

Immune thrombocytopenic purpura following the second dose of Pfizer COVID-19 vaccine

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SUMMARY

Immune thrombocytopenic purpura (ITP) is often a diagnosis of exclusion with presentations ranging widely from asymptomatic patients to those with life-threatening bleeding. Secondary ITP following vaccination is relatively uncommon and underdiagnosed as majority of patients remain asymptomatic. Cases of severe thrombocytopenia associated with SARS-CoV-2 messenger RNA (ribonucleic acid) vaccinations have been described previously, mostly as isolated occurrences, and typically occurring following the first dose. Here we present a case of severe ITP associated with the second dose of the Pfizer-BioNTech/BNT16B2b2 mRNA vaccine and provide a review of the current literature.

BACKGROUND

Immune thrombocytopenic purpura (ITP) is relatively rare with an annual incidence of roughly three cases per 10 000 adults. The predominant pathogenesis is thought to be secondary to an antibody-mediated disorder characterised by destruction of circulating platelets and manifesting as bruising or bleeding.¹ ITP is a known but unusual complication of routine vaccinations, commonly reported in children following the Mumps Measles Rubella (MMR) vaccines.^{2,3} Occasionally, it has also been reported in the elderly in association with the influenza vaccine, possibly due to structural similarities between the vaccine constituents and the antigens present on platelets.⁴ Hence, the observation of thrombocytopenia following SARS-CoV-2 vaccinations is not entirely a surprise. Recent data primarily describe development of ITP following the first dose of the SARS-CoV-2 mRNA vaccines with increasing reports warranting caution.^{5–9} However, ITP may also be associated with subsequent doses of the COVID-19 vaccines. Continued reporting and monitoring of cases is warranted to determine if a causal relationship exists. Here we describe a case of severe thrombocytopenia and purpura following the second dose of the Pfizer-BioNTech mRNA vaccine.

CASE PRESENTATION

The patient was a female in her early 50s who developed new, atraumatic, bilateral upper and lower extremity ecchymoses 4 days after receiving the second dose of the Pfizer-BioNTech/BNT16B2b2 mRNA vaccine. Eight days after vaccination, the bruising continued to worsen prompting further evaluation by her primary care physician. She was found to have a platelet count of 21 000 platelets/mm³. Of note, the patient's last platelet

count almost 7 years ago was 255 000 platelets/mm³. She had an otherwise unremarkable medical history and denied any clinical signs or symptoms following her first dose of the vaccine. She had no personal history of malignancy, autoimmune disease or prior bleeding diathesis. No preceding viral syndrome was noted. She was not taking any medications.

INVESTIGATIONS

She was sent to the emergency department for further work-up where her platelet count 12 hours later was found to be 3000 platelets/mm³. Other than ecchymoses shown in [figure 1](#), physical examination was unremarkable. There was no splenomegaly. Other laboratory parameters were unrevealing ([table 1](#)). Peripheral smear showed the presence of giant platelets ([figure 2](#)). She was transfused one unit of platelets with transient improvement in platelet count to 55 000 platelets/mm³.

Development of transient chest pain prompted a CT angiogram of the chest which ruled out pulmonary embolism. Her chest pain was ultimately attributed to musculoskeletal aetiology and subsided with supportive measures. Doppler venous ultrasound of the bilateral lower extremities was negative for thrombosis. The patient was not taking any medications recently. After exclusion of alternative causes, including but not limited to liver disease, bone marrow processes, medication induced, infectious processes, COVID-19 infection, and nutritional deficiencies, she was diagnosed with secondary ITP associated with COVID-19 vaccination.

TREATMENT

She received 40 mg dexamethasone daily for 4 days with improvement in her platelet count to 101 000 platelets/mm³ by day 16 postvaccination ([figure 3](#)).

Approximately 47 days following her second vaccination, she presented again with recurrent ecchymosis and was found to have a platelet count of 7000 platelets/mm³. She was then treated with a combination of intravenous immunoglobulin (IVIG) and dexamethasone. This was followed by four doses of weekly rituximab (375 mg/m² per dose). Since completion of rituximab, the patient has not shown any further evidence of thrombocytopenia, with platelet counts ranging from 190 000 to 250 000 platelets/mm³ (most recently 214 000 platelets/mm³, 1 year after her last dose of COVID-19 vaccine). She has deferred a booster vaccine.



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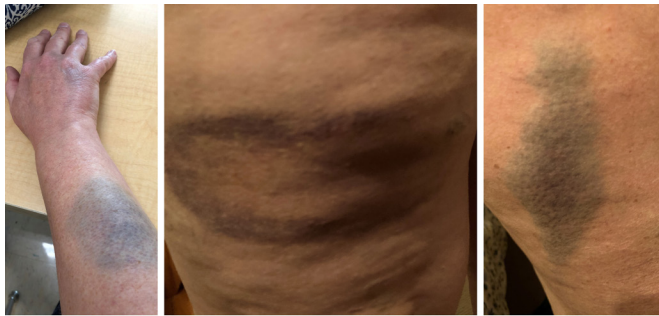


Figure 1 Ecchymoses on upper and lower extremities.

DISCUSSION

There has been growing concern with emergence of vaccine-related haematologic adverse events including new cases of ITP secondary to the mRNA vaccines.^{5–7–9} A handful of cases of thrombocytopaenia have been reported to the Vaccine Adverse Event Reporting System among the millions of administered doses of the Pfizer-BioNTech and mRNA-1273/Moderna vaccine.² It is important to distinguish this entity from Vaccine-induced Immune Thrombotic Thrombocytopaenia (VITT) which is a prothrombotic state with significant mortality and morbidity and has been reported in association with adenovirus vector-based vaccines (namely the Vaxzevria by AstraZeneca vaccine, ChAdOx1 nCoV-19 and Johnson & Johnson/Janssen vaccine, AD26.COV2.S).^{10–12} In contrast to VITT, ITP predisposes to bruising and bleeding.

ITP secondary to vaccinations typically occurs within 1–2 weeks following the first dose of vaccination. Severe thrombocytopaenia with platelet counts less than 10 000 platelets/mm³ have been described, although many cases remain underdiagnosed as most patients do not present with clinically significant symptoms or undergo routine laboratory investigations postvaccination.^{3,7,8}

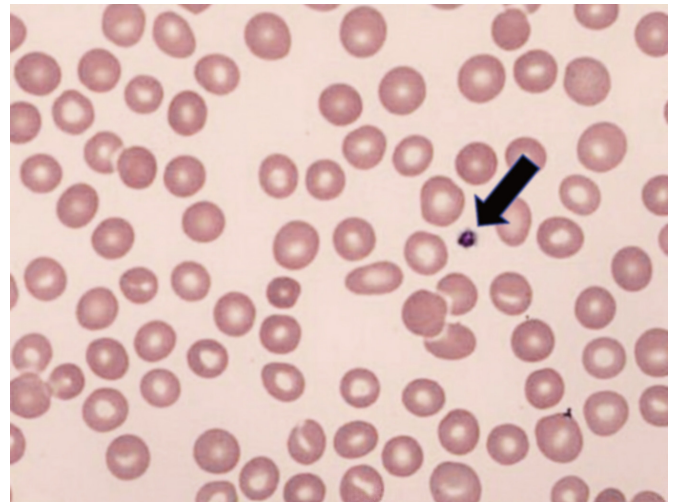


Figure 2 Peripheral smear showing a 'giant platelet' as indicated by an arrow (Leishman's stain).

The pathophysiology remains unclear, but proposed mechanisms include myelosuppression, consumption as seen in disseminated intravascular coagulation and immune-mediated humoral or cell-mediated destruction.³ The successful use of corticosteroids and IVIG in these patients seem to suggest an antibody-mediated platelet failure like that seen in de novo ITP.^{5,6} Other treatment strategies extrapolated from de novo ITP suggest that thrombopoietin receptor agonists may play an important role in platelet recovery and potentially minimise the use of immunosuppressive agents.⁷ The latter is of particular importance, as decreased SARS-COV-2 antibody responses have been described in patients on immunosuppressants.¹³ Other treatments explored in these patients include platelet transfusions, shown to be of minimal

Table 1 Laboratory values on days following Pfizer COVID-19 vaccination

Days since vaccination	Day 8 07:00 hours	Day 8 19:00 hours	Day 9	Day 10	Day 16	Day 33	Day 47	Day 48	Day 49	1 year later
Haemoglobin (gm/dL)	14.5	13.8	12.8	13.4	14.5	14.1	14.2	14.5	12.9	14.3
White blood cells (k/mm ³)	6.2	8.5	7.8	6.1	9.1	8.9	11.0	7.9	5.6	5.8
Platelets (k/mm ³)	21	3	55*	24	101†	441	7	26‡	47	214§
Mean platelet volume (femtoliters)	*	*	12.1	14.7	12.9	11.2	¶	13.7	13.2	12.1
International Normalized Ratio (INR)	–	1.0	–	–	–	–	1.0	–	–	–
Prothrombin time (s)	–	10.4	–	–	–	–	10.1	–	–	–
Activated prothrombin time (s)	–	24.5	–	–	–	–	27.3	–	–	–
Fibrinogen (mg/dL)	–	287	–	–	–	–	377	–	–	–
D-Dimer (mg/L)	–	1.64	–	–	–	–	0.21	–	–	–
Haptoglobin (mg/dL)	–	59	–	–	–	–	72	–	–	–
Lactate dehydrogenase (units/L)	–	210	–	–	–	–	217	–	–	–
Total bilirubin (mg/dL)	1.3	0.7	–	–	–	–	0.6	–	–	–
Aspartate aminotransferase (units/L)	21	–	–	–	–	–	–	–	–	–
Alanine aminotransferase (units/L)	20	–	–	–	–	–	–	–	–	–
Alkaline phosphatase (units/L)	100	–	–	–	–	–	–	–	–	–
COVID-19 RT-PCR	Negative		–	–	–	–	–	–	–	–
Vitamin B ₁₂ (pg/mL)	1466		–	–	–	–	–	–	–	–

'–' refers to not obtained

*Platelet transfusion.

†Oral dexamethasone 40 mg for 4 days.

‡Oral dexamethasone 40 mg for 4 days + 2 doses of 40 mg intravenous immunoglobulin 24 hours apart.

§Rituximab (375 mg/m²) every week for 4 weeks.

¶Could not be measured.

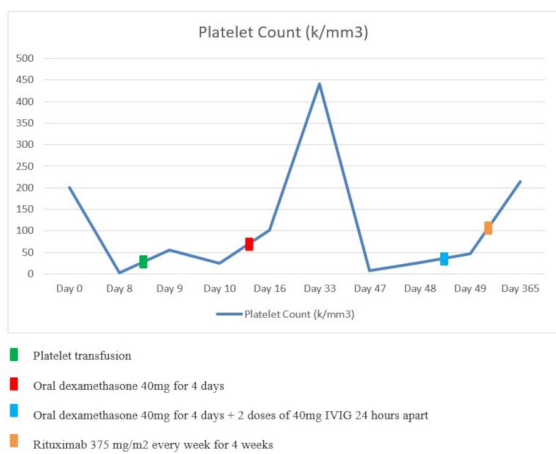


Figure 3 Trend of platelet count and medical interventions. A platelet transfusion was given at the time of admission, 8 days after vaccination. Oral dexamethasone was started on day 10. The patient developed recurrent thrombocytopenia and was treated with intravenous immunoglobulin and oral dexamethasone on day 48 followed by four doses of weekly rituximab (375 mg/m² per dose).

and temporary benefit, and rituximab, which can take 6–8 weeks to produce a response.⁵ Whereas, approximately 80% of patients with de novo ITP relapse within 2 years, recurrence rates with secondary ITP associated with mRNA vaccines remain unknown.¹⁴

The development of new thrombocytopenia with severe bruising in our patient within 1 week of receiving the second dose of the COVID-19 vaccine is suggestive of secondary ITP. It is also possible that our patient may have been presensitized by the first dose of COVID-19 vaccine. Work-up for other aetiologies was unrevealing. Of note, the patient did not undergo comprehensive autoimmune work-up and it is possible that the vaccine unmasked either a pre-existing ITP or a predisposing condition for de novo ITP. In the absence of a recent prevaccination platelet count, it is nearly impossible to distinguish between these entities. However, in the presence of a preceding clinical event, secondary ITP remains the most likely diagnosis. Our patient then developed recurrent thrombocytopenia, almost 7 weeks after vaccination, which is worrisome for a refractory process. It is unclear if these reactions are self-limiting or if they may persist and lead to chronic ITP.^{2,6} Furthermore, the role of rechallenging with either the same or another SARS-CoV-2 vaccine is uncertain. In these cases, close surveillance should be strongly recommended. It is important to note that the incidence of clinically meaningful thrombocytopenia is relatively low, and the benefit of COVID-19 vaccine in preventing a disease with high mortality and significant long-term sequelae needs to be considered.¹⁵

Awareness of new cases of thrombocytopenia following the administration of mRNA SARS-CoV-2 vaccines continues to grow. Fortunately, most patients rarely manifest severe thrombocytopenia and many cases remain clinically occult. Our patient developed clinical symptoms of severe thrombocytopenia with bruising after the second dose of the vaccine and may have been presensitized by the prior dose. The reporting of this clinical vignette highlights the importance of continued surveillance and increased clinician awareness. It also encourages close outpatient monitoring for patients at potentially higher risk for secondary ITP associated with vaccinations. These events do not in any way undermine the benefit of SARS-CoV-2 vaccines.

Learning points

- ▶ Secondary immune thrombocytopenia is commonly described in association with the first dose following the COVID-19 mRNA vaccines but can also be observed following subsequent doses.
- ▶ Most cases of secondary ITP associated with the COVID-19 vaccines appear to be relatively self-limited, however clinically significant as well as refractory cases have been described.
- ▶ Rituximab appears to be an effective treatment option with a more durable response but can cause immunosuppression.
- ▶ Subsequent COVID-19 vaccines should not be withheld in these patients, instead close outpatient surveillance is warranted particularly for patients with a prior history of ITP.

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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.

REFERENCES

- 1 Terrell DR, Beebe LA, Vesely SK, *et al*. The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. *Am J Hematol* 2010;85): :NA–80.
- 2 Welsh KJ, Baumblatt J, Chege W, *et al*. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the vaccine adverse event reporting system (VAERS). *Vaccine* 2021;39:3329–32.
- 3 Perricone C, Ceccarelli F, Neshor G, *et al*. Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. *Immunol Res* 2014;60:226–35.
- 4 Saudagar V, Patil S, Goh S, *et al*. Vigilance regarding immune thrombocytopenic purpura after COVID-19 vaccine. *Ir J Med Sci* 2022;191:919–920.
- 5 Lee E-J, Cines DB, Gernsheimer T, *et al*. Thrombocytopenia following pfizer and Moderna SARS-CoV-2 vaccination. *Am J Hematol* 2021;96:534–7.
- 6 Lee E-J, Beltrami-Moreira M, Al-Samkari H, *et al*. SARS-CoV-2 vaccination and ITP in patients with de novo or preexisting ITP. *Blood* 2022;139:1564–74.
- 7 Helms JM, Ansteatt KT, Roberts JC, *et al*. Severe, refractory immune thrombocytopenia occurring after SARS-CoV-2 vaccine. *J Blood Med* 2021;12: :221–4.
- 8 Malayala SV, Mohan G, Vasireddy D, *et al*. Purpuric rash and thrombocytopenia after the mRNA-1273 (Moderna) COVID-19 vaccine. *Cureus* 2021;13:e14099.
- 9 Tarawneh O, Tarawneh H. Immune thrombocytopenia in a 22-year-old post Covid-19 vaccine. *Am J Hematol* 2021;96:E133–4.
- 10 Parums DV. Editorial: SARS-CoV-2 mRNA vaccines and the possible mechanism of vaccine-induced immune thrombotic thrombocytopenia (VITT). *Med Sci Monit* 2021;27: :e932899.
- 11 Greinacher A, Thiele T, Warkentin TE, *et al*. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;384:2092–101.
- 12 Cines DB, Bussell JB. SARS-CoV-2 vaccine-induced immune thrombotic thrombocytopenia. *N Engl J Med* 2021;384:2254–6.
- 13 Deepak P, Kim W, Paley MA, *et al*. Effect of Immunosuppression on the Immunogenicity of mRNA Vaccines to SARS-CoV-2 : A Prospective Cohort Study. *Ann Intern Med* 2021;174:1572–85.
- 14 Schwartz J, Leber MD, Gillis S, *et al*. Long term follow-up after splenectomy performed for immune thrombocytopenic purpura (ITP). *Am J Hematol* 2003;72:94–8.
- 15 Adeloye D, Elneima O, Daines L, *et al*. The long-term sequelae of COVID-19: an international consensus on research priorities for patients with pre-existing and new-onset airways disease. *Lancet Respir Med* 2021;9:1467–78.

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