



COVID-19-associated atypical hemolytic uremic syndrome and use of Eculizumab therapy

Jasmeet Gill¹ · Christopher Alan Hebert² · Gates Burton Colbert²

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Abstract

There is a high incidence of acute kidney injury with COVID-19 infections. The etiologies of acute kidney injury could be ischemic acute tubular necrosis or a complex process of complement activation leading to thrombotic microangiopathy. We present a case of 32-year-old Hispanic male with a history of heart transplant, admitted with COVID-19 and atypical hemolytic uremic syndrome, which was successfully treated with Eculizumab.

Keywords Thrombotic microangiopathy · COVID-19 · Eculizumab · Acute kidney injury

Introduction

In December 2019, COVID-19 infection caused by severe acute respiratory syndrome—Coronavirus-2 (SARS-CoV-2) initially presented with involvement of the respiratory tract alone. However, over time it has manifested as a complex, multiorgan disorder involving the heart, liver, kidney, lung and brain. The pathophysiology is rooted in the over-activation of the immune system with cytokine storm and activated complement system leading to multiorgan failure [1]. The United States of America is one of the countries associated with the highest incidence of COVID-19 infection and death.

Case presentation

We present a case of a 32-year-old Hispanic man admitted to the hospital in December 2020 with ongoing fever, pleuritic chest pain, cough, and dyspnea for one week who was

subsequently diagnosed with COVID-19 infection. His past medical history is significant for childhood leukemia treated at age six with anthracycline therapy resulting in an orthotopic heart transplant in 2015. In May 2020, he was diagnosed with antibody-mediated rejection with positive donor specific antibody for both Human Leukocyte Antigen (HLA) class I and II. He was treated with methylprednisone, plasma exchange, Bortezomib and IVIG. His last cardiology follow up showed stable cardiac allograft function, controlled hypertension, and chronic kidney disease stage 3 (baseline creatinine of 1.8–2.0 mg/dL). Home medications included Mycophenolate 500 mg BID, Prednisone 5 mg daily, Sirolimus 3 mg daily, Hydrochlorothiazide 12.5 mg daily, Aspirin 81 mg daily and Atorvastatin 40 mg daily. On admission he had sinus tachycardia, blood pressure of 155/110 mmHg, was afebrile, and oxygen saturation on room air was 97%.

Laboratory results demonstrated elevated inflammatory makers with markedly elevated ferritin: 2,581 ng/mL and CRP 3.6 (0.0–0.3) mg/dL. Other laboratory results (Table 1) included white blood cells: 4000/ μ L, hemoglobin: 13.5 g/dL, platelets: 43,000/microL, BUN: 99 mg/dL, creatinine: 7.75 mg/dL, sodium: 135 meq/L, potassium: 4.1 meq/L, chloride: 104 meq/L, bicarbonate: 20 meq/L, anion gap: 11, and peripheral blood smear revealed 1 + schistocytes. Chest computed tomography showed multifocal ground glass opacities affecting all lobes with consolidation consistent with COVID-19 pneumonia. He was started on broad spectrum antibiotics and intravenous dexamethasone 6 mg every 12 h. Urinalysis (Table 2) showed protein 2+, blood 2+, with RBC 2–3/HPF. Further labs revealed creatine kinase: 578 U/L, low

✉ Jasmeet Gill
Gilljasmeet30@gmail.com

Christopher Alan Hebert
Christopher.hebert@kahdallas.com

Gates Burton Colbert
Gates.colbert@bswhealth.org

¹ Baylor University Medical Center at Dallas, 3500 Gaston Avenue, Barnett Tower, Ste 904, Dallas, TX 75246, USA

² Division of Nephrology, Baylor University Medical Center at Dallas, Dallas, USA

Table 1 Chemistry Panel

Serum chemistry		Reference range
BUN	99 mg/dL	6–24
Creatinine	7.75 mg/dL	0.76–1.27
Sodium	135 mEq/L	134–144
Potassium	4.1 mEq/L	3.5–5.2
Chloride	104 mEq/L	97–108
Bicarbonate	20 mEq/L	18–29
Total protein	8.6 g/dL	6.0–8.5
Albumin	4.1 g/dL	3.5–5.5
Calcium	9.6 mg/dL	8.7–10.2
Phosphorus	6.1 mg/dL	2.5–4.5
Alkaline phosphatase	85 mg/dL	39–117

Bolded values are in abnormal range

Table 2 Urinalysis

Urinalysis	
pH	5.0
Specific gravity	1.016
Glucose	Negative
Ketones	Negative
Protein	2+
Nitrite	Negative
Occult blood	3+
RBC urine	3/HPF
Bacteria	none

Bolded values are in abnormal range

haptoglobin < 5 (40–240 mg/dL), elevated LDH 1054 U/L, normal fibrinogen, low fibrin degradation product < 5 µg/ml, normal INR 0.8, and normal reticulocyte count. There was great concern for thrombotic microangiopathy due to the laboratory markers suggestive of intravascular hemolysis, worsening kidney failure, and thrombocytopenia. After multidisciplinary discussion with the cardiology, hematology, and nephrology teams, plasma exchange was initiated. He received daily plasma exchange (one plasma volume and no plasma substitutes were used) for 3 days without any improvement in serum creatinine and thrombocytopenia. Plasma exchange was discontinued on the 3rd hospital day as the ADAMTS13 activity test resulted in the normal range. Serum complements including C3, C4, and CH50 were normal, and ANCA and the antiphospholipid antibody panel were negative. He was also initiated on intermittent hemodialysis on the 3rd hospital day for azotemia. On the 7th hospital day platelet count decreased to 15,000/µL and schistocytes increased to 3+ on blood smear. On the 10th hospital day he underwent a kidney biopsy which had 32 glomeruli, four of which were globally sclerotic. Eight of the glomeruli showed variable fibrin thrombi (Fig. 1) in

some of the capillaries, both afferent and efferent, without endocapillary hypercellularity or inflammation. The capillary walls are single layered. There was no necrosis or crescent formation. There was some evidence of acute tubular injury but interstitial fibrosis/tubular atrophy was less than 10%. Immunofluorescence was negative. The biopsy was consistent with mild thrombotic microangiopathy (TMA) with only mild chronic changes. He was continued on intermittent hemodialysis three times a week and initiated on Eculizumab 900 mg weekly on hospital day 13. Laboratory values prior to, and after, Eculizumab can be seen below in Table 3. He was dialysis-free on hospital day 21. He was discharged on Eculizumab 900 mg weekly for 2 more doses followed by 1200 mg once and then 1200 mg every two weeks. On discharge, platelets were normal > 150,000/µL and creatinine was 2.29 mg/dL. Pre and post Eculizumab platelet count trend can be seen in Fig. 2. His respiratory status and oxygenation improved to pre-admission baseline without any oxygen requirements. On

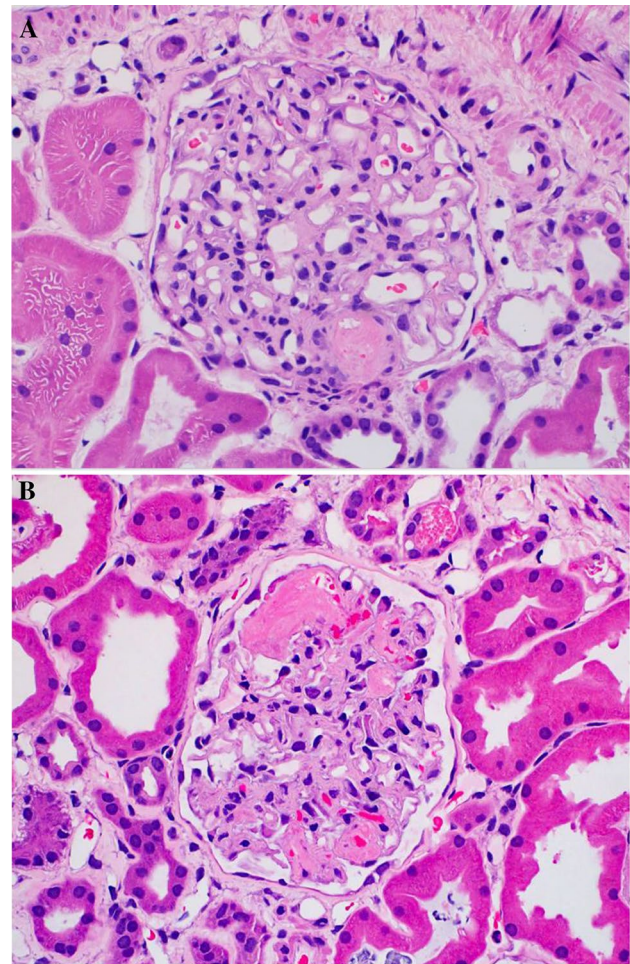
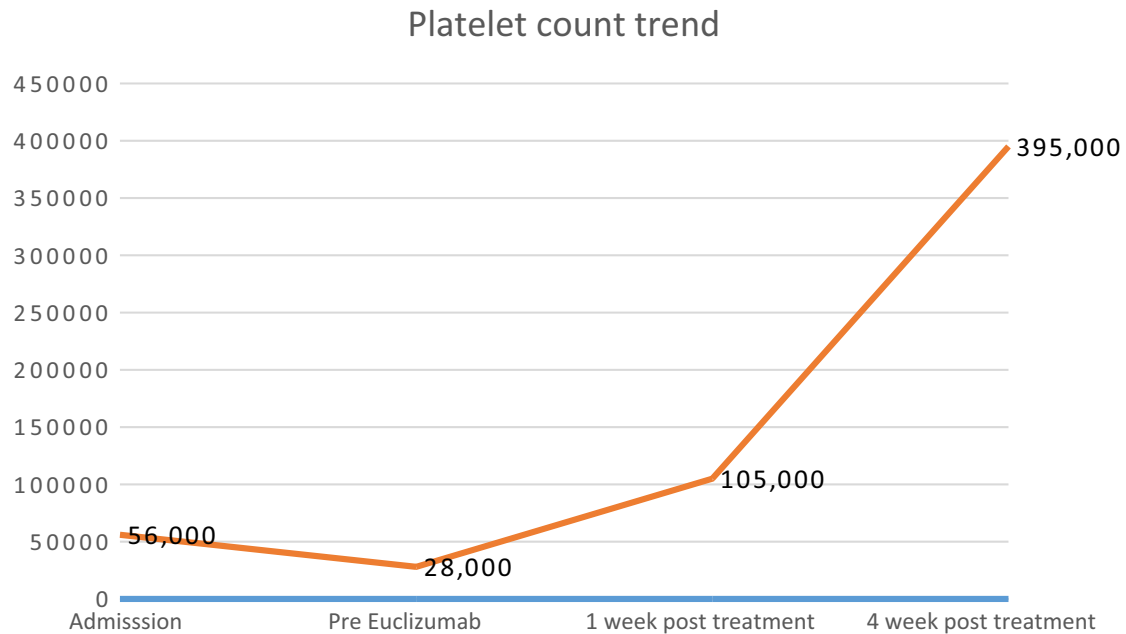


Fig. 1 Renal Biopsy Slides: Fibrin Thrombi in arteriole without endocapillary hypercellularity or inflammation consistent with thrombotic microangiopathy

Table 3 Comparison of labs pre and post Eculizumab therapy

Lab values	On admission	Pre-Eculizumab	7th day post Eculizumab	Reference range
BUN	99	80	45	6–24 mg/dL
Creatinine	7.75	7.13	4.8	0.76–1.27 mg/dL
Hemoglobin	13.5	7.5	7.8	13.5–18.0 g/dL
Platelet count	56	28	105	140–400 k/uL
LDH	1054	2076	583	85–245 U/L
Ferritin	2581	827	472	26–388 ng/ml

Bolded values are in abnormal range

**Fig. 2** Platelets count trend during hospitalization and pre and post Eculizumab

outpatient follow up after 6 months his creatinine improved to 1.42 mg/dL. The patient continued to have proteinuria below 1 g/day but eGFR was holding stable. The patient transitioned to ravulizumab, for convenience of dosing, after 2 months and continued for at least 6 months as of publication of this manuscript.

Complement genetic testing panel was sent to the Mayo clinic laboratories and is negative for: ADAMTS13, CD46, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, C3, CFD, DGKE, PLG, THBD.

Discussion

The reported incidence of acute kidney injury in critically ill COVID-19 patients in New York has been as high as 36.6% with the most common cause being ischemic acute tubular necrosis (ATN) [2]. The finding of acute tubular necrosis

was confirmed on 26 kidney autopsy slides [4]. It has been reported that AKI in COVID-19 is a complex process including virus-mediated injury, cytokine storm, dysregulation of complements, hypercoagulation and microangiopathy [3].

Retrospective analysis of 6 autopsy slides by Diao et al. [5] from China showed severe ATN, C5b-9 deposition in the tubular lumen suggesting complement-mediated damage as normal kidney tissues do not have any C5-9 deposition. In 2003, during the SARS epidemic in China, blood and serum samples of 569 patients were studied and it was found that patients with low levels of serum mannose binding lectin (MBL) were more susceptible to SARS-CoV infection. MBL acts as an ante-antibody and inhibits antibody response [6]. In 2020, Gao et al. demonstrated increased serum C5a levels in severe COVID-19 infections and use of anti-C5a monoclonal antibody therapy (open label drug, phase 1 clinical trial). They reported two patients with severe respiratory illness who were found to have a decrease in

oxygen requirement and a reduction in inflammatory markers post recombinant C5a antibody therapy [7]. The above-mentioned studies suggested that complement system has a significant role in the COVID-19 disease process.

Another autopsy study of 5 patients with severe COVID-19 infection lung and skin capillaries showed extensive deposits of the terminal component of C5b-9 complexes as well as C4d deposition [8]. The injury pattern was suggestive of activation of an alternative complement pathway leading to complement-mediated microvascular injury and thrombosis. Gralinski et al. studied mice infected with SARS-CoV and reported activation of C3 and its deposits in the lungs of these mice [9]. Diurno et al. from Italy reported four confirmed cases of SARS-CoV-2 with severe pneumonia or ARDS who were treated with Eculizumab in combination with hydroxychloroquine, antivirals and ceftriaxone. All four cases recovered with a marked drop in inflammatory markers within two weeks [10]. Based on the available data, Noris et al. [1] proposed the plausible hypothesis that cells infected and damaged by SARS-CoV-2 activate lectin and classical pathways and increase the production of terminal complement pathway C5a and C5b-9 which leads to endothelial dysfunction. The group has two ongoing compassionate-use protocols in the actively recruiting phase involving the administration of Eculizumab C5a inhibitor in COVID-19 patients (Clinicaltrials.gov: NCT04288713, NCT04346797).

Our search of English language literature on PubMed as of May 2021 showed less than 10 cases of thrombotic microangiopathy with COVID-19 infection including both pediatric and adult populations. In the majority of cases biopsy was deferred due to severity of illness and patients were treated based on clinical diagnosis. COVID-19 incidence is low in the pediatric population, however, among them there are at least two cases reported with complement-mediated TMA. The first patient, a 16-month-old boy, presented with COVID-19, new onset DKA, hemolytic anemia, thrombocytopenia and kidney failure. He was given a trial of fresh frozen plasma, however there was no improvement. His CH50 complement activity was low with elevated factor H and C5b-9 levels. He was started on Eculizumab and showed improvement in laboratory markers. Genetic testing was unremarkable [11]. Mahajan et al. reported a 14-year-old female with COVID-19 who was treated with Eculizumab for clinically suspected complement-mediated TMA. Serum C5b-9 was elevated. The patient was able to discontinue dialysis within 24 h of Eculizumab, and recovery of kidney function to baseline occurred in 3 weeks [12]. Ville et al. reported a case of atypical HUS relapse in a 28-year-old woman who was positive for COVID-19. Again, Eculizumab was started based on clinical and laboratory parameters and within 7 days of therapy hematological parameters and kidney function improved [13]. Another case of a 69-year-old female with severe COVID-19 illness had concern for TMA

and underwent kidney biopsy which showed severe acute thrombotic microangiopathy. The patient was started on Eculizumab however she died after 48 h of initiating therapy due to worsening shock [14].

Based on the data presented above, it can be concluded that there is complement activation in COVID-19 illness which leads to systemic thrombotic microangiopathy in some patients. It has been reported in the past that TMA/atypical HUS can relapse in the setting of viral illnesses like influenza. Some authors have suggested adding COVID-19 as a triggering factor for aHUS relapse. (It is a prime area of interest to explore use of Eculizumab in COVID-19 patients in prevention of severe illness and other serious manifestations in microvascular level.)

Sirolimus, the mTOR inhibitor, inhibits the production of VEGF which is required for endothelial cell survival. Thus, sirolimus can cause endotheliosis and trigger TMA (however risk is increased with combination of cyclosporine or tacrolimus). Most of the time TMAs caused by immunosuppressive medications are renal-limited [15]. Our patient had been on sirolimus for several months prior to this incident and in addition, since starting treatment he has continued sirolimus and has not had any ongoing symptoms. Hence, it is less likely that TMA was triggered by sirolimus alone as the presentation was systemic and not renal-limited. Our case is one of the few reported in the world of COVID-19 and biopsy-confirmed TMA with resolution of COVID-19 combined with Eculizumab. At the six month follow up visit our patient's renal function is stable with a creatinine level of 1.42 mg/dL. He was switched to one infusion of Ravulizumab every eight weeks. Furthermore, this may be one of the first reported cases of COVID-19-induced HUS being treated with the newer complement inhibitor Ravulizumab. As of this manuscript writing, the patient is 6 months post initiation of treatment and ongoing aggressive treatment. (It is planned with coordination and education of the patient's wishes, to explore stopping complement inhibitor therapy between 6 and 12 months if the patient continues to have stable kidney function and no return of other symptoms.)

Author contribution JG: writing original draft, editing. CAH and GBC: review and editing. CAH and GBC: supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Declarations

Ethical approval The article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest No conflicts of interest, financial or other, exist.

Informed consent For this type of article formal informed consent is not required.

Consent for publication Yes.

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