

COVID-19 complicated by immune thrombocytopaenic purpura and internal jugular vein thrombosis

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SUMMARY

A 61-year-old woman who had tested positive for COVID-19 in the community 5 days prior to admission presented with new onset severe headache and mild shortness of breath. She had an acute reduction in her platelet counts from $153 \times 10^9/L$ to $5 \times 10^9/L$. She was diagnosed with immune thrombocytopenia purpura and after treatment with intravenous immunoglobulin, her platelet count increased to $15 \times 10^9/L$. Due to nonresolving headache, she had a magnetic resonance venogram, which showed bilateral internal jugular vein thrombosis. She was discharged from hospital and followed up in Haematology and Neurology clinics. Her platelet count returned to normal range 7 days later. She was commenced on anticoagulation for thrombosis.

BACKGROUND

COVID-19 has caused a public health emergency of international concern, with millions of infections and deaths worldwide. COVID-19 has been shown to have many effects on multiple bodily systems; this includes haematological and thrombotic manifestations.

Immune thrombocytopenia purpura (ITP) is characterised by an immune-mediated reaction resulting in a significant reduction in platelet counts. The normal platelet range for a healthy individual is $150\text{--}400 \times 10^9/L$. Mild thrombocytopenia, such as platelet counts of $100\text{--}150 \times 10^9/L$, has been frequently reported in patients with COVID-19; however, more severe thrombocytopenia has rarely been seen.^{1,2}

Our patient was found to have bilateral deep vein thrombosis (DVTs) in the internal jugular veins likely secondary to COVID-19, ITP or both. A focus of this case is to increase awareness of haematological complications of COVID-19 infection including ITP and thromboembolism. As the rates of COVID-19 continue to increase, complications of COVID-19 are likely to continue to emerge.

CASE PRESENTATION

A 61-year-old woman with a background of hypertension, fibromyalgia and previous lumbar spinal fusion surgery due to prolapsed disc presented with a sudden onset of severe occipital headache associated with nausea and mild photophobia. She was also noted to have a mild breathlessness and productive cough with white sputum for 3 days. She had a positive nasopharyngeal PCR swab for COVID-19 in the community 5 days prior. On

admission, she was afebrile, with normal oxygen saturations. Her full blood count was normal with haemoglobin (Hb) 134 g/L (normal range $117\text{--}155\text{ g/L}$), white cell count $3.4 \times 10^9/L$ (normal range $3.8\text{--}10.8 \times 10^9/L$), neutrophils $2 \times 10^9/L$ (normal range $2\text{--}7 \times 10^9/L$), lymphocytes $0.7 \times 10^9/L$ (normal range $0.8\text{--}3.9 \times 10^9/L$), platelets $153 \times 10^9/L$ (normal range $140\text{--}400 \times 10^9/L$), C reactive protein $<5\text{ mg/L}$ (normal range $0\text{--}5\text{ mg/L}$).

A CT scan of the brain was performed, this showed no abnormality. Her chest X-ray was also unremarkable. Due to previous lumbar spinal fusion surgery, she had an X-ray of the lumbar spine to identify whether a lumbar puncture would be possible to investigate further the cause of her headaches, specifically querying subarachnoid haemorrhage. X-ray lumbar spine showed four-level posterior transpedicular screw fixation from L3 to S1, with anterior lumbar interbody fusion at L3-L4. After discussions with the neurology team, it was agreed for the patient to have a magnetic resonance venogram (MRV) rather than fluoroscopic-guided lumbar puncture to reduce the risk of postprocedure complications.

While the patient was awaiting the MRI scan, she did not have blood tests for 3 days as she was otherwise clinically stable with mild COVID-19 symptoms. The repeated blood test showed an acute marked thrombocytopenia; platelets were $5 \times 10^9/L$. The rest of the blood results were unremarkable.

INVESTIGATIONS

The new acute thrombocytopenia was urgently discussed with the haematology team. A blood film was requested, which showed true thrombocytopenia with no red blood cell fragments or schistocytes present (figure 1).

An urgent repeated CT head was performed to rule out acute intracranial bleeding following a significant drop in platelets, this was reported as normal. Further investigations including rheumatological markers, viral panel (hepatitis B, hepatitis C, HIV, cytomegalovirus, Epstein-Barr virus), haematinics, thyroid function, coagulation screen and helicobacter pylori faecal antigen were all unremarkable.

Due to nonresolving headache, she underwent an MRV, which showed bilateral internal jugular vein occlusion with no evidence of infarct or haemorrhage.



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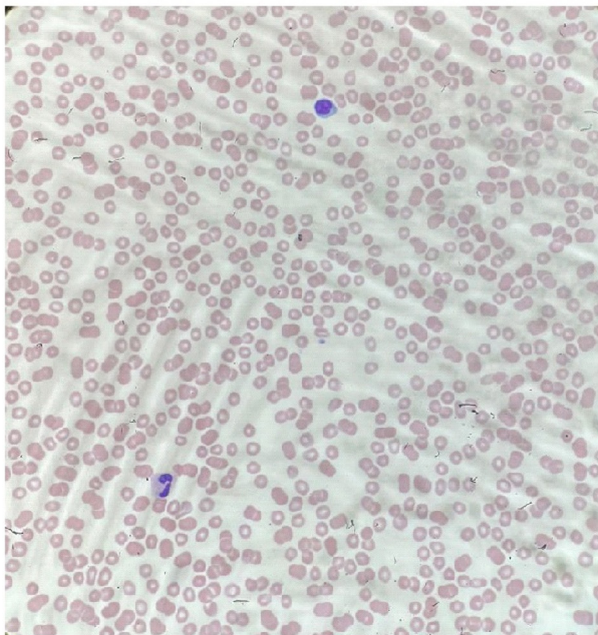


Figure 1 Blood films show true thrombocytopenia, red cells unremarkable, no red blood cell fragments, occasional giant platelets, pleomorphic lymphocytes, vacuolated monocytes and no immature cells.

DIFFERENTIAL DIAGNOSIS

The haematology team agreed that the acute reduction in patient's platelet counts was most likely due to ITP secondary to COVID-19 infection. It is not clear if COVID-19 or ITP had led to the occurrence of jugular venous thrombosis as both these conditions are associated with increased thromboembolic tendency.

The patient had been started on low-molecular weight heparin (LMWH) for venous thromboembolism (VTE) prophylaxis as per hospital protocol on admission. Therefore, heparin-induced thrombocytopenia (HIT) was also considered as a potential cause, but HIT usually occurs 5–14 days after heparin exposure. Patients with HIT usually have moderate platelet counts ($50\text{--}80 \times 10^9/\text{L}$).³ Using the 4Ts score, which calculates the risk of HIT based on the timing of heparin therapy, complications of thrombosis or thrombocytopenia, and likelihood of other causes, the differential of HIT could be excluded given the patient was low risk, so no HIT assay was conducted.⁴

Thrombotic thrombocytopenic purpura was also excluded as patient was clinically well with no evidence of microangiopathic haemolytic anaemia, red cell schistocyte or low ADAMTS13 (A Disintegrin and Metalloproteinase with a Thrombospondin Type 1 motif, member 13) activity.

Drug-induced thrombocytopenia was excluded as patient did not receive any medication such as quinine, sulphonamides, statin, gold, valproic acid or any antibiotics or other drugs known to cause low platelet counts.⁵ She was on amlodipine 5 mg/day and pregabalin prior to admission.

Secondary ITP can occur alongside autoimmune disorders like lupus, Sjogren's syndrome, antiphospholipid syndrome, dermatomyositis and seemingly in rarer cases of rheumatoid arthritis.⁶ These were excluded as patient's rheumatologic markers were negative.

Thrombocytopenia can also be associated with malignancy. This is often caused by myelosuppression due to bone marrow infiltration or myelodysplasia, for example, from acute leukaemia. It can also be caused by specific cancers, including small-cell lung

cancer, and more rarely, paraneoplastic syndromes such as idiopathic ITP as part of an association with some solid tumours such as breast and lung cancers.⁷ This was excluded as patient did not have any evidence of malignancy on examination or investigations.

Given the above differential diagnoses were excluded, the haematology team felt that the acute reduction in the patient's platelet counts was most likely due to ITP. Investigations to screen for common causes of ITP were unremarkable, for this reason, the ITP was thought to be likely secondary to COVID-19 infection.

TREATMENT

The patient had headaches throughout the admission. They were described as intermittent to severe, frontal headaches. She had ongoing mild COVID-19 symptoms—shortness of breath on exertion and cough but did not have any fevers and no oxygen requirement.

For ITP, she was treated with intravenous immunoglobulin (IVIg) 1 g/Kg for 2 days. IVIg is often used in those with a high risk of bleeding, due to platelet counts responding and rising quickly, usually within 12–48 hours.^{8,9} It was decided that the patient did not need a platelet transfusion as she had no bleeding and her CT brain was normal. Platelet transfusions have the effect of increasing circulating platelet mass straight away, however, have short-lived effects and hence are only used in cases of life-threatening bleeds.⁸ After 1 day of IVIg, blood showed an improvement in platelets to $10 \times 10^9/\text{L}$.

Neurology advised for a conservative approach for headaches, recommending symptomatic treatment with analgesia.

OUTCOME AND FOLLOW-UP

The patient was followed up in haematology clinic the day after discharge; platelets had increased to $41 \times 10^9/\text{L}$. A further haematology appointment was booked for 5 days later, which showed an improvement in platelets back to the normal range, platelets were $213 \times 10^9/\text{L}$ (figure 2).

She was commenced on anticoagulation low molecular weight heparin (LMWH); enoxaparin for jugular venous thrombosis. This was switched to a direct oral anticoagulant; apixaban 5 mg two times per day on the follow-up appointment 1 week

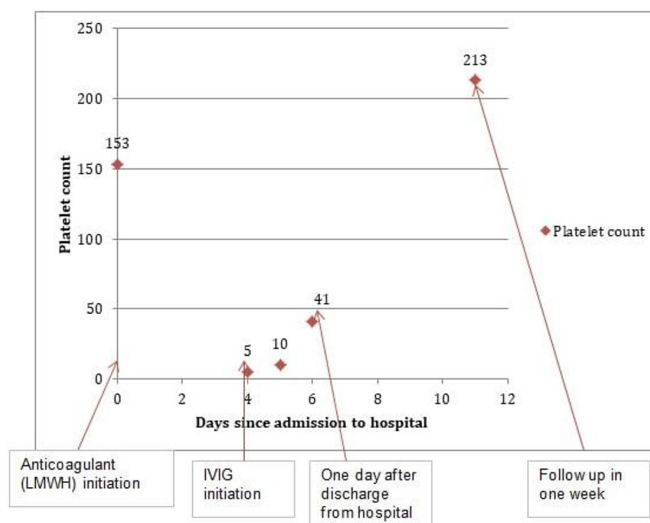


Figure 2 Graph shows patient's platelet count over time with key interventions. IVIg, intravenous immunoglobulin.

postdischarge. Anticoagulation is to be continued for at least 6 months, pending further discussions at the thrombosis multidisciplinary team meeting.

DISCUSSION

(ITP is a rare autoimmune disease (annual incidence: 3–4/105 inhabitants), leading to an increased risk of spontaneous bleeding. There have been few reports of ITP as a complication of COVID-19, especially, as in this case report, in a patient with very mild COVID-19 symptoms.¹

In a systemic review of 45 patients with ITP who tested positive for COVID-19 infection, 75% had moderate to severe COVID-19 symptoms, whereas only 18% reported mild symptoms and 7% were counted as asymptomatic in terms of COVID-19 symptoms. In our patient, a diagnosis of ITP was made 9 days after initial COVID-19 symptoms and positive test in the community. In the systemic review, the median day from COVID-19 symptoms starting to ITP being diagnosed was 13 days.⁹

The majority (71%) of patients in a systemic review with COVID-19 and new-onset ITP were >50 years and 7% were <18 years old.⁹ The study population median age was 62 years. As in our case, 31% of patients had no bleeding manifestations at diagnosis.⁹ Only one patient had fatal complications, this was a 67-year-old man who required Intensive care unit (ICU) and intubation on day 3 of admission due to respiratory failure. On day 12, his platelet counts dropped from $112 \times 10^9/L$ to $3 \times 10^9/L$, and subsequently he died of an intracerebral bleed 24 hours later.¹⁰

ITP has been reported and associated with many viral infections, including hepatitis C virus, HIV, cytomegalovirus, herpes simplex virus and many others. As with these viral infections, COVID-19 can also result in the haematological manifestation of ITP. Immune thrombocytopenia is often a retrospective diagnosis based on exclusion of other possible causes of thrombocytopenia and assessment of the response to treatment.¹¹ Assays for antibodies to specific platelet glycoproteins are not routinely recommended as they have high specificity and low sensitivity but may be helpful in complex and difficult cases.¹²

Several possible mechanisms of SARS-CoV-2-mediated thrombocytopenia have already been described. Mechanisms involve inhibition of platelet synthesis due to direct infection of the bone marrow cells or platelets by the virus. Another theory is virus-mediated liver damage leading to decreased thrombopoietin production; pulmonary endothelial damage followed by platelet aggregation in the lungs, subsequent formation of micro thrombi and platelet consumption; and finally, destruction of platelets by the immune system.^{13 14}

In a systemic review of 45 patients with ITP who tested positive for COVID-19 infection, as with our patient, the majority (29%) was treated with IVIG only. A further 24.5% of patients were treated with glucocorticoids and IVIG in combination and 22% were treated with glucocorticoids only. Twenty per cent of the patients were given thrombopoietin receptor agonist (TPO-RA), with either IVIG only or IVIG and glucocorticoid in combination.⁹ A combination of initial treatments, including IV corticosteroids and, usually IVIG, should be used in emergency situations, in which there are urgent needs to increase the platelet count within 24 hours (Grade C recommendation). Platelet transfusions may be helpful and must not be postponed in cases of life-threatening bleeding, especially intracranial haemorrhage.⁹ In the case of life-threatening bleeding and the absence of a significant response to IVIG and platelet transfusion

in a patient on corticosteroids, the use of a TPO-RA should be considered.¹⁵

Paradoxically, the risk of thrombosis is higher in patients with ITP in comparison with the general population, due to the release of young hyperactive platelets from bone marrow. The incidence of thrombosis in patients with ITP has been estimated between 0.5 and 3/100 patients-years.¹⁶ In the care and treatment of patients with ITP, it is important to understand risk of thromboembolism. Treatment should always be personalised to the individual to minimise bleeding and risk of thromboembolism.¹⁷

For the treatment of thrombosis in patients with ITP (with no bleeding, petechiae, hematomas or stable hb (WHO grade 0–II)), anticoagulation should be started at standard doses with a platelet count of $\geq 50 \times 10^9/L$ or at half-standard doses with a platelet count of $< 50 \times 10^9/L$ and increased to full doses if platelet counts rise to $\geq 50 \times 10^9/L$.¹⁸

There have been multiple reports in the literature highlighting the thrombotic manifestations of COVID-19, including venous thromboembolic disease and arterial thrombosis.^{19 20} A scoping review identified that 20% of patients hospitalised with COVID-19 developed VTE, and a case series of postmortem autopsies identified VTE in 58% of patients with COVID-19.²¹

There are few cases on reviewing the literature of COVID-19 and jugular vein thrombosis. Bilateral jugular vein thrombosis was reported in a 29-year-old woman with Hodgkin's lymphoma.²² She had tested positive for COVID-19 2 months prior and fully recovered from COVID-19 symptoms. She presented with several thromboembolic complications including right atrial clot, arterial brain emboli and bilateral jugular venous thrombosis. A further case has been reported of a 25-year-old woman, who presented with COVID-19 and was found to have extensive occlusive thrombus extending from the right transverse sinus through the sigmoid sinus into the upper right internal jugular vein.²³ Both these patients, unlike the patient in our case did have other risk factors leading to an increased prothrombotic state, in the first case, this was active malignancy and obesity, and in the second case, the patient was taking the contraceptive pill. However, they had no other personal or family history of note, and COVID-19 is likely to be a significant contributor to the coagulopathy.^{22 23}

Several mechanisms of SARS-CoV-2-mediated coagulopathy have been described. These mechanisms include cytokine-induced hyper inflammatory state, stasis, hypoxia and endothelial dysfunction.²⁴

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Contributors DB and KA identified the interesting aspects of the case and looked after the patient. DB, KA and SH studied the case, performed the literature review and drafted the manuscript. KA and SH were responsible for overall supervision of the project. All the authors contributed to, read and agreed to this submission.

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Learning points

- ▶ To be vigilant for COVID-19 complications regardless of the severity of symptoms.
- ▶ A systematic approach is essential to diagnose new-onset immune thrombocytopenia purpura (ITP) after excluding several concomitant factors or conditions that can cause thrombocytopenia in COVID-19.
- ▶ Treatment with intravenous immunoglobulin for ITP in the context of COVID-19 appears to be effective.
- ▶ Both COVID-19 and ITP are associated with increased risk of thromboembolism.
- ▶ In the management of ITP, platelet transfusions are only given in cases where bleeding is thought to be life threatening or in a potentially fatal site, such as intracranial.
- ▶ Frequency of doing a routine blood test for patients with COVID-19 with mild to moderate symptoms needs to be reviewed to assist with early identification of COVID-19 potential complications, such as ITP.

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