covid-19 pandemic, we describe a case of a Covid-19 patient presenting with frank haematuria and mild respiratory symptoms.

Case Report

On 11 October, 2020, a 30 years old man presented to the private clinic in Bagdad New City with fever, sore throat, headache and haematuria of two days duration not responding to the empirical antibiotic and analgesic therapy prescribed by the medical practitioner. At the same time, another 42 years old man presented with dry cough, headache, fever, sore throat and severe sweating. Both patients were suspected to be Covid-19 infected.

General physical examination revealed an alert conscious patient with mild pyrexia (37.8°C). The vital signs were

Department of Clinical Pharmacology, Medicine and Therapeutic, Medical Faculty, College of Medicine, Mustansiriyah University, Baghdad, Iraq.
Correspondence: Hayder Mutter Al-Kuraishy. Email: hayderm36@yahoo.com

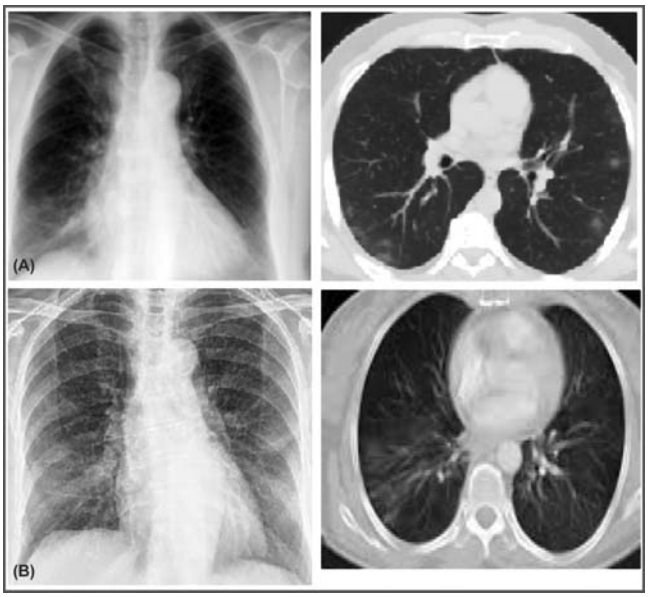

Figure: Chest X-ray and CT scan findings: (A): Covid-19 patient with AKI, (B): Covid-19 patient without AKI.

recorded; blood pressure 130/75mmHg, heart rate 98 beats/minute, respiratory rate 19 breath/minute and oxygen saturation (PaO2) was 95%. Chest examination revealed, bilateral basal lung bronchial breathing. Chest X-ray and computed tomography (CT) scan findings of both lungs were suggestive of Covid-19 pneumonia, score 2 of both patients (Figure). Scoring of CT scan findings was achieved to determine the severity of lung involvement. Score (0): normal lung, Score (1): lung damage involvement less than 5%, Score (2): lung damage involvement between 5-25%, Score (3): lung damage involvement between 26-50%, Score (4): lung damage involvement between 51-75%, Score (5): lung damage involvement more than 75%.[10]

Anti-SARS-CoV-2 antibody (IgM and IgG), and real-time reverse transcriptase polymerase chain reaction (RT-PCR) tests illustrated positive findings for SARS-CoV-2 infection. Complete blood count (CBC), blood urea, serum creatinine, uric acid, serum potassium and serum sodium was performed. Detail urine examination for assessment of proteinuria was done as suggested by a previous study.[11] Other routine biochemical investigations were ordered for both patients. Inflammatory biomarkers related to Covid-19 severity as C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), and serum ferritin were done by specific commercial kits according to the instructions of manufactured companies. The clinical, radiological and laboratory findings of both patients are listed in (Table-1). Abdominal sonographic imaging and related investigations were performed to exclude other causes of haematuria. The clinical, radiological and laboratory findings lead to the diagnosis of Covid-19 in one patient with the other having concomitant AKI. The patients were treated by supportive and standard care therapy including azithromycin 500mg/day orally for the first five days, famotidine 40mg/day, ivermectin tablet 12mg/day, ceftriaxone 1g/day and enoxaparin 60mg/day subcutaneously for ten consecutive days.

Table-1: Anthropometric, clinical, radiological and biochemical finding of Covid-19 patient with acute kidney injury compared with Covid-19 patient only at time of admission.

Parameters	Normal value	Covid-19	Covid-19+AKI
Age (years)	...	30	42
SBP(mmHg)	110-120	125	130
DBP(mmHg)	70-85	76	77
Serological test			
Covid-19 IgM(U/mL)	0.9-1.1	4.81	4.95
Covid-19 IgG(U/mL)	0.9-1.1	0.9	0.99
HR(beats/min)	60-90	110	104
RR(breath/min)	16-Dec	18	19
Oxygen saturation (%)	95-100	95	95
Radiological score (%)	0	2	2
Blood urea (mg/dL)	20-40	43.76	86
Serum creatinine(mg/dL)	0.5-1.5	1.4	3.2
Uric acid (mg/dL)	7-Apr	6.9	11.93
FBG(mg/dL)	70-90	135	143
Serum potassium (mEq/L)	3.5-5.0	4.4	5.4
Serum sodium(mEq/L)	135-145	149	155
CBC profile			
Hb(g/dL)	15-Dec	14	12
WBC(µ/L)	4000-11000	16000	19000
Neutrophils (%)	40-80	91	92
Lymphocytes (%)	20-40	15	14
CRP (mg/L)	0-5	19.7	33.97
Serum ferritin (ng/mL)	20-250	452.83	486.96
D-dimer (ng/mL)	50-10000	16912.956	19864.238
LDH(U/L)	230-460	684.62	605.91
GUE findings			
Pus cells (HPF)	2-Jan	6	7
Proteinuria	<1+	1	3
RBC(HPF)	0	1	58
RBC casts(HPF)	0	1	63

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate , RR: Respiratory rate, FBG: Fasting blood glucose, CBC: Complete blood count (CBC), Hb: Hemoglobin, WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, GUE: General urine examination, RBC: Red blood cells.
Proteinuria: Trace=less than 150mg/day, 1+=200-500mg/day, 2+=500-1500mg/day, 3+more than 2500mg/day.

On 21 October, 2020, following 10 days of admission, the patient with AKI showed a deterioration in the clinical status, developed severe vomiting and diarrhoea with elevation of blood urea and serum creatinine compared to the baseline values (blood urea=103mg/dL, serum creatinine=5.3mg/dL), however other laboratory findings

Table-2: Anthropometric, clinical, radiological and biochemical finding of Covid-19 patient with acute kidney injury compared with Covid-19 patient only at time of admission.

Parameters	Normal value	Covid-19	Covid-19+AKI
SBP(mmHg)	110-120	130	135
DBP(mmHg)	70-85	70	75
Serological test			
Covid-19 IgM(U/mL)	0.9-1.1	0.081	0.195
Covid-19 IgG(U/mL)	0.9-1.1	4.03	3.81
HR(beats/min)	60-90	84	80
RR(breath/min)	16-Dec	13	13
Oxygen saturation (%)	95-100	98	99
Radiological score (%)	0	0	0
Blood urea (mg/dL)	20-40	40.63	45.9
Serum creatinine(mg/dL)	0.5-1.5	1.1	1.5
Uric acid (mg/dL)	7-Apr	6.1	7.93
FBG(mg/dL)	70-90	135	143
Serum potassium (mEq/L)	3.5-5.0	4.1	4.7
Serum sodium(mEq/L)	135-145	145	142
CBC profile			
Hb(g/dL)	15-Dec	14	12
WBC(µ/L)	4000-11000	9000	7000
Neutrophils (%)	40-80	76	75
Lymphocytes (%)	20-40	24	25
CRP (mg/L)	0-5	7.84	5.94
Serum ferritin (ng/mL)	20-250	124.56	223.64
D-dimer (ng/mL)	50-10000	342.17	654.63
LDH(U/L)	230-460	257.9	342.64
GUE findings			
Pus cells (HPF)	2-Jan	2	2
Proteinuria	<1+	0	0
RBC(HPF)	0	0	0
RBC casts(HPF)	0	0	0

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate, RR: Respiratory rate, FBG: Fasting blood glucose, CBC: Complete blood count (CBC), Hb: Haemoglobin, WBC: White blood cell, CRP: C-reactive protein, LDH: Lactate dehydrogenase, GUE: General urine examination, RBC: Red blood cells.

were not remarkably altered. We added 1-α calcidol tablet daily, intravenous glucose saline drip with diet and fluid restrictions as well as the evaluation of current therapy to exclude any drug with potential nephrotoxic adverse effects.

Following two weeks of management, both patients exhibited good clinical outcomes with normal laboratory and radiological findings (Table-2). Both were discharged in a normal health status and could return to their work. An outpatient follow-up through mobile and Watts-up dialing was done to ensure doctor-patient communication for any new events after two weeks of discharge.

Both patients gave informed consent for publishing their case-reports which was approved by Ethical Committee and Scientific Board in College of Medicine, Al-Mustansiriyiah University, Baghdad, Iraq, 2020.

Discussion

AKI is an uncommon complication of Covid-19 infection and is encountered in 5% cases of mild-moderate cases with subclinical kidney abnormalities.[12] Therefore, AKI is seen more frequently in severe-critical Covid-19 cases and is the commonest extra-pulmonary manifestation in 29% patients compared to 23% of liver and cardiac injuries.[13]

In the present case study, the patient with Covid-19 and AKI presented with mild respiratory symptoms, protenuria and haematuria suggesting unusual presentation of Covid-19. Almeida et al.,[14] reported a case of SARS-CoV-2 infection in a child presenting with haematuria and mild respiratory symptoms. Besides, a retrospective study on 321 hospitalised Covid-19 patients illustrated that both haematuria and proteinuria are associated with poor outcomes and high mortality rate.[15] Different studies have confirmed that haematuria and/or proteinuria at the initial diagnosis, affects the final outcomes of Covid-19 patients. The risk for in hospital AKI is about 4.7 times higher.[12] However, in the present case-study the Covid-19 patient with AKI despite of haematuria and proteinuria with high blood urea and serum creatinine had moderate symptoms initially with severe deterioration at 10th day of admission. ICU admission or assist ventilation was not required and the patient recovered. Non-critical presentation of our case in Covid-19 with AKI could be due to mild ALI and non-severe elevation of inflammatory biomarkers. It has been confirmed that progression of ALI, ARDS and cytokine storm in patients with severe Covid-19 are associated with a high risk for development of AKI for up to 50%.[16]

The possible mechanisms of AKI in SARS-CoV-2 infection could be related to the direct ACE2 receptors binding, which are highly expressed in renal proximal tubular cells and podocytes. Damaging of these receptors contribute to pathogenesis of proteinuria and haematuria.[17] However, in another study, the findings of kidney biopsy and autopsy did not confirm the direct SARS-CoV-2 effect as the main mechanism of AKI in Covid-19.[18] Moreover, the entry of SARS-CoV-2 to ACE2 is facilitated by cellular transmembrane serine protease 2(TMPRSS2). Co-expression of ACE2/ TMPRSS2 is high in the kidneys mainly in podocytes, similar to that of the lung. This co-expression is higher in occidental populations compared to Asians, which might explain the higher incidence of AKI in Europe.[19]

Similarly, renal vascular endothelial dysfunction and injury by SARS-CoV-2 (endotheliitis), coagulopathy, immune-mediated hyper-inflammatory reaction and cytokine storm may lead to renal micro-thrombosis,

glomerular damage, and collapsing glomerulopathy.[20] On the other hand, Dudoignon et al.[21] illustrated that deregulation of ACE2 by SARS-CoV-2 leads to down-regulation of protective angiotensin (Ang1-7, Ang1-9) and augmentation of harmful AngII, that together causes AKI. Taken together, inter-related mechanisms are commonly proposed to be the potential common pathway in the development of AKI in Covid-19.

The present case-report had several limitations including; estimation of glomerular filtration rate (GFR), which reflects kidney function was not performed. Measurement of pro-inflammatory cytokines (IL-6, IL-1β, and IL-13) and anti-inflammatory cytokines (IL-10, IL-4) were not done to assess the inflammatory burden, which is correlated with Covid-19 severity and risk of AKI. However, this case-report highlights that proteinuria and haematuria can be associated with mild-moderate Covid-19.

Conclusion

Reversible AKI and associated haematuria can be the presenting features of Covid-19 and linked with mild-moderate SARS-CoV-2 infection. Though, we cannot outline any definitive conclusion from this case-report, but it does raise alertness. Large-scale observational and cohort studies are warranted in this regard to discover the incidence of haematuria and/or proteinuria in Covid-19 patients with mild-moderate pulmonary presentation.

Disclaimer: None.

Conflicts of Interest: None.

Source of Support: None.

References

1. Al-Kuraishy HM, Al-Naimi MS, Lungnier CM, Al-Gareeb AI. Macrolides and COVID-19: An optimum premise. Biomed Biotechnol Res J 2020; 4:189-92. DOI: 10.4103/bbrj.bbrj_103_20.
2. de Souza TH, Nadal JA, Nogueira RJN, Pereira RM, Brandão MB. Clinical manifestations of children with COVID-19: A systematic review. Pediatr Pulmonol 2020; 55:1892-99. doi: 10.1002/ppul.24885.
3. Al-Kuraishy HM, Hussien NR, Al-Naimi MS, Al-Buhadily AK, Al-Gareeb AI, Lungnier C. Is ivermectin-Azithromycin combination the next step for COVID-19? Biomed Biotechnol Res J 2020; 4(Suppl 1):s101-3. DOI: 10.4103/bbrj.bbrj_109_20
4. Al-Kuraishy HM, Hussien NR, Al-Naimi MS, Al-Buhadily AK, Al-Gareeb AI, Lungnier C. Renin-Angiotensin system and fibrinolytic pathway in COVID-19: One-way skepticism. Biomed Biotechnol Res J 2020; 4(Suppl 1):s33-40. DOI: 10.4103/bbrj.bbrj_105_20
5. Sohrabi C, Alsafi Z, O'Neill N, Khan M, Kerwan A, Al-Jabir A, et al. Corrigendum to "World Health Organization declares Global Emergency: A review of the 2019 Novel Coronavirus (COVID-19). Int J Surg 2020; 76:71-6. doi: 10.1016/j.ijsu.2020.03.036.
6. Rasheed HA, Al-Naimi MS, Hussien NR, Al-Harchan NA, Al-Kuraishy HM, Al-Gareeb AI. New insight into the effect of lycopene on the oxidative stress in acute kidney injury. Int J Crit Illn Inj Sci. 2020; 10(Suppl 1):11-16. doi: 10.4103/IJCIIS.IJCIIS_113_19.
7. Fanelli V, Fiorentino M, Cantaluppi V, Gesualdo L, Stallone G, Ronco C, et al. Acute kidney injury in SARS-CoV-2 infected patients. Crit Care 2020; 24:155. doi: 10.1186/s13054-020-02872-z.
8. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol 2020; 31:1157-65. doi: 10.1681/ASN.2020030276.
9. Ronco C, Reis T, Husain-Syed F. Management of acute kidney injury in patients with COVID-19. Lancet Respir Med 2020; 8:738-42. doi: 10.1016/S2213-2600(20)30229-0.
10. Francone M, Iafrate F, Masci GM, Coco S, Cilia F, Manganaro L, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol 2020; 30:6808-17. doi: 10.1007/s00330-020-07033-y.
11. Regeniter A, Freidank H, Dickenmann M, Boesken WH, Siede WH. Evaluation of proteinuria and GFR to diagnose and classify kidney disease: systematic review and proof of concept. Eur J Intern Med 2009; 20:556-61. doi: 10.1016/j.ejim.2009.03.006.
12. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney Int 2020; 97: 829-38. doi: 10.1016/j.kint.2020.03.005.
13. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8:475-81. doi: 10.1016/S2213-2600(20)30079-5.
14. Almeida FJ, Olmos RD, Oliveira DBL, Monteiro CO, Thomazelli LM, Durigon EL, et al. Hematuria Associated With SARS-CoV-2 Infection in a Child. Pediatr Infect Dis J 2020; 39:e161. doi: 10.1097/INF.0000000000002737.
15. Chaudhri I, Moffitt R, Taub E, Annadi RR, Hoai M, Bolotova O, et al. Association of Proteinuria and Hematuria with Acute Kidney Injury and Mortality in Hospitalized Patients with COVID-19. Kidney Blood Press Res 2020; 45:1018-32. doi: 10.1159/000511946.
16. Al-Kuraishy HM, Al-Gareeb AI, Alzahrani KJ, Cruz-Martins N, Batiha GE. The potential role of neopterin in Covid-19: a new perspective. Mol Cell Biochem 2021; 476:4161-66. doi: 10.1007/s11010-021-04232-z.
17. Martinez-Rojas MA, Vega-Vega O, Bobadilla NA. Is the kidney a target of SARS-CoV-2? Am J Physiol Renal Physiol 2020; 318:F1454-62. doi: 10.1152/ajprenal.00160.2020.
18. Golmai P, Larsen CP, DeVita MV, Wahl SJ, Weins A, Rennke HG, et al. Histopathologic and Ultrastructural Findings in Postmortem Kidney Biopsy Material in 12 Patients with AKI and COVID-19. J Am Soc Nephrol 2020; 31:1944-47. doi: 10.1681/ASN.2020050683.
19. Moubarak M, Kasozi KI, Hetta HF, Shaheen HM, Rauf A, Al-Kuraishy HM, et al. The Rise of SARS-CoV-2 Variants and the Role of Convalescent Plasma Therapy for Management of Infections. Life 2021; 11:734. doi: 10.3390/life11080734.
20. Al-Kuraishy HM, Al-Gareeb AI, Faidah H, Al-Maiahy TJ, Cruz-Martins N, Batiha GE. The Looming Effects of Estrogen in Covid-19: A Rocky Rollout. Front Nutr 2021; 8:e649128. doi: 10.3389/fnut.2021.649128.
21. Dudoignon E, Moreno N, Deniau B, Coutrot M, Longer R, Amiot Q, et al. Activation of the renin-angiotensin-aldosterone system is associated with Acute Kidney Injury in COVID-19. Anaesth Crit Care Pain Med 2020; 39:453-55. doi: 10.1016/j.accpm.2020.06.006.