Severe case of refractory immune thrombocytopenic purpura requiring splenectomy after the COVID-19 vaccine

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SUMMARY

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder caused by autoantibodies against platelet antigens resulting in platelet destruction and inhibition of platelet production. Occasionally, an inciting event such as a virus or vaccination can precipitate ITP. Several cases of ITP have been reported after the BTN162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) SARS-CoV-2 (COVID-19) vaccines. All reported cases of post-vaccination ITP have resolved with medical therapy until this case.

A man in his mid-20s developed bleeding from ITP 2 weeks after receiving the second dose of the Pfizer SARS-CoV-2 vaccine. All inpatient medical treatment attempts failed. On hospital day 40, a splenectomy was performed and he ultimately recovered and was discharged.

Awareness of potential vaccination side effects is a fundamental element of refining and improving patient safety. This case illustrates that given the right circumstances, serious refractory ITP can develop in response to the second dose of the Pfizer SARS-CoV-2 vaccine.

BACKGROUND

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder caused by autoantibodies against platelet antigens, resulting in platelet destruction and inhibition of platelet production. It is the second most common cause of acquired thrombocytopenia following chemotherapy-induced thrombocytopenia.[1] Clinical manifestations of ITP include petechiae, easy bruising, mucosal bleeding, and sometimes severe or critical haemorrhage. As ITP is a diagnosis of exclusion, treatment response is the only way to confirm the diagnosis. Most patients can be treated with an initial course of corticosteroids with or without intravenous immunoglobulin (IVIG) infusions. Some patients, however, develop refractory ITP that requires further treatment with bone marrow-stimulating agents, immunosuppressive therapies and even splenectomy.[2]

In some patients, an inciting event such as a virus or vaccination can precipitate ITP. In particular, several cases of ITP have been reported after the BTN162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) SARS-CoV-2 (COVID-19) vaccines.[3] The estimated risk of ITP after an mRNA-based SARS-CoV-2 vaccine is approximately 1 per every 36 000 doses, which is similar to the incidence of ITP after the measles, mumps and rubella (MMR) vaccine.[4] To date, however, all reported cases of ITP after an mRNA-based SARS-CoV-2 vaccine have responded to medical management. Here, we present a case of severe, refractory ITP that failed to respond to several medical treatments over the course of 2 months and eventually required a splenectomy for the management of severe thrombocytopenia.

CASE PRESENTATION

A man in his 20s with a medical history of obesity presented after a cat scratch to the right arm with persistent bleeding. He also reported gum bleeding over the past 1 week. The patient received the second dose of the Pfizer SARS-CoV-2 vaccine 2 weeks prior to presentation. Family history is notable for refractory ITP in his mother. Vital signs were normal and body mass index was 30.2 kg/m^2. Physical examination revealed a generalised petechial rash and bleeding from the scratch site.

INVESTIGATIONS

His initial labs were notable for severe thrombocytopenia with a platelet count of less than 1 x 10^9/L (139 000–361 000 µL), normal haemoglobin, normal white cell count, elevated prothrombin time of 14.9 s (9.5–13.3 s), normal partial thromboplastin time, normal lactate dehydrogenase and haptoglobin, normal ferritin and increased reticulocyte per cent 2.49% (0.50%–2.20%) (table 1). *Bartonella* serology was negative.

He received three units of platelets without significant elevation in platelet count. Peripheral blood smear showed absent platelets without schistocytes or blasts (figure 1).

DIFFERENTIAL DIAGNOSIS

The patient was suspected to have ITP and was started on high-dose intravenous steroids and IVIG for 2 days. On the fourth day of hospitalisation, platelet count remained low at 1000 µL and the patient was started on weekly rituximab, an immunosuppressive agent. A bone marrow biopsy was performed and showed increased iron storage and hypocellular marrow (figure 2). On the 11th day of hospitalisation, the platelet count remained less than 1000 µL despite daily steroid therapy. The patient was started on daily eltrombopag, a thrombopoietin receptor agonist, and received a second dose of rituximab.

Throughout hospitalisation, his haemoglobin was steadily trending down. On the 15th day of

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Table 1 Laboratory values to investigate for differential diagnoses in the case of thrombocytopenia

Lab test	Lab value
Platelets	<1000 µ/L (139 000–361 000 µ/L)
Prothrombin time	14.9 s (9.5–13.3 s)
Partial thromboplastin time	30 s (26.2–37.2 s)
INR	1.3
Fibrinogen	284 mg/dL (197–448 mg/dL)
D-dimer, quant	287 ng/mL (≤500 ng/mL)
Heparin, antibody interpretation	Negative
ANA screen	Negative
Anticardiolipin IgA	Negative
Anticardiolipin IgG	Negative
Anticardiolipin IgM	Negative
DNA antibody (double-stranded)	<1 IU/mL (≤4 IU/mL)
ADAMTS13 assay	90% (≥70%)

INR, international normalised ratio.

hospitalisation, the patient became encephalopathic requiring intubation for airway protection and transfer to the intensive care unit. Haemoglobin was found to be 23 g/L (12.6–16.7 g/dL) despite receiving a total of four units of packed red blood cells in the previous days, and massive transfusion protocol was initiated. Faecal occult blood test was positive and gastroenterology was consulted for suspected gastrointestinal bleed. However, endoscopy could not be performed as platelet counts remained between 1000 and 2000 µL. The patient required vasopressor support and bicarbonate infusion for severe metabolic acidosis with a lactate of 21.5 mmol/L (0.5–2.2 mmol/L) secondary to suspected haemorrhagic shock. Eltrombopag was discontinued and the patient was started on romiplostim, another bone marrow-stimulating agent.

TREATMENT

On the 16th day of hospitalisation, the patient was started on plasmapheresis for a total of 5 days for persistent thrombocytopenia although the suspicion for thrombotic thrombocytopenic purpura was low and ADAMTS13 was normal. The patient was extubated after 9 days.

At this point, there was concern that the patient may have haemophagocytic lymphohistiocytosis (HLH) as he failed to respond to multiple ITP treatments. The patient met five out of nine diagnostic criteria for HLH including fever, splenomegaly, elevated ferritin, hypertriglyceridaemia, anaemia and thrombocytopenia. Romiplostim was discontinued and the patient was started on ciclosporin, an immunosuppressive agent, for possible

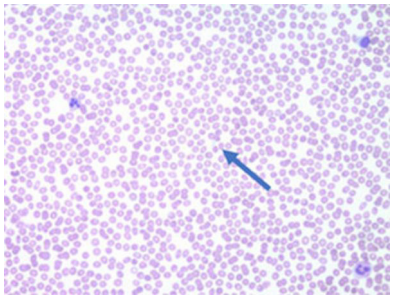

Figure 1 Initial peripheral blood smear with severe thrombocytopenia and otherwise normal red blood cells and white blood cells. A single hypogranular platelet (arrow) is present in the centre of the image.

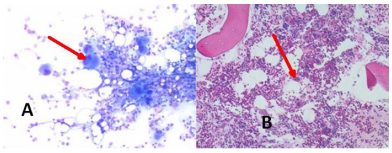

Figure 2 Bone marrow aspirate (A) and biopsy (B) with increased number of morphologically normal megakaryocytes (red arrows). Background trilineage haematopoiesis is preserved.

HLH. On hospital day 25, the platelet counts remained less than 1000 µL despite being on steroids and ciclosporin, and the patient was restarted on IVIG for 8 days. The platelet counts remained low and romiplostim was restarted on hospital day 31. Ultimately, ciclosporin and romiplostim were discontinued, platelet counts failed to improve beyond 2000–7000 µL, and the patient underwent an elective splenectomy on hospital day 40.

Spleen pathology revealed diffuse white pulp depletion, consistent with ITP (figure 3).

OUTCOME AND FOLLOW-UP

Platelet counts began to slowly improve and eventually reached 300 000 µL 16 days after the splenectomy. The patient was discharged to inpatient rehab on a steroid taper. Throughout his hospital stay, the patient received a total of 77 units of platelets.

DISCUSSION

ITP is the second most common cause of acquired thrombocytopenia and can be triggered by an inciting event, including mRNA-based vaccines. Thrombocytopenia in ITP can be severe and subsequently result in an increased risk of spontaneous bleeding, particularly when platelets drop below 20 000 µL. ITP can cause oral mucosal bleeding, epistaxis, menorrhagia, ecchymoses, and the most feared complication, intracranial haemorrhage.[5] Due to the absence of a single diagnostic test, definitive diagnosis of ITP can be difficult.[1]

Treatment for ITP usually occurs in a stepwise fashion and includes an initial course of high-dose corticosteroids and/or IVIG. If platelet counts fail to improve after these initial measures, thrombopoietin receptor agonists, rituximab or other immunosuppressants, and ultimately splenectomy, can be considered.[6] While invasive, splenectomy is associated with 70%–80% response rate.[2] Although there are multiple therapeutic options available for the treatment of ITP, many are associated with adverse effects (table 2). If several treatments are unsuccessful, ITP is less likely and patients should have a bone marrow biopsy to rule out other pathologies.[7]

ITP is a rare but known complication of several routine vaccines, including the MMR, pneumococcus and human

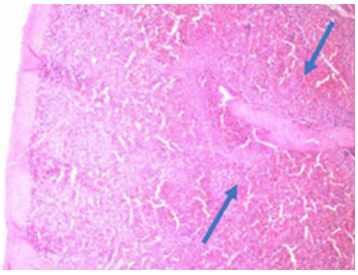

Figure 3 The spleen is diffusely depleted of white pulp with absent lymphoid follicles, germinal centres and perifollicular zones. The periarteriolar lymphoid sheath (arrow) has diminished lymphocytes.

Table 2 Treatment options for ITP

Treatment	Adverse effect(s)
Corticosteroids (dexamethasone/prednisone)	Weight gain, hypertension, diabetes
IVIG	Anaphylaxis, renal and pulmonary insufficiency
Rho(D)	Haemolysis, nausea, fever, headache
Splenectomy	Infection, bleeding, thrombosis, relapse
Rituximab	Infusion reactions, serum sickness, cardiac arrhythmias
Azathioprine	Leucopenia, elevated transaminases, alopecia, GI effects, increased risk of malignancy
Cyclophosphamide	Neutropenia, deep vein thrombosis, psoas abscess
Ciclosporin A	Hirsutism
Danazol	Weight gain, arthralgias, rash, amenorrhoea, breast discomfort, weakness
Dapsone	Skin rash, methaemoglobinaemia, sulfa allergy, neuropathy
Mycophenolate mofetil	Nausea, vomiting, myalgias, abdominal pain
Vinblastine/vincristine	Peripheral neuropathy
Thrombopoietin receptor agonists	Headache, nasopharyngitis, upper respiratory infection, fatigue, hepatotoxicity, arthralgias, vision changes

GI, gastrointestinal; ITP, immune thrombocytopenic purpura; IVIG, intravenous immunoglobulin.

papilloma virus vaccines.[8] Additionally, several cases of ITP or thrombocytopenia after the mRNA-based Pfizer and Moderna SARS-CoV-2 vaccines have been reported to the FDA's Vaccine Adverse Event Reporting System in patients both with and without previously diagnosed thrombocytopenic disorders. The mechanism of vaccine-induced thrombocytopenia is suspected to be immune-related in nature. Although the onset of post-vaccine thrombocytopenia is variable, many cases occur within 1–2 weeks of vaccination.[3]

The severity of ITP secondary to an mRNA-based SARS-CoV-2 vaccine is also heterogeneous, with some patients recovering spontaneously and others requiring more aggressive treatment with immunosuppressive therapies, such as rituximab or thrombopoietin receptor agonists, such as eltrombopag or romiplostim.[8] However, there are currently no documented cases in the literature reporting failure of post-SARS-CoV-2 vaccine ITP to respond to medical therapy. This case highlights an extremely severe case of refractory ITP after the Pfizer vaccine. The patient had a prolonged, complicated hospital course due to severe thrombocytopenia and even became critically ill secondary to haemorrhagic shock. Despite treatment with high-dose steroids, IVIG, rituximab, eltrombopag, romiplostim, plasmapheresis, ciclosporin and 77 platelet transfusions, platelets remained undetectable and the patient underwent a splenectomy with eventual improvement in platelet counts.

Although the development of ITP after mRNA-based SARS-CoV-2 vaccination is rare, it is important to note that some cases of post-vaccine thrombocytopenia may be life-threatening. This patient's family history of refractory ITP, however, may have increased his risk of developing severe ITP. It is still uncertain which vaccine is preferred in patients with underlying ITP or in patients at increased risk of ITP, as thrombocytopenia is a reported complication of both the Pfizer and Moderna vaccines. However, the rate of thrombocytopenia, including ITP, after both vaccines is 0.80 per million, which is less than the annual incidence of ITP in the general adult population.[3] As such, the benefits of vaccination outweigh the potential risks of post-vaccine ITP.

Millions of people around the world have been vaccinated with mRNA-based SARS-CoV-2 vaccines. Given the relatively recent development of these vaccines, it is crucial to document vaccine events and identify patients that may be susceptible to adverse outcomes. While post-vaccine ITP is rare, severe thrombocytopenia is possible and can lead to bruising, mucosal bleeding and even life-threatening haemorrhage. After vaccination with an mRNA-based SARS-CoV-2 vaccine, patients should be monitored for haemorrhagic events, especially those with previously diagnosed immune-related haematopoietic disorders. It is essential to note that vaccine events are rare and do not diminish the overwhelming utility of vaccination.

Learning points

- Despite immune thrombocytopenic purpura (ITP) being a rare side effect from mRNA-based SARS-CoV-2 vaccines, it is important to consider in the differential diagnosis of conditions following vaccination.
- While most cases of mRNA-based SARS-CoV-2 vaccine ITP appear to be easily treated with a medical therapy, this case illustrates splenectomy may be necessary ultimately.
- Both patients and providers should be aware of the signs of ITP and access laboratory facilities accordingly. As of now, there is not a method for home self-platelet testing.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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