Autoimmune heparin-induced thrombocytopenia: a rare manifestation of COVID-19

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SUMMARY

We describe the case of a 65-year-old male who presented to an outside hospital for shortness of breath, nausea and vomiting 8 days after testing positive for COVID-19. Initial workup revealed massive bilateral pulmonary emboli and thrombocytopenia. The patient was then admitted to our hospital, received an inferior vena cava filter and initially started on argatroban for autoimmune heparin-induced thrombocytopenia (HIT) prophylaxis. On hospital stay day 6, labs revealed a diagnosis of HIT in the setting of COVID-19. This case highlights the rare occurrence of a patient developing HIT without heparin exposure and in the setting of a novel infectious agent, COVID-19.

BACKGROUND

The COVID-19 pandemic has manifested as a major public health crisis in the USA by infecting more than 30 million patients and resulting in over 500 000 deaths.[1] Infection with SARS-CoV-2 continues to challenge healthcare providers due to its wide variety of clinical manifestations and complications. In addition to the respiratory symptoms displayed by most patients with COVID-19, haematological manifestations remain a significant clinical concern. In the setting of COVID-19, a recent meta-analysis found that thrombocytopenia is associated with increased risk of severe disease and mortality.[2] In addition, many other haematological abnormalities can be observed with COVID-19. One such rare complication is the development of heparin-induced thrombocytopenia (HIT).[3]

HIT is a prothrombotic type II hypersensitivity reaction characterised by the development of antibodies against complexes of platelet factor 4 (PF4) and heparin.[4] The resulting heparin–PF4–IgG complex activates platelets and results in the release of prothrombotic platelet-derived microparticles, platelet consumption and subsequent thrombocytopenia. Additionally, the immune complex causes antibody-mediated endothelial injury and leads to further activation of the coagulation cascade.[5]

The incidence of HIT in patients exposed to heparin is between 0.2% and 5%, and occurs more commonly with exposure to unfractionated heparin (UFH) than low molecular weight heparin (LMWH).[6] The diagnosis is made clinically by taking several factors into account. These include baseline platelet count, drop to platelet count to <100 k/μL or >50% from baseline, onset of thrombocytopenia within 5–10 days after initiation of heparin, acute thrombotic event, resolution of thrombocytopenia after cessation of heparin and (+) HIT

antibody seroconversion. In addition, other causes of thrombocytopenia must be excluded.[5]

Although rare, spontaneous HIT is characterised as an autoimmune HIT that develops in the absence of heparin exposure.[7] The pathogenesis of this condition is incompletely understood, but several proposed mechanisms exist. First, autoimmune HIT antibodies may activate platelets through recognition of non-heparin glycosaminoglycans and PF4 on platelet surfaces. Second, activated platelets release polyphosphates that are able to bind to PF4 and autoimmune HIT antibodies. Third, autoimmune HIT antibodies are able to strongly bind to PF4, and the resulting PF4–IgG complexes result in larger platelet-activating immune complexes.[8]

HIT is a potentially life-threatening complication of heparin therapy due to its association with venous thromboemboli, such as pulmonary embolism or deep vein thrombosis. The mortality rate of HIT is approximately 20%–30%,[9] and complications include deep vein thrombosis, pulmonary embolism, myocardial infarction, end-organ damage and death.

CASE PRESENTATION

A 65-year-old male with medical history significant for psoriatic arthritis, hypertension, urinary retention and recent COVID-19 infection presented to an outside hospital 8 days after testing positive for COVID-19 with dyspnoea, nausea and vomiting. Initial workup revealed massive bilateral pulmonary emboli with D-dimer of 15.39 (normal<0.54) and thrombocytopenia with platelet count of 6 k/μL (normal 150–450 k/μL). The patient was referred to our institution for platelet transfusion, which was not available at the outside hospital, and consideration for advanced interventions for pulmonary embolism. Imaging showed right ventricular strain on transthoracic echocardiogram and deep vein thromboses in the left lower extremities visualised via Doppler ultrasound. The patient initially received cefepime, vancomycin, dexamethasone, intravenous immunoglobulin (IVIG), 2 L normal saline, platelet transfusion and 3 L nasal cannula supplemental oxygen. On presentation to our hospital, the patient was deemed to be a poor surgical candidate due to his severe thrombocytopenia. In order for an inferior vena cava filter to be placed, the patient's platelets needed to be >50 k/μL, and therefore, the decision to transfuse platelets was made. The aetiology of the thrombocytopenia was unclear at this time. His platelets rose from 6 to 77 k/μL after the transfusion but subsequently
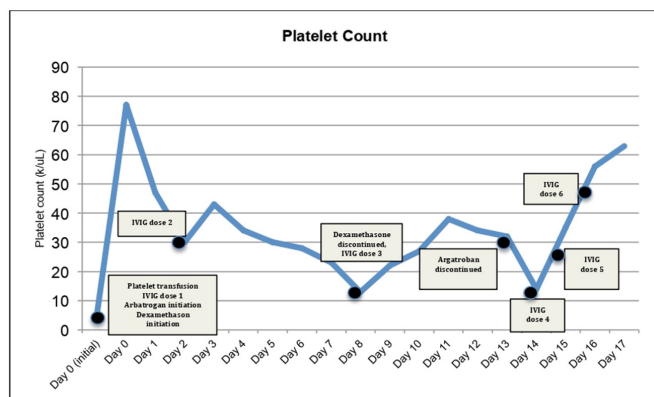
Figure 1 Platelet count throughout hospital admission labelled with relevant interventions. IVIG, intravenous immunoglobulin.

dropped back to 30 k/μL. Platelet counts for the patient's entire hospital stay are depicted in figure 1.

Anticoagulation for pulmonary embolism was initially held due to thrombocytopenia, but the patient then received argatroban 50 mg for prophylaxis of HIT. Labs revealed elevated haptoglobin at 294 mg/dL (normal 30–200 mg/dL), elevated lactate dehydrogenase at 480 units/L (normal 135–250 units/L), normal reticulocyte count at 56.1 k/μL (normal 16.7–96.7 k/μL), normal ADAMTS13 at >100% (normal≥70%) and normal bone marrow biopsy. Pertinent labs are outlined in table 1. The patient did not start remdesivir for COVID-19 due to dyspnoea explained by pulmonary emboli. This patient continued intravenous dexamethasone 40 mg/day for 7 days and received six intermittent doses of IVIG throughout his hospital stay.

On hospital stay day 7, labs revealed (+) HIT antibody and (+) serotonin reactive assay (SRA) with >20% positivity at low heparin exposure and <20% (6%) positivity at high heparin exposure. Both findings are consistent with a diagnosis of HIT. The patient was still taking intravenous argatroban at this time but needed to transition to an oral anticoagulant and was discharged on apixaban 5 mg two times per day. He was instructed to follow up with haematology outpatient.

INVESTIGATIONS
Due to the rarity of spontaneous HIT, this diagnosis was not initially thought to be very likely in this patient. However, due

Table 1 Pertinent labs

Test	Result	Reference
Haptoglobin	294 mg/dL (H)	30–200 mg/dL
ALT	48 unit/L (H)	0–41 unit/L
AST	82 unit/L (H)	0–40 unit/L
BNP	3681 pg/mL (H)	<125 pg/mL
SCr	0.83 mg/dL	0.7–1.3 mg/dL
LDH	480 unit/L (H)	135–250 unit/L
Retic Hgb	29.3 pg	30.8–36.6 pg
ADAMTS13	>100	≥70
PTT	117 s (H)	23–35 s
Fibrinogen	337 mg/dL	208–435 mg/dL
D-Dimer	15.39 (H)	<0.54

(H) indicates an elevated lab value greater than the upper limit of normal.

ALT, alanine transferase; AST, aspartate transferase; BNP, B-type natriuretic peptide; LDH, lactate dehydrogenase; PTT, partial thromboplastin time; Retic Hgb, reticulocyte haemoglobin content; SCr, serum creatnine.

to the novelty of COVID-19 and unknown infection sequelae, the initial workup revealing thrombocytopenia and presentation of multiple pulmonary emboli, HIT antibody screening was ordered to rule out this diagnosis. Two key diagnostic tests used to confirm a HIT diagnosis are the HIT antibody assay and SRA. The HIT antibody assay has a specificity of >95% and measures IgG antibodies generated against the PF4–heparin complex; however, many patients develop these antibodies but do not develop HIT.[10] The SRA test is much more sensitive (88%–100%) for a HIT diagnosis by measuring the amount of radioactive serotonin released by platelets that have been activated by heparin. A positive SRA test shows >20% release of serotonin when low-dose heparin is mixed with the patient's serum and greater than 50% decrease when the patient's serum is exposed to high-dose heparin.[10] A positive test therefore indicates that the platelet activation is heparin dependent. In this patient's case, both the HIT antibody and SRA yielded positive results.

DIFFERENTIAL DIAGNOSIS
We considered several diagnoses for this patient's thrombocytopenia. First, we considered thrombotic thrombocytopenic purpura (TTP), a disorder characterised by deficiency of ADAMTS13 and small vessel thrombosis. Because acquired TTP is more common in patients with a history of autoimmune disease, we thought this may be likely due to the patient's history of psoriatic arthritis. However, the peripheral blood smear did not reveal any morphological evidence of microangiopathic haemolytic anaemia; his haptoglobin level was elevated; and his ADAMTS13 level was normal (>100, normal≥70). We also considered a myelodysplastic syndrome, but bone marrow biopsy revealed no abnormalities. Third, immune thrombocytopenic purpura (ITP) was considered due to the patient's severe thrombocytopenia. While the clinical suspicion for ITP was initially very high due to the patient's severe thrombocytopenia, the patient experienced only a modest improvement in platelet count after starting dexamethasone treatment, making this diagnosis less likely. Disseminated intravascular coagulopathy (DIVC) was also considered, given this patient's presentation of thrombocytopenia and thrombosis. While this patient did have elevated PTT and elevated D-dimer, his fibrinogen level was normal at 337 mg/dL (normal 208–435 mg/dL). In addition, his peripheral blood smear did not show schistocytes, making this diagnosis less likely. Additional consideration was given to post-transfusion purpura, but the patient initially presented with severe thrombocytopenia before receiving transfusion of platelets. Another differential diagnosis was drug-induced thrombocytopenia. Several drugs most commonly associated with causal relationships include beta-lactam antibiotics, heparin, phenytoin, quinidine, sulfonamides and vancomycin.[11] The only medications our patient was taking prior to admission were acetaminophen–hydrocodone, amlodipine, furosemide, methotrexate and metoprolol tartrate. The patient had been tolerating these medications well previously, and there was no reason to suspect drug-induced thrombocytopenia.

TREATMENT
The patient was initially started on argatroban, a highly selective direct thrombin inhibitor, to decrease hypercoagulability. In addition to the direct thrombin inhibition, argatroban also inhibits fibrin, formation, activation of protein C and platelet aggregation, and activation of factors V, VIII and XIII. Argatroban was selected because it is a non-heparin anticoagulant and does not cross react with HIT antibodies. Argatroban also

has a short half-life (39–51 min in normal hepatic function) and can be discontinued quickly if needed.[12]

In addition to argatroban, this patient also received IVIG. These treatments were targeted toward an autoimmune-mediated, spontaneous HIT. Since our patient did not receive heparin, consideration of an autoimmune HIT was important. Autoimmune HIT refers to a subset of patients with HIT whose antibodies are able to activate platelets in the absence of heparin. Although IVIG was initially started as treatment for suspected ITP, it is also an effective treatment for autoimmune HIT. Previous studies have shown that intact IgG fragments inhibit platelet activation by antibodies.[13] It is important to note that IVIG exhibits prothrombotic effects and may exacerbate symptoms and increase morbidity in a patient presenting with existing blood clots. The patient was also initially started on dexamethasone since TTP was a differential diagnosis. However, limited response to corticosteroids made this diagnosis less likely.

OUTCOME AND FOLLOW-UP

The patient was discharged at a platelet count of 63 k/µL. Two days later, follow-up labs at an outside hospital revealed increased platelet count at 121 k/µL. He reported clinical improvement and resolving dyspnoea.

DISCUSSION

Within the past year, the COVID-19 pandemic has challenged and overwhelmed the US healthcare system. The initial uncertainty and rapidly changing knowledge surrounding SARS-CoV-2 has left many healthcare providers unsure of how to best care for their patients. As a result, many clinical presentations must now include sequelae of COVID-19 as a differential diagnosis. Here, we outlined the rare case of a 65-year-old man who presented with spontaneous HIT 8 days after testing positive for COVID-19. Heparin is a commonly administered anticoagulant that counteracts a prothrombotic state induced by COVID-19. Current NIH guidelines recommend anticoagulation for DVT prophylaxis in hospitalised COVID-19(+) patients.[14] Additional guidelines from the Italian Society of Hemostasis and Thrombosis advise using LMWH for VTE prophylaxis in hospitalised COVID-19(+) patients.[15] While DVT prophylaxis is medically necessary in patients with a prothrombotic state, it is important to recognise the signs of HIT in this vulnerable patient population. A retrospective cohort analysis performed in the USA found a high incidence of (+)HIT antibodies in patients with severe COVID-19 treated with UFH, suggesting that this diagnosis may be unrecognised in the clinical setting.[16] History of autoimmune conditions, such as psoriatic arthritis in this patient, may increase the risk of developing a subtype of autoimmune HIT.[17] This case calls attention to HIT serving as an additional rare sequela of COVID-19. Additional differential diagnoses for COVID-19(+) patients with thrombocytopenia include ITP, TTP, DIVC, post-transfusion purpura and drug-induced thrombocytopenia.

The present case is a unique example of HIT development without previous heparin exposure. Although this diagnosis is rare, the case highlights an important clinical dilemma. This presentation in particular is extremely difficult to manage due to the combination of concurrent thrombocytopenia and thromboses in the form of pulmonary emboli. It is important to promptly arrive at the correct diagnosis and follow evidence-based guidelines regarding management in order to prevent harm to the patient. In related situations, recently updated guidelines from the British Society for Haematology outline proposed management of COVID-19 vaccine-induced thrombosis and thrombocytopenia.[18] There are reported cases of cavernous sinus thrombosis and thrombocytopenia after receiving the ChAdOx1 COVID-19 vaccine.[19] In addition, a recent report details 23 patients who developed a pathogenic PF4-dependent syndrome, unrelated to heparin therapy, after receiving the same vaccine.[20] Prompt recognition of thrombosis and thrombocytopenia in the setting of COVID-19 or recent COVID-19 vaccination, consideration of appropriate workup and initiation of proper management is vital to provide high-quality medical care to these patients.

Learning points

- ► Autoimmune heparin-induced thrombocytopenia (HIT) is a rare sequelae of COVID-19 infection.
- ► Treatment for spontaneous HIT is argatroban, a highly selective direct thrombin inhibitor.
- ► Differential diagnosis of thrombocytopenia in the setting of COVID-19 includes ITP, TTP, DIVC and drug-induced thrombocytopenia.

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