Complicated case of COVID-19 disease with overlapping features of thrombotic thrombocytopenic purpura and haemophagocytic lymphohistiocytosis

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SUMMARY
Haemophagocytic lymphohistiocytosis has been reported as an uncommon complication of severe COVID-19 disease while thrombotic thrombocytopenic purpura has been rarely reported. Here, we are reporting a 21-year-old man who developed a combination of these complications during the hospital stay in the post-COVID-19 recovery period. He presented with fever and bilateral COVID-19-related pneumonia requiring invasive ventilation. His hospital course was complicated by the development of pneumothorax, ventilator-associated pneumonia, thrombotic thrombocytopenic purpura and haemophagocytic lymphohistiocytosis. He received remdesivir, IVIG, steroid, fresh frozen plasma and supportive care but had a fatal outcome.

BACKGROUND
This COVID-19 pandemic has made us aware of various haematological and nonhaematological manifestations of the SARS-CoV-2 virus.1 Common haematological presentations include neutrophilia, lymphopenia, secondary immune thrombocytopenia, thrombotic tendency and disseminated intravascular coagulation (DIC).2 Still, many haematological presentations are uncommon and not frequently reported in the literature. Haemophagocytic lymphohistiocytosis (HLH) is a rare phenomenon and occurs due to cytokine storms.3 Thrombotic thrombocytopenic purpura (TTP), a classical type of microangiopathic haemolytic anaemia, is a very rare entity reported in the COVID-19 disease.4 We report the first case of a complicated COVID-19 disease that had features of both HLH and TTP.

CASE PRESENTATION
A 21-year-old man presented to holding area emergency of King George's medical university, Lucknow with a history of fever for 2 weeks and breathlessness, dry cough and high-grade fever for 7 days. Fever was not associated with chills and rigour, chest pain, expectoration, haemoptysis or any skin rash. There was no history of addiction, previous illness, tuberculosis, contact with known tuberculosis or significant comorbidities.

On physical examination, he was conscious oriented but severely breathless. He was very thin built, cachexic and his body mass index (BMI) was 15 kg/m². His vitals were: BP—118/70 mm Hg, pulse rate—104/min, respiratory rate 24/min. Pallor was present and there was no icterus, oedema or lymphadenopathy. Chest examination shows bilateral diffuse crackles. Cardiovascular examination was normal. Abdominal examination shows splenomegaly 3 cm below the left costal margin and neurological examination was normal at presentation. He was not maintaining saturation on noninvasive ventilation and developed multiple episodes of seizure needing intubation and invasive ventilation. Seizures subsided with antiepileptic medications, but he developed altered sensorium with sensorium of E2VTM5 on Glasgow Coma Scale. His COVID-19 test by reverse transcription PCR (RT-PCR) was positive, so he was shifted to COVID-19 intensive care unit (ICU) setup. On day 3, in COVID-19 ICU, he was not maintaining...
relevant investigations are given in table 1.

**Figure 3** Bone marrow biopsy section showing erythroid hyperplasia along with presence of many haemophagocytes (H&E,1000×).

The patient showed improvement as his clinical and haematological parameters improved initially. There was an improvement in platelet count along with a decrease in white cell count, C reactive protein (CRP), lactate dehydrogenase (LDH), ferritin and D-dimer. He became COVID-19 negative after 2 weeks of ICU admission. His ventilator parameters improved and he was extubated and kept on noninvasive ventilation. He was shifted to a non-COVID ICU setup in the department of medicine for convalescence. He required 2–3 L of oxygen and intercostal drainage (ICD) closure was also done. The patient again developed right-sided pneumothorax on the 10th day after the closure of the ICD. He also developed high-grade fever, sepsis and rapid clinical deterioration. Pneumothorax with a secondary lung infection, progressive cachexia and the possible progression of TTP led to the rapid clinical deterioration of the patient. Patient died after 2 months of prolonged hospital stay despite all possible measures.

**DISCUSSION**

COVID-19 is a global pandemic. It has affected approximately one billion people worldwide and leads to the mortality of two million people. COVID-19 can present with various haematological manifestations and some of them have predictive value for the outcome and some are associated with high mortality. We report this case of severe COVID-19 who presented with COVID-19 pneumonia and further got complicated by the development of pneumothorax, TTP and HLH and had mortality after a prolonged hospital stay. All secondary causes of TTP were excluded in this case and his COVID-19 report by RT-PCR was positive, so the SARS-CoV-2 virus was the most probable cause of TTP and HLH in this case.

It is well known that both primary and secondary HLH can be triggered by many viral infections like the Epstein-Barr virus and others. The mechanism behind SARS-CoV-2 and the
development of HLH were not clearly understood. Underlying extensive cytokine release in severe COVID-19 is probably responsible for the occurrence of HLH. Tholin et al reported a case of a 71-year-old man, having COVID-19 disease and HLH suspected by marked elevation in his inflammatory markers. His CRP was 334 mg/dL, lactate dehydrogenase was 1074 U/L and ferritin was 36023 µg/L. He also met five out of eight criteria for HLH according to HLH-2004 diagnostic criteria along with evidence of bone marrow haemophagocytosis. The patient was treated with tocilizumab (anti-IL-6 antibody) with other supportive care and his inflammatory parameter improved gradually.7 The mechanism of TTP in COVID-19 disease is even poorly understood. Altowyan E et al have reported a 39-year-old woman, with COVID-19 disease and TTP which was suspected by peripheral smear examination showing evidence of thrombocytopenia and microangiopathic haemolytic anaemia. This patient developed an ischaemic stroke. He was treated by plasma exchange therapy along with supportive care and showed excellent recovery.4 In the non-COVID setup, there is another case report by Daniel et al who had overlapping features of autoimmune haemolytic anaemia, TTP and haemophagocytic lymphohistiocytosis.5 She was a 26-year-old woman presented with features of Autoimmune hemolytic anemia (AIHA), HLH and TTP and complicated by multiorgan failure, DIC and gastrointestinal bleeding. She was managed by IVIG, steroid, splenectomy, haemodialysis, broad-spectrum antibiotics and vasopressor support.

CONCLUSION(S)
COVID-19 can present with a myriad of clinical manifestations. Haematological manifestations can vary from very benign to life-threatening conditions. The occurrence of haemophagocytic syndrome or TTP in COVID-19 is very rare and has a poor outcome. The co-occurrence of both these entities has not been reported in the literature. The involvement of expert haematologists and haematopathologists in the COVID-19 management team is much needed for timely diagnosis and management of such cases.

Learning points
► COVID-19 disease may present with various haematological manifestations.
► COVID-19 disease can also present with features of thrombotic thrombocytopenic purpura and haemophagocytic lymphohistiocytosis simultaneously, so there is a need for high suspicion and awareness of these conditions especially in patients with severe COVID-19.
► Haematologists and haematopathologists should be part of the COVID-19 management team with physicians and intensive care experts for better management of these cases.

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Case report

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REFERENCES