

Thrombotic Microangiopathy Causing Acute Kidney Injury in a COVID-19 Patient

Abstract

Acute Kidney Injury (AKI) in COVID-19 patients is common and independently associated with higher mortality. The pathophysiology of AKI is multifactorial and may be either direct viral trophism or immune mediated injury and hypercoagulability. This case highlights AKI in a young female with severe COVID-19 due to complement-3 mediated thrombotic microangiopathy with pre-existing chronic kidney disease likely because of IgA nephropathy.

Keywords: AKI, COVID-19, complement mediated microangiopathy, TMA

Introduction

Acute kidney Injury (AKI) is common in patients with severe coronavirus disease 2019 (COVID-19) and increases the risk of mortality.^[1] The risk factors for COVID-19 related AKI are severe illness, older population and comorbidities like hypertension or diabetes.^[1,2] The pathophysiology of AKI in COVID-19 is multifactorial and suspected to be a viral invasion of renal tubular cells through expressed angiotensin converting enzyme (ACE)-2 receptors, immune related injury and hypercoagulability, or may be activation of Renin-Angiotensin-Aldosterone System (RAAS).^[3,4] We present a case of young female with AKI and severe COVID-19 with renal biopsy showing features suggestive of thrombotic microangiopathy (TMA) on pre-existing chronic kidney disease (CKD) likely because of IgA nephropathy.

Case Presentation

A 25-year-old female presented with dyspnoea, fever and unproductive cough since three days. She was at home quarantine for the last seven days after testing positive on reverse transcriptase-polymerase chain reaction (RT-PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There was no previous history of any chronic

illness, self-medications and surgery. On presentation, she was conscious, tachypnoeic (respiratory rate 28/min), blood pressure 146/70 mmHg, heart rate 108/min, oxygen saturation (SpO₂) 80% at room air. The patient was immediately shifted to intensive care unit (ICU) with oxygen support and started on non-invasive ventilation (NIV). Injection methylprednisolone intravenous (IV) 60 mg (1 mg/kg/day) in two divided doses was started for seven days. The chest X-ray showed bilateral heterogenous infiltrates more on peripheries. Baseline urine analysis showed protein 3+, red blood cells (RBC) 20-25/high-power field, urine protein/creatinine ratio of 2.1 mg/mmol. Her significant laboratory investigations on admission are shown in Table 1. Renal ultrasound showed normal-sized kidneys and no features of obstructive uropathy. She was started on haemodialysis (HD) on day 1 through right jugular temporary double lumen HD catheter. Her respiratory distress stabilised over 72 hours and she was off NIV support in five days. The lactate dehydrogenase showed progressive decreasing trend from 1392 U/L to 221 U/L over seven days. She was shifted out of ICU on day 8.

Her renal biopsy was done on day 16 after stabilisation of patient's clinical condition [Figure 1]. A total of 37 glomerulus were found; 17 showed global glomerulosclerosis. There were no crescents or fibrinoid necrosis. Arterioles

**Amitabh Kulkarni,
Prashant Nasa¹,
Srinivasa
Polumuru²,
Aanchal Singh¹**

Departments of Nephrology,
¹Critical Care Medicine and
²Internal Medicine, NMC
Specialty Hospital, PO Box
7832, Al Nahda 2, Dubai, UAE

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Address for correspondence:
Dr. Prashant Nasa,
NMC Specialty Hospital, PO
Box 7832, Al Nahda 2,
Dubai, UAE.
E-mail: dr.prashantnasa@
hotmail.com

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Table 1: Laboratory investigations of the patient

Test (units)	Patient's Value	Normal
Hemoglobin (gm%)	4.2	11.5-16.4
TLC ($\times 10^9/L$)	17.98	4.0-11.0
Platelet count ($\times 10^9/L$)	149	150-450
Sod/pot (mmol/L)	139/4.6	135-145/3.5-5.0
CRP/procalcitonin (ng/ml)	4.3/0.19	0-5
PTT/INR	36.0/1.08	30-45/0.8-1.2
D-Dimer (ng/ml)	More than 5000	0-500
Iron/ferritin (mcg/dl/ng/dl)	162/1645	45-160/10-204
HbA1C (gm%)	3.9	Less than 5.7
Urea/Serum Creatinine (mg/dl)	143/9.3	17-50/0.55-1.02
Interleukin- 6 (pg/ml)	38.9	Upto 7
LDH (U/L)	1392	Less than 247
Phosphorous (mg/dl)	5.7	2.3-4.7
Calcium/magnesium (mg/dl)	8.3/2.5	8.8-10.6/1.8-2.6
Chloride (mg/dl)	104	95-106
G6PD (U/gHb)	10.32	10.1-14.9
Fibrinogen (g/L)	4.6	2-4.8
C-ANCA, p-ANCA, titer	Less than 1:20	1:20
Atypical p-ANCA titer	Less than 1:20	1:20
ANA (IFA)	Negative	
Anti-Cardiolipin Antibody (IgG) (U/ml)	1.6	0.0-19.9
Complement- 3 (mg/dl)	69	82-167
Complement- 4 (mg/dl)	30	14-44
HIV I and II, Hepatitis B and C antibodies	Negative	
Peripheral Smear	Red blood cells are predominantly normocytic and normochromic with mild anisopoikilocytosis. Mild increase in polychromatophilia. Few fragmented red cells seen with decreased red cells. No hemoparasite seen.	
ADAMTS-13 activity (%)	76.4	>66.8

Acronyms: TLC: Total leucocyte count, CRP: C-reactive protein, LDH- Lactate dehydrogenase, G6PD- Glucose-6-phosphate dehydrogenase, ANCA- Anti neutrophilic cytoplasmic antibody, ANA: Anti neutrophilic antibody. IFA- Immunofluorescence

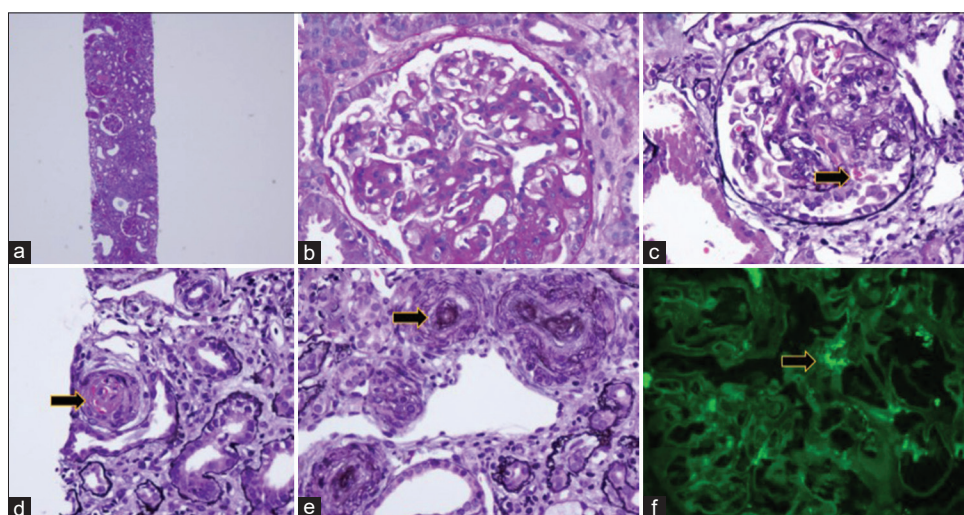


Figure 1: Renal Biopsy of the patient. (a) Tubulointerstitial nephritis (b) Glomeruli with mesangial expansion (c) Glomeruli with multiple microthrombi (arrow) and focal segmental glomerulosclerosis with mild collapsing (d) Arteriole with intimal red blood cells fragments (arrow). (e) Concentric arteriolar intimal thickening (arrow) (f) IgA staining on Immunofluorescence (arrow)

showed intimal fragmented RBCs and glomerulus showed micro-thrombi suggestive of TMA. There were very limited deposits on electron microscopy, most likely because glomeruli had significant ischemic changes. The diagnosis of

IgA nephropathy was largely made on immunofluorescence staining. There is also evidence of chronicity by extensive focal segmental glomerulosclerosis with mild collapsing features and 70-80% tubulointerstitial fibrosis.

The patient was discharged on intermittent HD thrice a week on day 20. She continued to remain dialysis dependent two months after the initial hospital admission.

Discussion

The renal biopsy of this case, showed AKI because of TMA on a pre-existing CKD likely because of IgA nephropathy. Although patient did not have any previous renal function tests, we cannot exclude a preexisting renal disease. Severe anaemia at presentation, fragmented RBCs on peripheral smear and renal biopsy showing TMA helped to make current diagnosis. The patient was managed with steroids as recommended for severe COVID-19. A detailed evaluation for differential diagnosis of TMA was done in this case [Table 1]. The platelet count of 1,49,000 and normal ADAMTS 13 activity were against thrombotic thrombocytopenic purpura (TTP).^[5] There was no evidence of disseminated intravascular coagulation. The patient did not have any family history of thrombophilic disorders and any self-medication. There was no evidence of any other autoimmune disease with negative ANA immunofluorescence profile. There was no evidence of Haemolytic Uremic Syndrome (HUS) as no preceding diarrhoea with stool culture and PCR tested negative for *Shigella* species. The Pneumococcal HUS was also excluded with sterile tracheal secretions culture and negative urinary antigen test. The genetic work-up for loss-of-function mutations and autoantibodies for Factor H (FH), FI, and CD46 was negative.

The evidence of antiphospholipid antibody syndrome cannot be completely excluded as antibodies have to be repeated after 12 weeks. The anaemia seen in this case can be explained by thrombotic microangiopathy and/or anaemia of a CKD [Table 1].

The pathogenesis of AKI in COVID-19 is multifactorial and association with respiratory disease in severe illness reflects likely role of host dysregulated immune response.^[3] Our patient had low complement-3 (C3) levels which can explain the C3 mediated TMA. The C3-mediated TMA is also described in pathophysiology of atypical HUS, transplant-associated TMA and HELLP (haemolysis, elevated liver enzyme and low platelet count) syndrome.^[6] SARS-CoV-2 is suspected to cause C3 activation (C3a) through classic and lectin pathway and C3 convertase formation.^[7] The high concentration of ACE-2 receptors on pericytes may also be target of SARS-CoV-2 causing endothelial dysfunction and intravascular thrombosis.^[7]

This case highlights the C3a mediated TMA as one of the plausible pathophysiological mechanism of AKI in COVID-19 patients. The complement pathway inhibitors (CPI) like eculizumab and ravulizumab can be explored as therapeutic potential for these patients, however we could not use these medications as they were not available in our country.^[8] Timely diagnosis of TMA is critical because of potential role of definitive therapy like plasma exchange or CPI. In conclusion, TMA should be considered in the differential diagnosis of AKI with COVID-19 especially presenting with other features of TMA.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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