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Limb ischemia due to spontaneous heparin-induced thrombocytopenia as the primary presentation of acute COVID-19 infection

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Abstract

Heparin-induced thrombocytopenia (HIT) occurs with the development of IgG antibodies that bind complexes of heparin and platelet factor 4 (PF4), which activate platelets and result in a profoundly prothrombotic condition. In rare instances, this syndrome develops in the absence of proximate heparin administration, referred to as spontaneous HIT, for which less than three dozen cases have been reported. Spontaneous HIT is considered a subtype of “autoimmune HIT” (aHIT), characterized by platelet activation in the serotonin release assay (SRA) without the addition of exogenous heparin. Here, we report spontaneous HIT as the presenting feature in a patient with 2019 coronavirus disease infection (COVID-19).

A 66-year-old male presented with progressive leg pain and was found to have a platelet count of $39 \times 10^9/L$ and multiple lower extremity arterial thromboses requiring fasciotomy and thrombectomy. He had no recent hospitalization, heparin exposure, vaccinations, or known thrombophilia. He had a strongly positive IgG-specific enzyme-linked immunosorbent assay for heparin-PF4 antibodies, and the SRA was strongly positive both with and without the addition of heparin. He was treated successfully with bivalirudin, intravenous immunoglobulin, and apixaban.

Keypoints

- Spontaneous HIT is rare and occurs in the absence of proximate heparin exposure.
 - COVID-19 infection may lead to the development of spontaneous HIT.
 - Autoimmune HIT is characterized by platelet activation in the SRA in the absence of heparin.
 - Growing evidence suggests a role for intravenous immunoglobulin in select cases of HIT.

Keywords COVID-19 · Heparin · Immunoglobulins, Intravenous · Thrombocytopenia · Thrombosis

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Introduction

Heparin-induced thrombocytopenia (HIT) is an acquired hypercoagulable disorder due to the development of platelet activating IgG antibodies that bind complexes of heparin-platelet factor 4 (PF4) leading to thrombocytopenia and thrombosis. These antibodies typically appear between five and ten days after heparin exposure and are frequently accompanied by acute venous or arterial thrombotic events. [1] The laboratory diagnosis utilizes a screening enzyme-linked immunosorbent assay (ELISA) for anti-heparin/PF4 antibody detection and a confirmatory functional assay, most often the serotonin release assay (SRA). [1].

HIT is a clinicopathologic diagnosis. Among individuals diagnosed with HIT, a distinct subset will demonstrate platelet activation in the SRA without the addition of heparin, which is characteristic of autoimmune HIT (aHIT). [1, 2] As with classical HIT, sera from these cases also induce robust platelet activation in the presence of low dose heparin with appropriate suppression with high dose heparin. [2] Though extremely rare, this syndrome may present without any recent administration of heparin, known as spontaneous HIT, a subtype of aHIT. There are less than three dozen reported cases of spontaneous HIT, many occurring post-operatively after orthopedic surgery [3–7] or in the context of infection. [8] Here, we report a case of laboratory-confirmed spontaneous HIT as the primary presenting feature in a patient with 2019 coronavirus disease infection (COVID-19).

Case description

A 66-year-old male with hypertension, alcoholic cirrhosis, and splenomegaly presented to the emergency department in April 2021 with left lower extremity pain and cramping. There were no noted exam findings suggesting decreased arterial perfusion. The platelet count was $74 \times 10^9/L$ (Fig. 1). His baseline platelet count was unknown, and his thrombocytopenia was attributed to cirrhosis with splenomegaly and alcohol-induced bone marrow suppression. Venous duplex ultrasound showed no deep vein thrombosis. Three days later, he returned with acutely worsening symptoms with cool distal lower extremities, dusky discoloration, and diminished pulses. The platelet count had declined in the interval period to $39 \times 10^9/L$. CT angiogram demonstrated multiple acute bilateral lower extremity arterial occlusions. He had no recent hospitalizations, surgeries, heparin exposure, vaccinations, or known thrombophilia. He was admitted to the hospital and started on unfractionated heparin. He tested positive for SARS-CoV-2 by RT-PCR on admission. Chest x-ray revealed bilateral pulmonary opacities

consistent with COVID-19 infection, but he did not have significant hypoxia or require supplemental oxygen. At the time of his presentation there were more than 800,000 confirmed cases of COVID-19 in Tennessee, 31 million cases in the United States, and 141 million cases worldwide.

Within hours of his admission, he was transferred to our facility for vascular surgery evaluation. On arrival, the platelet count was $27 \times 10^9/L$. The 4T score was 5 (platelet fall > 50% and nadir > 20,000/uL, no recent heparin exposure, new thrombosis, possible other causes of thrombocytopenia). A HIT ELISA returned positive at 2.056 optical density units (ODU). Bivalirudin was initiated, and he was taken emergently to the operating room for fasciotomy and thrombectomy due to progressive vascular compromise. A confirmatory SRA was positive with 76% release in the absence of heparin (0.0 IU/mL), 73% release in the presence of therapeutic heparin (0.3 IU/mL), and appropriate suppression (6% release) in the presence of supratherapeutic heparin (100 IU/mL). The anti-factor Xa assay for unfractionated heparin confirmed the absence of heparin contamination in the patient sample (< 0.10 IU/mL). After five days on appropriate therapy, there was no significant improvement in his thrombocytopenia. He received intravenous gammaglobulin (IVIg, Gamunex-C) at a dose of 1 gm/kg daily (ideal body weight) for two consecutive days. There was a marked and rapid improvement in his thrombocytopenia following IVIg administration. Following this the ELISA remained strongly positive (2.106 ODU) while the SRA was now negative both with and without heparin (Fig. 1). He was eventually transitioned to apixaban and discharged to outpatient care without further issues and with a normal platelet count.

Methods

Plasma was prepared from venous blood collected into 1/10th volumes of 3.2% sodium citrate. Antibodies to PF4-heparin were identified by IgG-specific ELISA (Immucor GTI Diagnostics). Results were reported as ODU reflecting absorbance at 450 nm. A value ≥ 0.4 ODU was considered positive. The capacity of patient plasma to activate normal donor platelets was assessed with an in-house SRA, using heparin concentrations of 0.0, 0.3, and 100 IU/mL. Dilutions of known SRA-positive plasma served as a control. Release values of $\geq 20\%$ were considered positive.

Discussion

There are several unique aspects in this case of laboratory-confirmed spontaneous HIT presenting with COVID-19

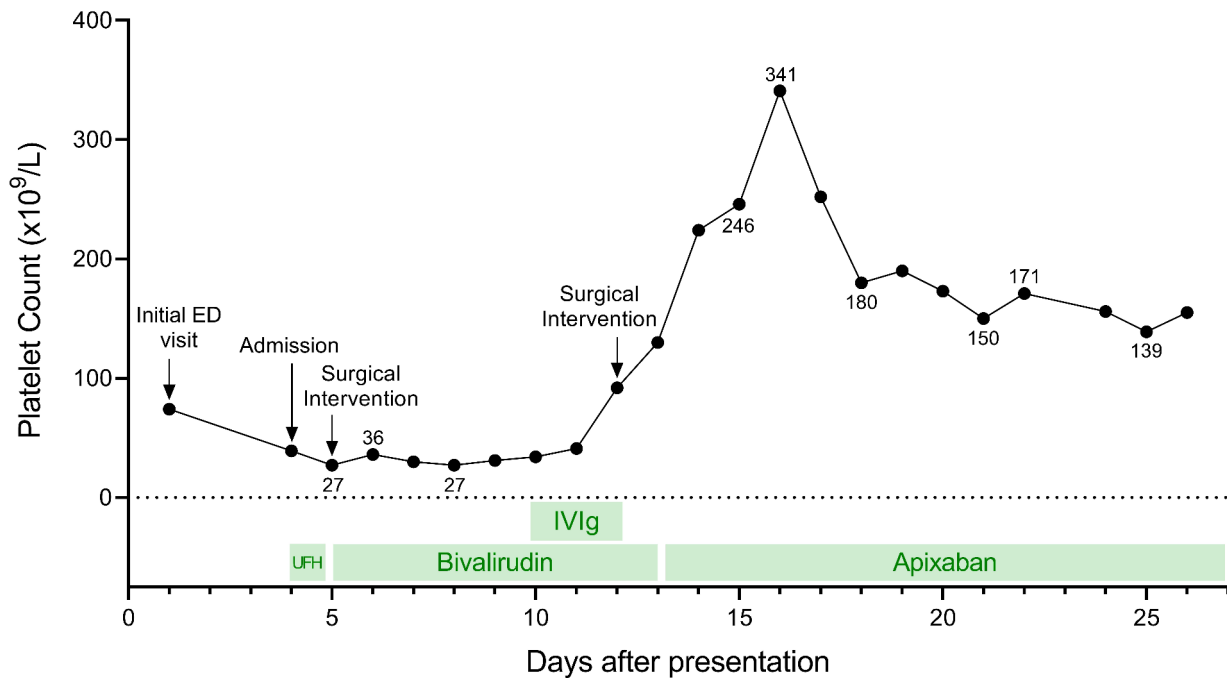


Fig. 1 Treatment and clinical course of spontaneous HIT in a patient with COVID-19 infection

Platelet counts (black circle, left y-axis) throughout the duration of patient's hospitalization with spontaneous HIT. Results of PF4-heparin ELISA experiments were 2.056 and 2.106 ODU on day 5 and 12 after initial presentation, respectively (not shown). While the ELISA remained strongly positive before and after the administration of IVIg, the SRA reactivity both in the absence of heparin and the presence of low dose heparin was markedly reduced (negative) after this therapy. The anticoagulation and adjuvant therapies are labeled on the bottom of the graph along the timeline for which each was administered. Each data point shown is a single measurement. ED=emergency department; PLT=platelet count; UFH=unfractionated heparin; IVIg=intravenous immunoglobulin

infection. COVID-19 induces a hypercoagulable state associated with increased risk for venous and arterial thrombosis. Comparisons between COVID-19 and other acquired thrombotic conditions including HIT have been made, but the pathophysiology of hypercoagulability in HIT and COVID-19 infection appears to be distinct.[9, 10] While COVID-19 alone is a contributing factor, the thrombocytopenia with a strongly positive ELISA and SRA in this case indicate the hypercoagulable state was driven primarily by development of spontaneous HIT. Importantly, he had no preceding adenoviral vector vaccines against the SARS-CoV-2 virus, distinguishing this from the recently described syndrome of vaccine-induced immune thrombotic thrombocytopenia (VITT), which shares overlapping features and clinical presentation as spontaneous HIT.[11, 12] In contrast to HIT, platelet activation in the SRA of VITT patients is often decreased by the addition of heparin. Spontaneous HIT has been reported in patients without any known inflammatory trigger[13], but most develop following surgery or in the presence of a concomitant infection. It is suspected that his COVID-19 infection directly led to aberrant immune activation precipitating the development of pathologic IgG antibodies to heparin-PF4. In fact, several cases of

spontaneous HIT have been associated with COVID-19.[14, 15] In addition, cases of other COVID-associated immunohematologic phenomenon, including immune thrombocytopenic purpura and autoimmune hemolytic anemia, have been well-documented.[16, 17] The regional, national, and global number of cases at the time of presentation with the paucity of reported spontaneous HIT cases highlight the rarity of this acquired thrombogenic complication of COVID-19. There has been intense focus on thrombotic complications of COVID19, but a meta-analysis concluded that the incidence of HIT in COVID19 patients was similar to the non-COVID19 population.[18].

Acute thrombosis presenting with progressive thrombocytopenia led the clinical team to consider HIT while evaluating multiple potential variables contributing to thrombocytopenia. The majority of thrombotic events with HIT are venous thromboses, however, some will present with arterial events as seen in this patient. Consistent with other reported cases of aHIT, the SRA release assay was strongly positive in the absence of heparin. This was confirmed with additional platelet donors for the SRA. The SRA reactivity in the absence of heparin administration demonstrates the strength of the antibody to unexpectedly bind two

cationic platelet factor 4 molecules without the assistance of the negatively charged (anionic) heparin component to the equation. The possibility of heparin in the clinical sample was considered as a confounding factor for this laboratory finding, but the anti-factor Xa assay identified no heparin in the patient sample. In addition, the duration of several hours of heparin administration was too brief to have caused the development of pathologic heparin-PF4 antibodies, which indicates that the antibodies were present at the time of admission. There were no other recent exposures that would have suggested rapid-onset HIT due to pre-existing antibodies from recent (within 100 days) heparin exposure.

After administration of IVIg, the SRA was negative at both no and low dose heparin concentrations, while the ELISA remained strongly positive. This is consistent with a persistent heparin-PF4 antibody but disruption of platelet activation via competitive inhibition of the IVIg for the platelet Fc receptor with the heparin-PF4 antibody. When the IVIg binds and blocks the Fc receptor the pathogenic heparin-PF4 antibody is no longer able to access and activate the platelet Fc receptor which inhibits the release of highly thrombogenic granules. The rapid increase in the platelet count following IVIg administration and eventual normalization of his platelet count support that IVIg was effective in inhibiting further platelet activation and aggregation and confirm HIT was the predominant cause of his presenting thrombocytopenia.[3, 4, 19] The transition from bivalirudin to apixaban was effective in maintaining adequate anticoagulation without recurrence or worsening of thrombosis or thrombocytopenia. It is important to note that the patient presented with limb threatening ischemia requiring vascular surgery intervention as well as fasciotomies. Individuals with HIT are at risk of limb loss in complicated cases and this was avoided here, potentially due to the timely recognition of the problem, intervention, and adjunctive therapy, specifically the administration of IVIg. The role for IVIg in complicated or challenging cases of HIT continues to gain support and should continue to be considered. Additionally, growing evidence supports the use of direct oral anticoagulants (DOACs) in HIT,[20, 21] including spontaneous HIT with similar success.[6] The greatest experiences with DOACs in HIT is with rivaroxaban but we have treated cases in our institution with both rivaroxaban and apixaban with positive outcomes.

In summary, we report this biochemically confirmed case of spontaneous HIT in a patient with COVID-19 and no proximate heparin exposure or adenoviral vaccines, implying that aHIT was a direct result of the COVID-19 infection. It is important to always consider HIT with acute thrombosis and thrombocytopenia as the history of recent heparin administration is not required, and the diagnosis may be missed if this is not considered. Our patient was

effectively managed with surgical revascularization for limb ischemia, as well as IVIg and alternative anticoagulation with bivalirudin and apixaban. Our case study expands on the growing number of immunohematologic complications from COVID-19 infection and provides additional experience for the use of IVIg and DOACs in HIT. The clinical and laboratory features of this case of spontaneous HIT in COVID19 are similar to those cases of spontaneous HIT in the literature unrelated to COVID19 infection. The rarity of spontaneous HIT and risk for limb loss highlight the need for prompt recognition and intervention. Prospective studies on the use of IVIg in the management of challenging cases of HIT are needed.

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Informed consent Written patient consent was obtained for the submission of the case report to the journal.

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