Severe thrombocytopenia secondary to COVID-19

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SUMMARY
The SARS-CoV-2 infection has caused a pandemic with a case rate of over 290,000 lab-confirmed cases and over 40,000 deaths in the UK. There is little evidence to inform the optimal management of a patient presenting with new or relapsed acute idiopathic thrombocytopenia purpura with concurrent SARS-CoV-2 infection. We present a case of severe thrombocytopenia complicated by subdural haematoma and rectal bleed associated with COVID-19. A 67-year-old man, admitted with a non-productive cough and confusion, was found to be positive for COVID-19. Ten days after admission, his platelets decreased from 146×10⁹/L to 2×10⁹/L. His platelets did not increase despite receiving frequent platelet transfusions. He was non-responsive to corticosteroids and intravenous immunoglobulins. Romiplostim and eltrombopag were given and after 9 weeks of treatment, his platelet count normalised. He was deemed medically fit with outpatient follow-up in a haematology clinic.

BACKGROUND
COVID-19 is a global pandemic caused by infection from SARS-CoV-2. At the time of writing, it has a case rate of over 290,000 in the UK, with over 40,000 case fatalities.1 Its presentation ranges from asymptomatic to severe illness and mortality. The most common symptoms include fever, dyspnoea and a non-productive cough. COVID-19 has been documented to induce systemic coagulation abnormalities, including pulmonary microvascular thrombosis.2

An additional haematological sequela to COVID-19 that has been documented is idiopathic thrombocytopenia purpura (ITP)—an immune-mediated condition thought to involve platelet destruction and inhibition of platelet biosynthesis. As of yet, there have been very limited documented reports of ITP secondary to COVID-19 infection.3 Furthermore, the vast majority of severe thrombocytopenia cases involved patients with severe presentations of COVID-19.4,5 However, this case involved a patient with only mild–moderate symptoms of COVID-19 and no known prior haematological history that manifested as a subacute frontoparietal haematoma and rectal bleed.6 This paper therefore demonstrates the novel finding that patients with ITP secondary to COVID-19 may have severe thrombocytopenia in mild–moderate forms of COVID-19 that result in serious haematological and intracranial manifestations. By examining the mechanisms of COVID-19 that are presently known, this report evaluates the processes by which COVID-19 may induce thrombocytopenia. Furthermore, we evaluate our therapeutic decisions and compare it to known evidence.

As a result of the increasing case rate of COVID-19 worldwide, it is likely the incidence of ITP secondary to COVID-19 will rise. Thus, the authors of this paper believe that greater awareness of its presentations should be disseminated to the medical community.

CASE PRESENTATION
A 67-year-old man with a background of angina, non-diabetic hyperglycaemia, glaucoma, dementia, depression and diverticulitis presented with confusion and a non-productive cough of unknown duration. The patient has not had any coronary intervention or antiplatelet therapy in the past, and he did not have a history of autoimmune disease. On admission, he was without fever, with a respiratory rate of 16 breaths/min, with an oxygen saturation of 99% on room air, a heart rate of 46 beats/min and blood pressure of 95/54 mm Hg. Prior to admission, he was on sertraline 50 mg orally once per day.

INVESTIGATIONS
He had the following blood tests on admission: haemoglobin (Hb), 142 g/L; white cell count (WCC), 7.7×10⁹/L; neutrophils, 6.8×10⁹/L; lymphocytes, 0.5×10⁹/L; platelets, 118×10⁹/L; C reactive protein, 215 mg/L; sodium, 137 mmol/L; potassium, 4.2 mmol/L; urea, 7.5 mmol/L; creatinine, 90 mmol/L; estimated glomerular filtration rate, 76 mL/min/1.73 m²; bilirubin, 14 µmol/L; alanine transaminase, 21 IU/L; alkaline phosphatase, 60 IU/L; albumin, 41 g/L; prothrombin time, 14.1 s; internationalised normal ratio, 1.2; partial thromboplastin time ratio, 1.07; folate, 5.1 µg/L; and B₁₂ levels, 425 pg/mL. His thyroid stimulating hormone was 1.8 mU/L, and his erythrocyte sedimentation rate was 11 mm/hour. Hepatitis B surface antigen and core antibody, hepatitis C antibody, HIV antibody/p24 antigen, toxoplasma IgG and Cytomegalovirus (CMV) IgM antibody were not detected. Epstein-Barr virus (EBV) serology was consistent with a past (non- consequential) infection. A confusion screen including a CT of the brain was also unremarkable. Chest X-ray revealed bilateral opacifications suspicious for COVID-19, and nasopharyngeal swab confirmed this diagnosis (figure 1).
New disease

DIFFERENTIAL DIAGNOSIS
In response to his thrombocytopaenia, the haematology team was consulted and a preliminary diagnosis of ITP was established secondary to COVID-19, as the rest of the cell lines in his full blood count were normal. D-dimer and other coagulation studies did not suggest disseminated intravascular coagulation. A viral screen ruled out a viral-induced thrombocytopaenia.

TREATMENT
The patient was initially treated for COVID-19 with secondary delirium. He was mildly symptomatic for COVID-19 for about the first 14 days of his admission. However, throughout this period, he was without fever and had no additional oxygen requirements. On day 10, the patient experienced an isolated episode of rectal bleeding but was haemodynamically stable, and it resolved with tranexamic acid. A new set of bloods on the same day revealed an Hb of 121 g/L, WCC of 3.3×10^9/L and platelets of 5×10^9/L. A peripheral smear was performed (figure 2).

The patient was started on prednisolone (1 mg/kg) and intravenous (IV) immunoglobulins. Daily monitoring of Hb and platelets were recommended. On day 13 twice daily platelet transfusions were initiated as the platelet count had dropped significantly (2×10^9/L). These platelet transfusions continued throughout his admission. On day 15, prednisolone was tapered due to potential adverse effects on the concurrent COVID-19 infection and because the patient did not have a good response regarding his platelet count. On the same day, the patient had a witnessed fall without head injury. Due to the persistent confusion and an unremarkable CT of the head on admission, an MRI of the head was performed on day 23, which revealed a subacute subdural haematoma with possible evidence of encephalitis (figure 3). Due to the subdural haematoma, advice was given from haematology to aim for an Hb count above 80 g/L and a platelet count above 100×10^9/L.

A lumbar puncture was requested to confirm encephalitis but had to be abandoned due to patient non-compliance, even though his platelet count was above the necessary threshold to perform safely. Daily platelet counts did not rise above 32×10^9/L, and on day 22, steroids were stopped and eltrombopag was started. The patient’s response to eltrombopag was limited as the patient had found it difficult to swallow tablets and thus was stopped. Subcutaneous romiplostim was started on day 26. His Hb declined from 142 g/L on admission to a steady level of between 80 and 100 g/L; the patient’s anaemia was considered to be iron deficiency anaemia due to the rectal bleed. This was managed from day 32 with the introduction of intravenous iron. The source of the patient’s confusion was diagnostically difficult to identify. As described initially, it was believed to be a delirium secondary to COVID-19. However, when his confusion persisted despite recovery from infection, a provisional diagnosis of acute psychosis was made. Finally, after consultation with the psychiatric team and from collateral histories, it was thought more likely to be a deterioration of his dementia. On day 38, the platelet count dropped to 53×10^9/L. From day 54 onwards, the dose of romiplostim was titrated up to gain benefit; however, the platelets still remained around 36×10^9/L. A bone marrow (BM) biopsy was attempted but unfortunately had to be abandoned due to patient non-compliance.

OUTCOME AND FOLLOW-UP
On day 66, platelet count increased to 423×10^9/L and romiplostim was stopped, with a plan to be restarted if the platelet count dropped below 150×10^9/L. Platelet count had been stable for over 7 days, and the patient is now being considered as medically fit, with haematological and psychiatric follow-up.

DISCUSSION
ITP is an autoimmune condition which involves the autoimmune destruction of the body’s own platelets, resulting in thrombocytopaenia (platelets<100×10^9/L). Its presentation ranges from asymptomatic to purpura or, in severe cases, epistaxis or fatal haemorrhaging. Acute ITP is thought to be triggered by viral infections including HIV, Hepatitis C (HCV), CMV, EBV and Varicella Zoster virus (VZV). Its treatment includes antiviral therapy, glucocorticoids, intravenous immunoglobulins and thrombopoietin receptor agonists (TPO-RAs). There are relatively few cases of reported ITP secondary to SARS-CoV-2 in the UK as compared with the Chinese population. The
most common haematological manifestations in patients with COVID-19 are lymphopenia and thrombocytopenia. Lymphopenia is the result of decreased CD4+ or CD8+ T lymphocytes related to the onset of the disease. There are a number of proposed reasons for why thrombocytopenia results, and these will be discussed after considering the three main suggested locations for platelet biogenesis.

Although megakaryocytes (MKs) originated in the BM, it is believed that they translocate via the bloodstream to extra-BM sites. As a result, there are three main areas for thrombopoiesis, first in the BM. This involves megakaryoblast formation into demarcation membrane systems via endomitosis, before they mature and result in platelet release. MKs are found in the extravascular space on the abluminal side of sinus endothelial cells and possibly project platelets into the lumens of sinusoids. Second, there are proposals that thrombopoiesis occurs in the bloodstream. It has even suggested that the final stages of platelet maturation occur exclusively in the blood circulation. Third, thrombopoiesis occurs in the lungs. There are many studies that have reported the presence of MKs in lung vessels, but their significance to thrombopoiesis in health and disease have been controversial. First described by Aschoff, it was proposed that MKs originate in the BM and migrate via the bloodstream to the lungs, where due to their size they would become embedded in the pulmonary vasculature and become platelets. It is estimated that 250,000 MKs enter the lung from the bloodstream per hour. Platelet counts are greater in the pulmonary vein and artery, and 10-fold more abundant than in the aorta, providing evidence for pulmonary thrombopoiesis. MKs have also been found abundantly in the lungs in diagnostic and forensic autopsies. There is now evidence to suggest that the lung uses a distinct mechanism of proplatelet release from intravascular MKs (of extrapulmonary origin) in the lung microcirculation. Furthermore, mature and immature MKs and haematopoietic progenitors may reside in reservoirs in pulmonary extravascular spaces. If thrombocytopenia develops, these cells can migrate intracellularly to restore levels of platelets. There remains, however, controversy as to the proportion of biogenesis that occurs in the lungs relative to the BM and bloodstream. However, evidence exists that the lungs may be responsible for up to 50% platelet biogenesis.

There have been multiple proposed mechanisms for how COVID-19 causes thrombocytopenia. The first mechanism is through a cytokine storm and macrophage activation which possibly results in decreased haematopoietic progenitor cells. The second mechanism is by direct infection of haematopoietic and BM stromal cells. The third mechanism is by lung injury—there are several proposals for how the final mechanism may occur. This includes platelet activation, aggregation and microthrombi formation, resulting in increased platelet consumption. It may also include persistent hypertension and hypoxaemia, which result in areas of lung fibrosis, and therefore less surface area for platelet biogenesis. The fourth mechanism is via an increase in autoantibodies resulting in platelet destruction: SARS-specific IgG antibodies are produced in the late acute stage (at around 2 weeks) and gradually increase with the course of the disease. As the thrombocytopenia was first recorded in our case in the latter disease stages on day 10, we propose that autoantibody platelet destruction may be a prominent mechanism.

We describe a patient with COVID-19 with secondary ITP, presenting with a subacute subdural haematoma. This is the first documented example of a patient with only mild–moderate COVID-19 symptoms with a secondary subdural haematoma. This was not considered secondary to his fall as no head injury was sustained. The cause of the rectal bleed was unknown as the patient would not tolerate a sigmoidoscopy. Therefore, this could be attributable to his diverticulosis or a spontaneous bleed secondary to ITP. Furthermore, our case reiterates the finding that thrombocytopenia can occur at a late presentation following the onset of COVID-19—in our case, occurring on day 10. The patient’s platelet count in December 2019 was $152 \times 10^3$ /L and therefore he did not have thrombocytopenia before admission. Platelet autoantibodies were not requested as evidence suggests they do not seem to direct treatment. If they were negative, the diagnosis could still be ITP.

According to the UK practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic, there is little evidence to inform the optimal management of a patient presenting with new or relapsed acute ITP. In our case of newly diagnosed ITP and concomitant infection by SARS-CoV-2, the treatment dilemma was pronounced. The prothrombotic risk of COVID-19 needed to be balanced between the prohaemorrhagic risk from ITP. The patient received platelets because he experienced rectal and intracranial bleeds. After reviewing the blood film, there was no evidence of schistocytes to suggest thrombocytic thrombocytopenic purpura, and therefore there was no risk of arterial thrombosis and subsequent death from giving platelet transfusions. It is well known that steroids as first-line treatment need to be avoided if there are alternative treatment options. There is concern about secondary infection and higher risk of mortality, but a recent study of patients with Middle East respiratory syndrome (MERS) receiving corticosteroids showed delayed clearance of MERS-CoV from the lower respiratory tract and no effect of corticosteroids on mortality. Following the limited evidence for the treatment of ITP secondary to COVID-19, steroid therapy was attempted as first-line treatment. However after 14 days, prednisolone was stopped due to a poor response and concerns regarding infection/mortality risk. Intravenous immunoglobulin was attempted second-line but was relatively ineffective at increasing platelet counts. There is an even greater paucity of evidence regarding their effectiveness in these cases. Regarding the TPO-RAs, eltrombopag and romiplostim, there is concern in terms of their prothrombotic potential. In a systematic review of trials for TPO-RAs versus controls, the former were found to have higher rates of thromboembolic events. The prescription of eltrombopag was inconsistent due to the patient’s difficulty swallowing the tablets. In our case, the response to romiplostim was initially very limited; however, the patient slowly responded, and it was stopped after 33 days, following a return to normal platelet count. This prolonged lag between the initiation of ITP treatment and the resolution of thrombocytopenia appears contrary to the mild–moderate presentation of COVID-19. In fact, such a

Learning points

- COVID-19 presents clinicians with diagnostic dilemmas that require a systematic investigatory work-up.
- Proposals for the exact mechanisms by which SARS-CoV-2 infection induces thrombocytopenia are not fully understood and require further research.
- Further guidance regarding the management of idiopathic thrombocytopenic purpura secondary to COVID-19 is required.
- Haematological manifestations may be present regardless of the severity of COVID-19 and should be examined thoroughly.
limited initial response to first-line and second-line ITP therapy is unusual.5

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Dr Charles Grimley, consultant gastroenterologist.

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