CASE REPORT

COVID-19 Vaccination-Associated Spontaneous Heparin-Induced Thrombocytopenia Syndrome

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has emerged as the deadliest outbreak in recent American history, surpassing the estimated U.S. fatalities from the 1918 influenza pandemic. Since its identification in December 2019 in Wuhan, China, COVID-19 has contributed to the death of nearly six million people worldwide. The United States (U.S.) Food and Drug Administration (FDA) initially issued emergency use authorization for three vaccines for prevention of COVID-19, and currently two have received full FDA approval. Herein, we report a case of severe thrombocytopenia in a man following heterologous booster vaccination with the Pfizer-BioNTech COVID-19 vaccine with concomitant presence of a heparin-P4 antibody but without proximate heparin exposure. The degree of thrombocytopenia was severe, but the patient had a natural recovery of platelet count over the next 2 weeks without need for any immunomodulatory therapies. This is the first case report of COVID vaccine-associated heparin-induced thrombocytopenia (HIT)-like platelet disorder without proximate heparin exposure, also called spontaneous HIT syndrome.

KEY WORDS: Thrombocytopenia, Coronavirus disease 2019, COVID19 vaccine, Heparin induced thrombocyotpenia, Spontaneous HIT syndrome.

Introduction

Heparin-induced thrombocytopenia (HIT) is a transient, autoimmune-like, prothrombotic disorder caused by platelet-activating immunoglobulin reactive against the self-protein, platelet factor 4 (PF4), bound to heparin. A similar syndrome that can occur without preceding heparin exposure called spontaneous HIT syndrome, which is serologically indistinguishable from HIT, is mostly seen post-operatively[1,2]. Thrombocytopenia may also occur following vaccinations against various infectious agents, especially measles-mumps-rubella (MMR), but also *Haemophilus influenzae*, hepatitis B virus, human papilloma virus, varicella-zoster, polio, and pneumococcus[3].

A recent report emphasized three independent descriptions of 39 people with a newly defined syndrome characterized by thrombosis and thrombocytopenia that occurred 5 to 24 days after initial vaccination with ChAdOx1 nCoV-19 (AstraZeneca), a recombinant adenoviral vector encoding the spike protein of SARS-CoV-2[4]. In addition, several cases of severe thrombocytopenia have occurred after SARS-CoV-2 vaccination with both the Pfizer and Moderna vaccines[5]. Prothrombotic states, like HIT, have also been reported in patients with coronavirus disease 2019 (COVID-19)[6]. Herein, we report a case of spontaneous HIT syndrome occurring in a man who had previously received two doses of the Moderna COVID-19 mRNA vaccine without event. He then received a booster dose of the Pfizer-BioNTech COVID-19 vaccination, which resulted in severe but short-lived thrombocytopenia which resolved without the need for pharmacologic intervention.

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Case presentation

A 51-year-old Caucasian man received the first dose

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of the Moderna COVID-19 mRNA vaccine in March 2021 and a second dose four weeks later and without overt side effects. Eight months later, in December 2021, he received a booster dose with the Pfizer-BioNTech COVID-19 vaccine. Ten days later, he sought medical attention at the Emergency Department (ED) at Virginia Mason Medical Center, Seattle, Washington, USA. He was experiencing dull aching pain in the left flank which radiated anteriorly to the left groin. The pain gradually worsened over a 72-hour period. He did not have fever or chills, myalgia or arthralgias, coryza symptoms, headache, abdominal pain, rectal bleeding, dysuria, diarrhea or altered sensorium. His past medical history was significant for morbid obesity (body mass index 56.44 kg/m2), type 2 diabetes, hypothyroidism, hypertension, hyperlipidemia, and obstructive sleep apnea. He had no prior history of thrombocytopenia or exposure to heparin, and there had been no change to his chronic medications over the past several years.

In the ED, he was diaphoretic and had a heart rate of 110 beats/minute, a temperature of 37.6°C and oxygen saturation of 96% on room air. He did not have ecchymosis or petechiae but had involuntary guarding on abdominal exam and left flank tenderness to percussion. The remaining portion of the physical exam was unremarkable.

A complete blood count (CBC) was notable for a platelet count of 17 x 10^9/L (normal, 150-400 x 10^9/L). His white blood count, hematocrit, and red cell indices were normal. Peripheral blood film did not show platelet clumping or schistocytes and a recheck platelet count collected in a citrate tube showed persistent thrombocytopenia. Electrolytes were within normal limits, blood urea nitrogen (BUN) was 38 mg/dL (normal, 9 to 25) and serum creatinine was 1.77 mg/dL (normal, 0.72-1.25). Other blood studies including liver transaminases and bilirubin, as well as thyroxine and thyroid stimulating hormone levels were all within normal limits and hemoglobin A1C was 6.9% (normal, < 5.7%). A urine analysis showed 3+ red blood cells but was without proteinuria and was leucocyte esterase negative. There were no granular casts. A respiratory panel, including tests for Influenza A and B, Respiratory Syncytial Virus, and SARS-CoV-2, was negative for infectious pathogens. Serologic tests for Hepatitis B and C viruses and Human Immunodeficiency Virus were non-reactive. A hemostasis panel consisting of a prothrombin time, activated partial thromboplastin time and thrombin time was normal. A d-dimer returned elevated at 4.26 mcg/ml FE (normal, < 0.51). Of relevance, he had had a normal platelet count (234 x 10^9/L) three months earlier.

Computed tomography (CT) imaging of the abdomen and pelvis showed that the patient had a left ureteropelvic junction stone measuring 7 x 5 mm with associated moderate hydronephrosis and without retroperitoneal adenopathy. His spleen measured 13.8 cm. He underwent immediate cystoscopy and a left ureteric stent placement. Blood tests following stent placement and after he received additional intravenous hydration showed improvement in renal function (BUN 19 mg/dL and creatinine 0.81 mg/dL) but he had a persistently low platelet count of 12 x 10^9/L. Enzyme-linked immunosorbent assay (ELISA) for serum heparin-PF4 IgG antibody was positive with an optical density (OD) reading at 0.570 (positive > 0.40) and with a heparin inhibition of 50%. Doppler studies of his lower extremities were unremarkable. The patient did not receive heparin injections for deep vein thromboprophylaxis, and only normal saline flushes were used to maintain patency of his venous catheters.

On day two of the patient's hospitalization and in the absence of overt thrombosis, we initiated anticoagulation with apixaban at a dose of 10 mg twice daily and with plans to reduce the dose to 5 mg twice daily after a week. The platelet count improved to 57 x 10^9/L on day 4 of hospitalization. We were anticipating maintaining anticoagulation for likely somewhere between six weeks and three months, but discontinued apixaban when a serotonin release assay returned negative (0% release) several days after he was discharged from the hospital. A follow-up CBC two weeks later showed a normal platelet count of 320 x 10^9/L (Figure 1).

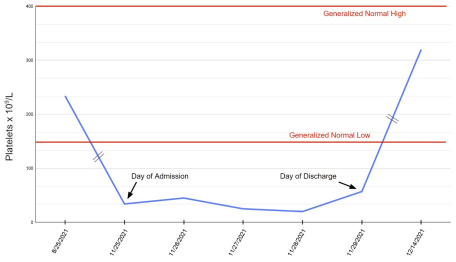

Figure 1: Platelet count before, during, and after hospitalization for thrombocytopenia

Discussion

Thrombotic thrombocytopenia mimicking HIT has occurred in patients with severe COVID-19 infection and after immunization with adenoviral vector-based vaccines against SARS-CoV-2. Increasing evidence suggests that SARS-CoV-2 is an independent risk factor for PF4 autoantibody development, regardless of previous heparin therapy, however, this phenomenon is rare following vaccination except for a few cases following AstraZeneca ChAdOx1-S/nCoV-19 COVID-19 vaccination[7].

The association of thrombocytopenia after COVID-19 vaccination is a relatively new phenomenon which has emerged as the vaccines have become more widely employed. It is only recently, that a few case series have described thrombocytopenia following vaccination[4,5,8–10]. The mechanism of COVID19 vaccine-associated thrombocytopenia remains unclear and is an area of active research. A double-hit model wherein the vaccine stimulates neoantigen formation (first hit) along with a systemic inflammatory response (second hit), which together lead to production of anti-PF4 antibodies has been proposed by Greinacher and colleagues[11]. The SARS-CoV-2 spike protein antigens in the vaccine do not appear to be a source of molecular mimicry[11].

How best to manage vaccine-induced hematologic complication is an area of current interest. Management recommendations are rapidly evolving, and several guidelines have been developed by expert groups, particularly when it comes to thrombocytopenia with or without thrombotic complications[12–15]. When a vaccine-associated thrombocytopenia is suspected with a platelet count < 30 x 10^9/L, recommendations are to consider treatment with steroids (e.g., prednisone 1 mg/kg) with or without intravenous immunoglobulin (IVIG) (e.g., 0.5 g/kg for 2 days) and avoid platelet transfusion (unless patient requires surgery), heparin, and vitamin K antagonists[16]. Non-heparin anticoagulants such as fondaparinux, argatroban, or a direct oral anticoagulant (e.g., apixaban, rivaroxaban) should be given if the platelet count is > 50 x 10^9/L and there is no serious bleeding. Early plasma exchange or fibrinogen substitution to > 1 g/L should be considered if the platelet count remains < 30 x 10^9/L despite IVIG and steroid treatment[12,13].

Our patient developed severe thrombocytopenia after receiving a heterologous booster dose with the Pfizer-BioNTech COVID-19 vaccine, following an initial immunization series with the Moderna mRNA vaccine. Interestingly, the patient also had concomitant strongly positive serum heparin-PF4 IgG antibody with no known prior exposure to heparin or history of thrombocytopenia. He had multiple risk factors for thrombosis, but thrombocytopenia resolved spontaneously and without bleeding or thrombotic complications.

It remains unclear why the HIT-like syndrome is observed with COVID-19 vaccines, particularly, the AstraZeneca ChAdOx1-S/nCoV-19 COVID-19 vaccine. Those affected were generally healthy or medically stable and few had previous thrombosis or a preexisting prothrombotic condition. Most of the patients included in these reports were women younger than 50 years of age, some of whom were receiving estrogen-replacement therapy or oral contraceptives. Many of these patients had thromboses at unusual sites— specifically, cerebral venous sinus thrombosis or thrombosis in the portal, splanchnic, or hepatic veins[4]. Other patients presented with deep venous thrombi, pulmonary emboli, or acute arterial thromboses. The median platelet counts at diagnosis were approximately 20 - 30 x 10^9/L. Approximately 40% of the patients died, some from ischemic brain injury, superimposed hemorrhage, or both conditions, often after anticoagulation[4].

Conclusion

Increasing evidence suggests that SARS-CoV-2 is an independent risk factor for PF4 autoantibody development, regardless of previous heparin therapy. As mass vaccination on a global scale continues, more data will be collected to better establish a cause-and-effect relationship of COVID-19 vaccination and associated thrombocytopenia. Additionally, and as we learn more about the frequency and extent of this problem, more research will be needed to make refinements in vaccine composition to prevent thrombocytopenia. One consideration is to screen for this antibody profile in individuals presenting with severe thrombocytopenia who are at high risk of thrombotic events, both following COVID-19 infection, and after COVID-19 vaccination.

Data Availability

The data used during the current study is available from the corresponding author on reasonable request.

Consent

Informed consent for publication was obtained from the patient.

Conflicts of Interest
The authors declare no conflicts of interest.

Authors' Contributions
PV and DMA were both responsible for conception of the work, manuscript preparation, data acquisition, and final approval of the manuscript.

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