Case Series

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# Hemolysis and COVID-19 infection: A fatal combination – An interesting series of three cases

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**Abstract:**

COVID-19 has wreaked havoc ever since its inception and with the protean manifestations of the disease, it is imperative that progressively data are added to the literature. COVID-19 infection is a multisystem disorder with a wide range of clinical symptomatology. Recent information garnered has laid emphasis on pathological changes at microvascular level causing thrombotic/hemostatic defects, leading to the assorted clinical presentation. We present a consortium of three confirmed COVID-19 cases whose hospital course got convoluted with grave hematological complications in the form of hemolytic uremic syndrome and autoimmune hemolytic anemia. Regrettably, all three patients succumbed to their illness.

**Keywords:**

Acquired hemolytic anemia, COVID-19, hemolytic uremic syndrome, microangiopathic hemolytic anemia

## Introduction

COVID-19 infection is caused by severe acute respiratory syndrome-coronavirus-2, which is a member of a large family of viruses called coronaviruses. It has wreaked havoc ever since its inception a few years ago. It started in December 2019, when the cluster of cases presented with respiratory symptoms alone. Since that, symptomatology has diversified and expanded to include a spectrum of clinical features with which a patient with COVID-19 can present. The basic pathophysiology which explains the protean manifestation can be explained by excessive activation of the immune system, leading to a cytokine storm and inappropriate complement system activation, leading to multisystem failure due to microangiopathies.[1]

COVID-19 infection is mischievous to initiate or trigger hematological complication/manifestation in COVID-19 in the form of isolated thrombocytopenia most commonly and infrequently pulmonary/cerebral thrombotic pathologies. Besides this, there have been few reports of rarer complications like thrombotic microangiopathies (TMAs) in the form of disseminated intravascular coagulation and hemolytic uremic syndrome (HUS)[2-5] or in some cases autoimmune hemolytic anemia (AIHA) which could be warm/cold autoantibody type.[6-9]

Herein, the authors would like to present a gamut of cases involving three COVID-19-confirmed cases whose hospital course took a drastic spin due to complications in the form of HUS and AIHA. All three cases succumbed to the complicated turn of events within no time.

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## Case Reports

### Case 1

The patient was a 68-year-old male with no known comorbidities, who reported complaints of high-grade fever, myalgia, cough, and breathlessness. On physical examination, he was tachypneic, his arterial oxygen saturation (SpO2) was on the lower side (86%), and he had rhonchi in both lung fields. He tested positive for COVID-19 on real-time polymerase chain reaction (RT-PCR) with a high viral load (cycle threshold [Ct] value-12). The individual was unvaccinated against COVID-19. His baseline investigations showed bilateral nonhomogeneous opacities on chest X-ray, raised serum ferritin (863 ng/ml; normal range 12–300 ng/ml), normal D-dimer levels (352.6 ng/ml; normal range < 500 ng/ml), and elevated interleukin-6 (IL-6) levels (124.3 pg/ml; normal range 0–43.5 pg/ml). He was admitted as a case of "moderate COVID-19 pneumonia" and was started on anti-COVID treatment as per the institutional guidelines including injection remdesivir at a loading dosage of 200 mg intravenously (IV), followed by 100 mg IV once daily for the next 6 days the 3rd day of admission. His other baseline hematological and biochemical parameters were within normal limits.

He continued to be on oxygen support during his course of hospital stay. On the 5th day of admission, he started deteriorating with reduced urine output and derangement of his laboratory parameters. He started developing thrombocytopenia along with altered renal function tests (RFT) (platelets – 49,000/mm3; urea – 271 mg/dl; creatinine – 10.4 mg/dl). Peripheral blood smear (PBS) evaluation showed features of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and compensatory reticulocytosis (~10%) [Figure 1a-c]. His lactate dehydrogenase (LDH) values were grossly elevated [Table 1]. He continued to deteriorate clinically which corroborated with his laboratory values and he developed anuria the following day and finally succumbed to his illness on Day 7 of his admission.

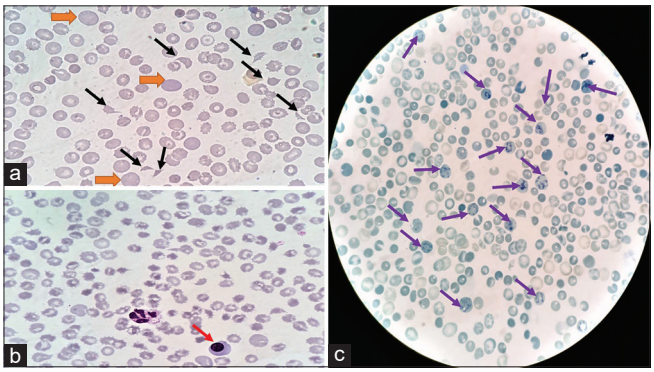


**Figure 1:** (Case 1)-PBS showing features of intravascular hemolysis in the form of numerous schistocytes/fragmented RBCs (black arrows), polychromatophilic cells (orange arrows), a nucleated RBC (red arrow), and marked reticulocytosis (purple arrows) (a and b) Leishman–Giemsa stain – ×1000 oil immersion; (c) supravital stain – ×1000 oil immersion). PBS = Peripheral blood smear, RBCs = Red blood cells

### Case 2

The patient was a 77-year-old male who presented with breathlessness. He was unvaccinated against COVID-19 and a known diabetic and hypertensive having good drug compliance with no documented end-organ damage. He tested positive for COVID-19 on RT-PCR with a Ct value of 14.3. On examination, he was tachypneic with an extremely low SpO2 of 57% and crepitations in both lung fields. He was admitted as a case of "severe COVID-19 pneumonia" and was started on high-flow oxygen support and other anti-COVID medications. He had raised serum ferritin (972 ng/ml) and IL-6 (78 pg/ml) levels. His other baseline hematological and biochemical parameters were within range.

On the 4th day of admission, he developed oliguria. Investigations revealed thrombocytopenia (79,000/mm3) and raised urea (131 mg/dl) and creatinine levels (4.3 mg/dl). His LDH levels were markedly raised [Table 1]. PBS showed features of intravascular hemolysis in addition to already documented thrombocytopenia [Figure 2a-c]. On the 5th day of admission, he developed anuria and passed away subsequently.

### Case 3

The patient was a 68-year-old male, who was partially vaccinated against COVID-19 and was a known hypertensive with early-stage nephropathy on regular medications. He presented with complaints of fever, cough, chest pain, and breathlessness. He was found to be positive for COVID-19 on RT-PCR with a Ct value of 15.9. On physical evaluation, he was febrile and tachypneic with a low SpO2 value (72%) and bilateral lung field

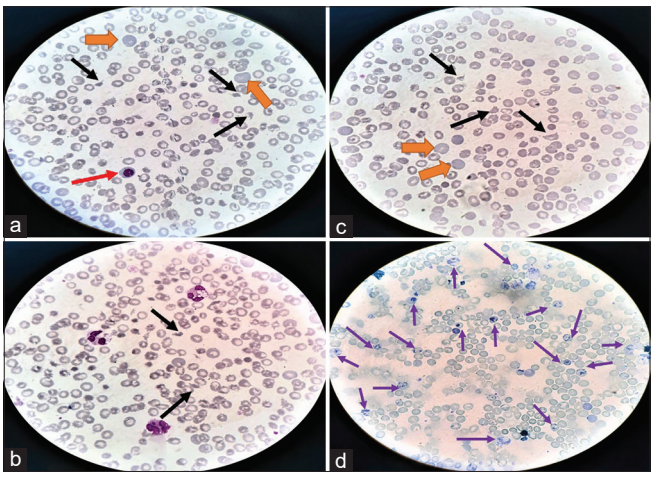


**Figure 2:** (Case 2)-PBS showing features of intravascular hemolysis in the form of numerous schistocytes/fragmented RBCs (black arrows), polychromatophilic cells (orange arrows), a nucleated RBC (red arrow), and marked reticulocytosis (purple arrows) (a-c) Leishman–Giemsa stain – ×1000 oil immersion; (d) supravital stain – ×1000 oil immersion). PBS = Peripheral blood smear, RBCs = Red blood cells

**Table 1: Extract of the chronology of investigations**

| Day | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Day 1 | CXR – Bilateral nonhomogeneous opacities<br>Ferritin – 863 ng/ml<br>D-dimer – 352.6 ng/ml<br>IL-6 (124.3 pg/ml)<br>Hb – 14.7 g/dl | Ferritin – 972 ng/ml<br>IL-6 – 78 pg/ml<br>Hb – 13.4 g/dl | Urea – 65 mg/dl<br>Creatinine – 1.6 mg/dl<br>D-dimer – 581 ng/ml<br>IL-6 – 62 pg/ml<br>PBS – Neutrophilic leukocytosis with left shift and toxic changes<br>Hb – 10.1 g/dl |
| Day 4 | - | PBS – Schistocytes, thrombocytopenia, and reticulocytosis (12%)<br>Urea – 131 mg/dl<br>Creatinine – 4.3 mg/dl<br>LDH – 5421 IU/L<br>Hb – 9.8 g/dl | - |
| Day 5 | Hb – 9.2 g/dl<br>PBS – Schistocytes, thrombocytopenia, and reticulocytosis (10%)<br>Urea – 271 mg/dl<br>Creatinine – 10.4 mg/dl<br>LDH – 22,760 IU/L | Died on the 5$^{th}$ day of admission | Hb – 8.8 g/dl<br>PBS – Marked polychromatophilia with reticulocytosis (6%)<br>DCT – Positive (2+ to 3+)<br>LDH – 840 IU/L |
| Day 6 | Hb – 8.4 g/dl<br>PBS – Neutrophilic leukocytosis with left shift and toxic changes, schistocytes, thrombocytopenia, and reticulocytosis<br>Urea – 306 mg/dl<br>Creatinine – 12 mg/dl<br>LDH – 22,260 IU/L | | Hb – 8.1 g/dl<br>PBS – Marked polychromatophilia with reticulocytosis (8%)<br>LDH – 1265 IU/L |
| Day 15 | | | Hb – 8.3 g/dl<br>PBS – Marked neutrophilic leukocytosis (TLC – 35,800/mm$^3$ on day 15) with left shift and toxic changes; Polychromatophilia with reticulocytosis (8%)<br>LDH – 1734 IU/L (died on the 17$^{th}$ day of admission) |

IL=Interleukin, PBS=Peripheral blood smear, LDH=Lactate dehydrogenase, DCT=Direct Coombs test, CXR=Chest X-ray, TLC=Total leukocyte count

crepitations. He was put on noninvasive ventilation with high oxygen flow rate along with other standard anti-COVID-19 medications. His initial laboratory investigations revealed neutrophilic leukocytosis with toxic changes, slight elevation of urea (65 mg/dl), creatinine levels (1.6 mg/dl), deranged IL-6 (62 pg/ml), and D-dimer levels (581 ng/ml).

He continued to deteriorate clinically with dependency on increasing oxygen flow rate and was subsequently put on mechanical ventilation. On the 5$^{th}$ and 6$^{th}$ day of admission, his PBS revealed marked polychromatophilia confirmed by a reticulocyte count of 6%–8% on supravital stain. Polyspecific direct Coombs test (DCT) was positive with a 2 + to 3 + reaction [Figure 3a and b]. All the investigations in search of a secondary cause were negative (normal glucose-6-phosphate dehydrogenase levels, negative antinuclear antibody and antiphospholipid panel, and negative serology for common infections such as human immunodeficiency virus, hepatitis B, hepatitis C, mycoplasma, influenza, Epstein–Barr virus, and cytomegalovirus). Abdominal and thoracic imaging

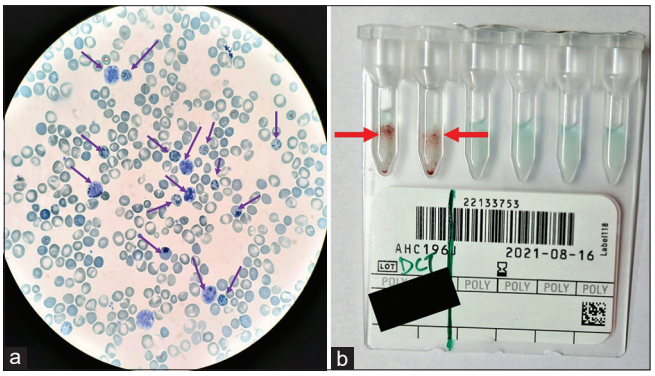


**Figure 3:** (Case 3) (a) Supravital staining on PBS showing marked reticulocytosis (purple arrows) (×1000 oil immersion). (b) Gel column agglutination technology for direct Coombs test (run in duplicate) showing a positive reaction (2+ to 3+) (red arrows) to a polyspecific reagent suggestive of autoantibodies causing hemolysis. PBS=Peripheral blood smear

was carried out to rule in/out a hematolymphoid malignancy which did not reveal any lymphadenopathy or organomegaly. He subsequently, during his course of hospital stay, developed features of overt septic shock in the form of continuous febrile episodes, hypotension,

and marked neutrophilic leukocytosis with left shift and toxic changes on PBS [Table 1]. He continued to be on ventilatory support with a dismal prognosis and expired on the 17th day of admission.

## Discussion

COVID-19 infection has caused major mayhem in our lives ever since its advent in the human race in late 2019 and still continues to evolve and evade treatment courtesy of the rapid mutation characteristic of virus. Only a smaller proportion of those infected go on to acquire a severe disease. The respiratory system is the one which is predominantly affected by this virus, although recent evidence suggests a complicated multisystem clinical affliction in the form of cardiomyopathies, cerebrovascular accidents, renal failure, and thrombo-vasculitic events.[3] Even in the patients who have had a typical course of the respiratory distress-like syndrome, thrombotic necrotizing pulmonary microvascular insult has been elucidated.[10]

The first two cases described in our report showed comparably similar hospital course and outcome. Both the patients were elderly and unvaccinated against COVID-19. The initial presentations in both the patients were similar and both of them were oxygen dependent. On the 4th–5th day of admission, both these patients strikingly developed oliguria progressing to a fatal anuric stage. During this stage, the evaluation revealed features of MAHA on PBS, thrombocytopenia, deranged RFT, and markedly elevated LDH levels.

The third case in our presentation is of an autoimmune hemolytic type. The patient, who was partially vaccinated against COVID-19 and was a known case of hypertensive nephropathy, presented with features of severe COVID-19 infection. He continued to be critical and was on ventilatory support throughout. On the 5th day of admission, PBS evaluation revealed features of hemolytic anemia which was confirmed as AIHA on a polyspecific DCT. Other infectious, autoimmune and malignant causes of AIHA were ruled out. The individual was already on steroids for his underlying COVID-19 infection and his medications were titrated to the present condition of AIHA. However, the course continued to be stormy and he also succumbed to the illness like the other two patients. None of the patients were subjected to postmortem evaluation due to the institutional policy of not performing an autopsy on confirmed COVID-19 casualties and also due to the consent not being granted by the kinfolks.

The stated frequency of acute kidney injury in COVID-19 patients is high as 36.6%[1] with the most common cause being acute tubular necrosis, ischemic type. Some rarer causes include cytokine storm, virus-mediated direct injury, complement dysregulation, and TMA1. Increased LDH and thrombocytopenia have been documented in many severe COVID-19 infections. On review of literature, we didn't find many documented reports of MAHA associated with COVID-19, probably because of the limited sampling and analysis of samples from COVID-19 infected patients due to the panic the current pandemic has put us all in, especially when it comes to maintaining the highest standards of COVID-19 protocols during sampling and testing.[2]

Gill *et al*. in their report have discussed a case of COVID-19 presenting with atypical HUS (aHUS) which was successfully treated with eculizumab, thereby proposing that there is widespread complement activation in COVID-19, leading to systemic TMA. It has been widely reported that aHUS and TMA can be triggered or can relapse in the setting of influenza-like illness, which rules in the possibility of COVID-19 as a plausible triggering factor for relapse of aHUS/TMA.[1,2]

Complement activation plays a key role in the etiopathogenesis of TMA. This COVID-19-associated TMA is an unusual condition, which can be due to the viral invasion of the endothelial cells itself, or due to complement activation with or without accompanying cytokine storm.[4]

There are a few reports of COVID-19-associated AIHA in the literature, with most of them being of warm autoantibody type and a handful of them being either cold type or mixed type. The proposed mechanism for the development of AIHA as per the literature is that the cytokine storm causes alteration in the antigen presentation creating cryptic antigens, which then go on to stimulate T-lymphocytes which further activate B-lymphocytes-producing autoantibodies.[7]

The cases mentioned in the literature have a variable onset of hemolysis from the detection/confirmation of COVID-19 infection. However, most of the cases reported in the literature were diagnosed within the 1st 2 weeks following COVID-19 infection. The case in the index report had presented with features of AIHA in the 1st week itself (5th day) in our institute. Researchers across the globe are hypothesizing that COVID-19 could be a potential infectious trigger for AIHA.[6-8] It is not known as to what is the exact frequency of DCT positivity in COVID-19 patients and what percentage of DCT-positive patients actually have hemolysis. As the cases reported are few, it is also blurry as to whether there are any other factors contributing to the development and/or progression of hemolysis in patients infected with COVID-19.

## Conclusion

COVID-19 is a multisystem disease with predominant involvement of the microvascular compartment giving rise to diverse clinical patterns. Hematological complications like TMA/HUS are rapidly fatal and should be recognized promptly to direct the line of management in the right course. Similarly, AIHA-complicating COVID-19 appears multifactorial, the exact cause of which remains to be made clear. An additional interesting angle to this series of cases reported is that vaccination might be beneficial and protective against serious microvascular complications as both the patients of TMA/HUS in our study who died were unvaccinated, whereas the case of AIHA was partially vaccinated.

## Acknowledgment

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## Declaration of patient consent

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

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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