Received: 28 August 2023 | Revised: 11 March 2024 | Accepted: 25 May 2024

DOI: 10.1002/ccr3.9070

Clinical Case Reports Open Access WILEY

CASE REPORT

COVID-19-induced immune thrombocytopenia management approach: A case report and literature review

Hatem Mahmoud Alahwal[1,2] | **Mansour Hani Alsharif**[3] | **Mada Hani Alsharif**[4] | **Abdullah Talal Almohammadi**[1,2] | **Adel Fahad Al-Marzouki**[1,2] | **Ahmed Saleh Barefah**[1,2] | **Salem Mohammad Bahashwan**[1,2] | **Osman Omer Radhwi**[1,2] | **Ghazi Abdullah Damanhouri**[1,2]

[1]Hematology Department, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

[2]Hematology Research Unit, King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia

[3]Internal Medicine Department, Al-Thagher General Hospital, Jeddah, Saudi Arabia

[4]Department of Preventive Medicine – Directorate of Health Affairs, Jeddah, Saudi Arabia

Correspondence
Hatem Mahmoud Alahwal, Hematology Department, Faculty of Medicine, King Abdulaziz University, Jeddah 21859, Saudi Arabia.
Email: halahwal@kau.edu.sa

Key Clinical Message

Vincristine therapy can be effective in refractory Immune thrombocytopenia (ITP) following COVID-19 vaccination. Our case report highlights the need for further research to establish standard management guidelines for COVID-19-vaccine-associated ITP.

Abstract

Adult immune thrombocytopenia (ITP) can occur as a rare complication following several viral infections or a rare adverse event or complication of vaccination. In this paper, we report a case of a 39-year-old male patient with severe refractory ITP that began 4-weeks after receiving his third (booster) dose of the COVID-19 vaccine (BNT162b2, Pfizer-BioNTech). He was given oral dexamethasone 40 mg daily for 4 days followed by prednisone at 1 mg/kg (85 mg daily) for 10 days. In the following weeks, we attempted several other lines of therapy to treat his ITP, including anti-RhD immunoglobulin, which, unfortunately, caused moderate hemolysis requiring packed red blood cell transfusion, intravenous immunoglobulin (given at a subtherapeutic dose of 0.4 g/kg for only 1 day since it was not available), rituximab, and eltrombopag. The patient, unfortunately, showed no response to any of these treatments. This was an indicator to initiate salvage therapy with vincristine 2 mg weekly for 3 weeks. The patient's platelet count started to increase remarkably during the third week of vincristine and normalized after 4 weeks. We review the findings, clinical characteristics, and management approaches that were reported in the literature regarding COVID-19-vaccine-induced ITP. More in-depth research is needed to delineate standard guidelines for the management of such cases. This report underscores the importance of resorting to vincristine and eltrombopag as great options for severe and refractory ITP related to the COVID-19 vaccine.

KEYWORDS

COVID-19, refractory, severe immune thrombocytopenic purpura, vaccination vincristine

1 | INTRODUCTION

The annual incidence of adult immune thrombocytopenia (ITP) is estimated to be 3.3 per 100,000 in the United States alone, which signifies the rarity of this disease.[1] ITP can occur as a primary or secondary disorder; the former is idiopathic and constitutes approximately 80% of ITP cases, while the latter is believed to be autoimmune in nature, accounting for 20% of cases. The condition is usually triggered by several factors, such as medications, infections, malignancies, and rheumatological disorders.[2] It can occur as a rare complication following several viral infections, including HIV, cytomegalovirus, and varicella-zoster virus. It can also occur as a rare adverse event or complication of vaccines including the measles-mumps-rubella (MMR), oral polio, diphtheria, tetanus, pertussis (DTP), hepatitis A, and even influenza vaccines.[3–6] Additionally, viruses such as SARS-CoV-2 have been associated with more than 45 cases of de novo ITP, as reported in a systematic review of studies published from the beginning of the COVID-19 pandemic until August 2020.[1] Similarly, from 2021 to 2022, more than 37 studies were reported worldwide associating vaccination against SARS-CoV-2 virus with de novo ITP.[7–16] According to another systematic review, published in September 2020, on the incidence of ITP secondary to COVID-19 infection, the overall response of ITP to first-line therapy, which included corticosteroids and intravenous immunoglobulin (IVIG), was good, and mortality was only reported in 1 case, due to intracranial hemorrhage (even though severe bleeding was not a common finding among all other cases).[17] In this paper, we report the case of a 39-year-old male patient who developed severe refractory ITP 4-weeks after receiving his third (booster) dose of the COVID-19 vaccine (BNT162b2, Pfizer-BioNTech). We also review the findings, clinical characteristics, and management approaches reported in the literature on COVID-19-vaccine-induced ITP. The total number of studies we reviewed is 26; the remainder of the studies were unretrievable.

1.1 | Case presentation (history/examination)

A 39-year-old man, previously in good health, presented four weeks after receiving his third (booster) dose of the COVID-19 vaccine with symptoms including epistaxis, petechiae, and intermittent hematuria. An initial evaluation conducted at a private hospital resulted in a diagnosis of Immune Thrombocytopenia (ITP), as investigations did not reveal any other causes for his thrombocytopenia. At the time of presentation, the patient did not exhibit additional cytopenias or signs of hemolysis. Physical examination revealed petechiae on his arms and legs but no palpable lymphadenopathy or organomegaly. Otherwise, his physical examination and medical history were unremarkable, with no other significant findings noted.

2 | METHODS

2.1 | Differential diagnosis

The differential diagnosis primarily focused on ITP, given the lack of other etiologies for thrombocytopenia. Conditions such as antiphospholipid syndrome, hepatitis B and C, and HIV were considered as triggers for his ITP and subsequently ruled out through negative testing results.

2.2 | Investigations

The patient's diagnostic workup included testing for various causes of ITP (Table 1), including antiphospholipid antibodies, hepatitis B and C, and HIV with all tests returning negative except for Helicobacter pylori antibodies, indicating an infection. Laboratory and radiological investigations, including a bone marrow biopsy and a CT scan of the neck, chest, abdomen, and pelvis, were performed. The CT scan did not reveal any lymphadenopathy or abnormalities, although its efficacy might have been compromised due to prior steroid treatment. The bone marrow biopsy showed active marrow with abundant megakaryocytes, suggesting peripheral destruction of platelets.

2.3 | Treatment

Initial treatment with oral dexamethasone (40 mg daily for 4 days) followed by prednisone (1 mg/kg or 85 mg/day for 10 days) did not improve the platelet count, which remained below $10 \times 103/\mu L$. A full course of triple therapy was completed for Helicobacter pylori. Subsequent treatments included anti-RhD immunoglobulin (causing moderate hemolysis), IVIG at a subtherapeutic dose due to unavailability, and a combination of rituximab (375 mg/m2 weekly for 4 weeks) and escalating doses of eltrombopag (up to 75 mg per day) along with another course of dexamethasone (40 mg daily x 4 additional days). The patient's condition did not respond to these treatments, leading to salvage therapy with vincristine (2 mg weekly for three doses), which ultimately normalized the platelet count.

3 | CONCLUSION AND RESULTS

We report a case of severe refractory ITP following COVID-19 vaccination that proved resistant to first-line

management measures and responded well to vincristine therapy. With the accumulating evidence and the possibility of underdiagnosing asymptomatic ITP, a temporal relationship could be inferred between COVID-19 vaccination and de novo ITP. Since the mechanism is still unclear, the discrepancy between the time of vaccination and time of onset also is unexplained. Also, whether these patients were going to develop ITP and the vaccine accelerated the process or the vaccine caused the ITP per se is unknown. More in-depth research is needed to delineate standard guidelines for the management of COVID-19-vaccine-associated ITP. This report underscores the importance of resorting to vincristine and eltrombopag as great options for severe and refractory ITP. Despite the reported complication in our case, it is essential to emphasize the profoundly positive impact vaccines have had on global health. Their role in preventing serious infections and associated morbidity far outweighs the relatively small risk of adverse effects. The patient's clinical course is demonstrated in Figure 1.

TABLE 1 Laboratory test results upon admission.

Parameter	Result
White blood cells (K/μL)	16.94
Hemoglobin (g/dL)	15
Platelets ($\times 10^3$/μL)	2
Aspartate aminotransferase (U/L)	19
Alanine aminotransferase (U/L)	34
Lactate dehydrogenase (U/L)	302
Blood urea nitrogen (mmol/L)	4.6
Creatinine (μmol/L)	67
Total bilirubin (μmol/L)	12
Total protein (g/L)	65
Albumin (g/L)	40
HBs Ag (IU/mL)	Negative
HBs Ab (mIU/mL)	Negative
HBc Ab (S/CO)	Negative
HCV Ab (S/CO)	Negative
Helicobacter pylori antigen	Positive
Lupus anticoagulant ratio	1.28
Antinuclear antibody	Titre = 1:80 (mildly positive)
HIV 1 & 2	Negative
Blood film	Thrombocytopenia

4 | DISCUSSION

The current American Society of Hematology (ASH) 2019 guidelines for the management of newly diagnosed ITP include steroids, IVIG, and anti-RhD immunoglobulin as first-line treatments. Second-line treatments include thrombopoietin receptor agonists (eltrombopag or romiplostim), rituximab, and splenectomy, depending on multiple factors such as symptoms, platelet counts, duration of ITP, and response to steroids.[18,19] Likewise, other treatments, considered salvage

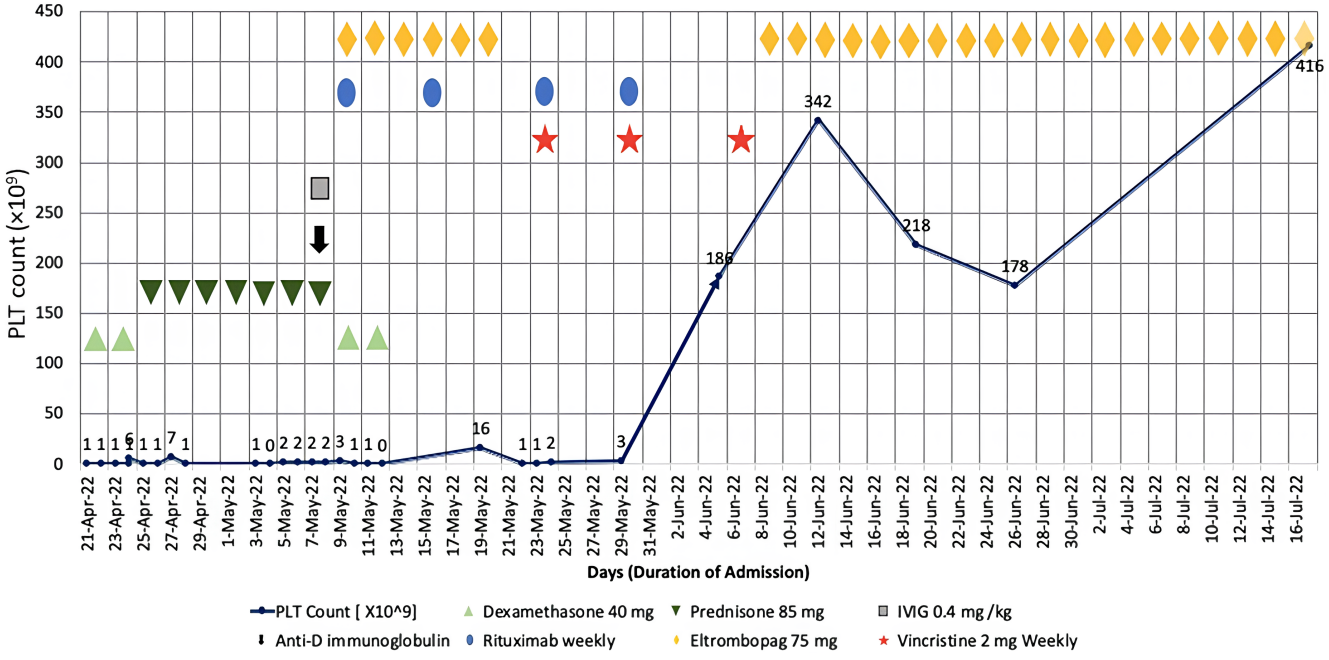

FIGURE 1 The patient's clinical course with serial platelet counts and treatments given during hospital admission showing his progress and response to therapy. IVIG, intravenous immunoglobulin; PLT, platelet.

therapy, have proven to be effective in the management of severe refractory ITP such as azathioprine, cyclophosphamide, mycophenolate mofetil, vinca alkaloids (vincristine), fostamatinib, danazol, and therapeutic plasma exchange.[19]

Regarding ITP induced by COVID-19 infection or vaccination, the approach does not differ remarkably. Steroids are still the first line of treatment, as there is no evidence to supports that they would increase the patient's susceptibility to the virus during infection with SARS-CoV-2 virus.[20] Nonetheless, prioritizing non-immunosuppressive agents for the management of COVID-19-induced ITP, such as fostamatinib, IVIG, or oral thrombopoietic agents (eltrombopag or avatrombopag), is deemed effective first-line management.[20]

The total number of de novo ITP cases we included in our review is 73. There would have been at least an additional 10 cases had their studies been publicly available. Table 2 summarizes the clinical details of the reviewed patients with ITP after COVID-19 vaccination. Patient age ranged from 20 to 97 years with a median of 54 years. The patient in our report was 39 years old, was previously healthy, and had no comorbidities. In most of the cases reported in the literature, the patients had single or multiple comorbidities, namely hypertension, congestive heart failure, aortic stenosis, diabetes, hyperlipidemia, hypothyroidism, anxiety and depression, polycystic ovary syndrome, diverticulosis, Crohn's disease, chronic kidney disease, epilepsy, hepatitis C and B liver cirrhosis, scleroderma, rheumatoid arthritis, mixed connective tissue disease, psoriasis, and others.

Fifty-four of the cases developed ITP following the first dose of the COVID-19 vaccine, and around 19 patients developed ITP following the second dose. The dose number was not mentioned in some of the case reports.

The time range from receiving the COVID-19 vaccine to the onset of ITP was 12 hours to 26 days, with a median of 7 days. In almost all cases of thrombocytopenia, the patients were thoroughly investigated for secondary causes of ITP, and the link with the vaccine was made on strong bases. The researchers even ruled out SARS-CoV-2 virus infection. Furthermore, the platelet count was 10×10^9/L or lower in 84% of the cases (in some reaching as low as 0), while only 1% of cases had platelet counts below 66×10^9/L and 1% had counts below 20×10^9/L.

As for the vaccines associated with ITP, the Pfizer-BioNTech vaccine ranked highest in this review (used in 34 of the cases), whereas AstraZeneca was reportedly used in 23 of the cases. Moderna was reported in 18 of the cases, and ChAdOx1 nCoV-19 (Covishield) was reported in 1 case.[28]

Overall, survival and normalization of platelet count were mostly attainable with first- and second-line treatments, while some cases, with refractory ITP, required second line as well as salvage therapy.[9,14,24,41,42] These results are in accordance with the overall outcome of another case series of chronic ITP patients who developed exacerbations post-COVID-19 vaccination,[12] which may indicate similarities between the course of chronic ITP and that of de novo ITP post-COVID-19 vaccination. This would help in the future when establishing standard lines of management for these conditions.

In 1 case, the patient developed ITP after the third (booster) dose, which is similar to our case but with differences in patient age (75 years) and onset of ITP (which was 4 days after vaccination).[35] Our patient was 39 years old and developed ITP 4-weeks after receiving the third dose. In Addition, the 75-year-old patient had multiple comorbidities including scleroderma, rheumatoid arthritis, hypertension, mixed connective tissue disease, cardiac disease, and osteopenia, while our patient was otherwise healthy.[35] The lowest platelet count in the 75-year-old patient's case was 18×10^9/L, and the patient improved markedly within 6 days after receiving platelet transfusion and dexamethasone 40 mg.[35] Our patient, on the other hand, had severe refractory ITP, with platelet counts as low as 1×10^9 /L, and required a long course of treatment where he responded to salvage therapy (similar to several other reported cases) with vincristine and eltrombopag. Among all these case series and reports, only 1 reported the use of vincristine, with a remarkable resulting response, making this study one of the first reports supporting the use of vincristine as a last resort in severe refractory ITP induced by the COVID-19 vaccine.[41]

In all but 1 case (where IVIG was used as first-line treatment without steroids) corticosteroids including prednisone, prednisolone, dexamethasone, methylprednisolone, hydrocortisone, and pulse steroids, were used.[36] The doses of steroids and IVIG varied according to patient weight. Only 2 cases showed improvement with steroids alone, within 1 month in one case; however, duration was not specified for the other.[28,38] Table 3 outlines the clinical course and lines of management for the reviewed patients.

Furthermore, the most effective and frequently used therapies were steroids, IVIG, and platelet transfusion, followed by thrombopoietin receptor agonists (eltrombopag or romiplostim). Rituximab was used in 3 cases. Splenectomy, cyclosporine, and plasma exchange were used in 2 refractory cases. Mycophenolate mofetil and vincristine were each reported once in the cases we reviewed.

Duration of treatment ranged from 3 to 126 days, with a median of 14 days. In 13 of the cases, treatment continued after discharge from the hospital, whereas, therapy was discontinued upon discharge in 7 cases. Our patient's course of therapy was extensive and long, exceeding 126 days.

TABLE 2 Clinical details of patients who developed immune thrombocytopenia after COVID-19 vaccination.

Number of cases	Age (years)	Comorbidities	Vaccine dose	Vaccine type	ITP onset	Reference
1	68	None	First	Moderna	7 days	[21]
19[a]	56–97	Not reported	First and second	AstraZeneca Pfizer-BioNTech	1–24 days	[22]
1	67	HTN, DM2, hypothyroidism, depression, vitamin B12 deficiency, and chronic cluster headaches	Second	Pfizer-BioNTech	2 days	[23]
1	63	COPD, DM2, HTN	Second	Pfizer-BioNTech	1 day	[24]
1	25	Bronchial asthma	Second	Moderna	26 days	[25]
1[a]	73	HTN, hyperlipidemia	First	Moderna	11 days	[26]
1[b]	31	None	Second	Pfizer-BioNTech	1 day	[11]
1	69	Intestinal obstruction, hypopharyngeal cancer	Second	Pfizer-BioNTech	10 days	[27]
1	34	Dysmenorrhea	Second	Moderna	3 weeks	[27]
1	Middle aged	None	Second	ChAdOx1 nCoV-19 (Covishield)	10 days	[28]
1	24	Dysfunctional uterine bleeding, asthma, vitamin D deficiency.	First	Pfizer-BioNTech	10 days	[29]
1	39	PCOS	Second	Pfizer-BioNTech	3 days	[30]
1	77	CAD, AF, HTN, CRF, anemia	First	Pfizer-BioNTech	8 days	[31]
1	79	Ischemic stroke	First	AstraZeneca	1 week	[32]
1	54	Not reported	First	AstraZeneca	17 days	[33]
1	33	Not reported	First	AstraZeneca	21 days	[33]
1	56	Not reported	Second	Pfizer-BioNTech	7 days	[33]
1	53	Crohn's disease	Second	Pfizer-BioNTech	8 days	[7]
1	90	HTN, Hyperlipidemia, MI	First	Pfizer-BioNTech	7 days	[34]
1	66	None	First	AstraZeneca	3 days	[8]
1	75	Scleroderma, RA, HTN, MCTD, cardiac disease, osteopenia	Third (booster)	Pfizer-BioNTech	4 days	[35]
1[c]	38	None	First	Moderna	4 days	[36]
1	60	Tobacco use, hepatitis C liver cirrhosis, CKD, HTN, CHF	First	Moderna	2 days	[37]
1	20	Not reported	First	Pfizer-BioNTech	17 days	[38]
1	54	Congenital epidermal dysplasia, HTN, overactive bladder, mild cognitive impairment, CKD anxiety	Second	Pfizer-BioNTech	5 days	[39]
1	41	None	First	AstraZeneca	14 days	[13]
1	41	Multiple allergies, hypothyroidism, HTN, and prediabetes	–	Pfizer-BioNTech	12 Hours	[40]
1	74	HTN, gout, hyperlipidemia, and nonischemic cardiomyopathy	First	Moderna	Within 24 days	[14]
25	22–82	HTN, DM, GERD, hyperlipidemia, depression, PCOS, diverticulosis, aortic stenosis, Crohn's disease, HBV, nephrolithiasis, AF, thyroid disease, epilepsy, migraines, psoriasis	First (23 patients) Second (2 patients)	Pfizer-BioNTech and Moderna	1–23 days	[9]
1	66	None	First	Pfizer-BioNTech	2 days	[41]
1	20	Obesity	Second	Pfizer-BioNTech	2 weeks	[42]

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM2, type 2 diabetes mellitus; GERD, gastroesophageal reflux disease; HBV, hepatitis B virus; HTN, hypertension; ITP, immune thrombocytopenia; MCTD, mixed connective tissue disease; MI, myocardial infarction; PCOS, polycystic ovary syndrome; RA, rheumatoid arthritis.

[a]Only de novo ITP cases were mentioned for the purpose of this report; chronic ITP patients were excluded.

[b]Also received MMR vaccine 2-months prior to onset of ITP.

[c]This patient had vaccine-induced myocarditis as well.

TABLE 3 Clinical course and lines of management of patients with immune thrombocytopenia after COVID-19 vaccination.

Platelet count[a] (lowest—highest)	Line of management	Duration of treatment	Line of management patient responded to	Therapy continued or terminated upon discharge	Reference
4×10^9/L—88×10^9/L	Prednisone 60 mg and IVIG 1 g/kg	3 days	Both	Continued on prednisone	[21]
(0×10^9/L—$>100\times10^9$/L)	Corticosteroids, IVIG 1–2 g/kg, and thrombopoietin receptor agonist	Not reported	Corticosteroids and thrombopoietin receptor agonist	Not reported	[22]
$<3\times10^9$/L—250×10^9/L	Prednisolone 1 mg/kg, platelet transfusion (1 unit), IVIG, aminocaproic acid, rituximab, and eltrombopag.	2 Months	Eltrombopag	Continued	[23]
0×10^9/L—201×10^9/L	Dexamethasone 40 mg, IVIG, prednisone, romiplostim, rituximab	33 days	Romiplostim and rituximab	Continued	[24]
1×10^9/L—324×10^9/L	Dexamethasone 40 mg, IVIG, tranexamic acid, platelet transfusion, romiplostim, and mycophenolate mofetil	6 weeks	Romiplostim and mycophenolate mofetil	Continued	[25]
1×10^9/L—248×10^9/ L	Prednisolone, IVIG, and eltrombopag 12.5 mg	11 days	Eltrombopag 12.5 mg	Not reported	[26]
1×10^9/L—472×10^9/L	Glucocorticoids, IVIG, and platelet transfusion (2 units)	3 days	Both	Continued	[11]
6×10^9/L—100×10^9/L	IVIG and prednisolone	14 days	Both	Discontinued	[27]
3×10^9/L—125×10^9/L	IVIG, prednisolone, and eltrombopag	15 days	Eltrombopag	Not reported	[27]
10×10^9/L—Normalized	Oral prednisolone 80 mg	1 Month	Prednisolone	Continued	[28]
1×10^9/L—427×10^9/L	Prednisone and IVIG	46 days	IVIG	Continued	[29]
1×10^9/L—92×10^9/L	Platelet transfusion (2 units), 1000 mg methylprednisolone, and IVIG 70 mg	3 days	IVIG mostly	Discontinued	[30]
17×10^9/L—205×10^9/L	IVIG 40 g, prednisone 100 mg, eltrombopag 50 mg	18 weeks	Eltrombopag	Continued	[31]
2×10^9/L—114×10^9/L	Hydrocortisone 300 mg then oral prednisolone	12 days	Hydrocortisone	Discontinued	[32]
10×10^9/L—50×10^9/L	IVIG 1 g/kg and prednisolone 1 mg/kg	8 weeks	Not specified	Continued	[33]
3×10^9/L—50×10^9/L	IVIG 1 g/kg, prednisolone 1 mg/kg, and romiplostim 3 μg/kg	3 days during second admission	Not specified	Not specified	[33]
2×10^9/L—226×10^9/L	Pulse steroids, IVIG 1 g/kg, prednisolone 100 mg/kg, eltrombopag 50 mg	10 days during second admission	Not specified	Not specified	[33]
2×10^9/L—Normalized	Dexamethasone 40 mg and IVIG 1 g/kg	4 days	Both	Not specified	[7]
3×10^9/L—148×10^9/L	IVIG 10 g, prednisolone 40 mg, platelet transfusion, and eltrombopag	67 days	Platelet transfusion and eltrombopag	Continued	[34]
4×10^9/L—100×10^9/L	High dose dexamethasone 40 mg and IVIG 1 g/kg	6 days	Dexamethasone and IVIG	Not specified	[8]
18×10^9/L—61×10^9/L	Platelet transfusion and dexamethasone 40 mg	6 days	Both	Discontinued	[35]
9×10^9/L—50×10^9/L	IVIG 400 mg/kg	6 days	IVIG	Discontinued	[36]

TABLE 3 (Continued)

Platelet count[a] (lowest—highest)	Line of management	Duration of treatment	Line of management patient responded to	Therapy continued or terminated upon discharge	Reference
–	The patient left the hospital against medical advice; his platelet count was being monitored without intervention	–	–	–	[37]
16×10^9/L—210×10^9/L	Prednisolone 50 mg/kg	13 days	Prednisolone	Not specified	[38]
0×10^9/L—114×10^9/L	Platelet transfusion (4 units), dexamethasone 40 mg, IVIG	Admitted twice; total duration of admissions around 15 days	IVIG	Discontinued	[39]
$<1\times10^9$/L—80×10^9/L	Prednisone 2 mg/kg, IVIG 1 g/kg, then prednisolone	29 days	Prednisolone	Continued	[13]
65×10^9/L—210×10^9/L	Dexamethasone 40 mg, and IVIG 24 g	5 days	Both	Discontinued	[40]
10×10^9/L—173×10^9/L	Dexamethasone 40 mg/kg, IVIG 400 mg/kg, platelet transfusion (1 unit), rituximab, eltrombopag, romiplostim, methylprednisolone, and plasma exchange	>25 days	Romiplostim	Continued	[14]
$<1\times10^9$/L—66×10^9/L Highest point was not mentioned	Steroids, platelet and red blood cell transfusion, eltrombopag, cyclosporine, rituximab, IVIG, and splenectomy	–	–	–	[9]
$<1\times10^9$/L	Platelet transfusion, prednisolone 1 mg/kg, IVIG, pulse methylprednisolone, romiplostim, danazol, and vincristine	22 days	Romiplostim, danazol, and vincristine	Not specified	[41]
1×10^9/L—300×10^9/L	Platelet transfusion (77 units), intravenous steroids, IVIG, rituximab, eltrombopag, romiplostim, plasmapheresis, cyclosporine, and splenectomy	56 days	Splenectomy	Continued	[42]

Abbreviation: IVIG, intravenous immunoglobulin.

[a]All platelet counts were converted to SI units for comparison.

Looking at similarities and differences between the refractory cases, we noticed that in 4 out of 5 cases the patient received the Pfizer-BioNTech vaccine and 1 in 5 received the Moderna vaccine. Patient age ranged from 20 to 74 years. Most of the patients developed ITP within 1 to 14 days post vaccination. Most of them also failed to respond to platelet transfusion, intravenous steroids, IVIG, rituximab, eltrombopag, and romiplostim. Two patients failed to respond to plasma exchange in addition to the previously mentioned lines of therapy.[14,42] As for medications that resulted in response: 1 patient responded to mycophenolate mofetil; 2 responded to splenectomy; 1 responded to vincristine, romiplostim, and danazol; and 1 responded to romiplostim.[9,14,24,41,42] Improvement was seen from 22 to 42 days. Our case failed to respond to intravenous steroids, IVIG, rituximab, anti-RhD immunoglobulin, and eltrombopag.

Although COVID-19 vaccines are mostly safe for patients with chronic ITP, they have been reported to cause exacerbations in such patients; and researchers recommend practicing caution and monitoring patients of chronic ITP after vaccination.[12,43,44] In one case series, for instance, 52 patients of chronic ITP were followed up after receiving the COVID-19 vaccine, and 12% showed a 96% drop in their platelet count within 5 days of vaccination.[43] In another case series of 117 chronic ITP patients, 33 developed exacerbations with over 50% drops in platelet count.[12] Those who were susceptible to exacerbation of their ITP were patients with history of splenectomy and the use of 5 or more lines of therapy.[12]

As per the Food and Drug Administration (FDA), the risk of ITP within 42 days after vaccination is very low. The Centers for Disease Control and Prevention recommends continuous monitoring in patients with additional risk and that clinicians have a full discussion with patients of chronic ITP on the risks of vaccination and possible need for platelet monitoring after vaccination.[45] For example, the rate of ITP induced by the Pfizer-BioNTech vaccine

was 2 per million, while the rate of ITP induced by the AstraZeneca vaccine was 8 to 10 per million.[22]

According to the Vaccine Adverse Event Reporting System, the rate of thrombocytopenia in general was 0.80 per million doses for both the Pfizer-BioNTech and Moderna vaccines, which is not greater than the number of expected ITP cases; thus, it does not pose a safety concern.[2] In one series that reported the occurrence of ITP among chronic ITP patients and healthy individuals who received the Pfizer-BioNTech and Moderna vaccines, the incidence of de novo ITP or ITP exacerbation was 15 per 18,841,309 people vaccinated with the Pfizer-BioNTech vaccine and 13 per 16,260,102 people vaccinated with the Moderna vaccine.[9] However, in Scotland a nested incident-matched case control study was conducted, and the incidence of ITP in association with AstraZeneca vaccine was 1.13 cases per 100,000 doses.[46] Similarly, in Australia ITP was the second most commonly reported hematological adverse event after receiving the AstraZeneca vaccine.[22]

In addition, a study from Thailand reported that the risk of ITP post ChAdOx1 nCoV-19 vaccine was similar to that of the MMR vaccine, at least 1 per 36,000 doses.[10] In our review there was 1 patient who received the Pfizer-BioNTech vaccine 1 day before the onset of ITP and the MMR vaccine 2 months prior to ITP onset.[11]

As for mortality due to COVID-19-vaccine-induced ITP, one case series reported 2 fatalities resulting from intracranial hemorrhage caused by ITP, acute myocardial infarction, and pulmonary embolism.[9]

Despite the rarity of the occurrence of ITP post COVID-19 vaccination, it is important to consider those who are susceptible to developing severe, refractory, and fatal ITP, such as patients with a family history, history of splenectomy, or history of refractory ITP requiring multiple lines of therapy.[12]

AUTHOR CONTRIBUTIONS

Hatem Mahmoud Alahwal: Conceptualization; methodology; supervision; writing – original draft; writing – review and editing. **Mansour Hani Alsharif:** Conceptualization; writing – original draft; writing – review and editing. **Mada Hani Alsharif:** Data curation; methodology; writing – original draft. **Abdullah Talal Almohammadi:** Investigation; methodology. **Adel Fahad Al-Marzouki:** Investigation; methodology. **Ahmed Saleh Barefah:** Conceptualization; data curation; investigation. **Salem Mohammad Bahashwan:** Supervision; writing – review and editing. **Osman Omer Radhwi:** Investigation; writing – review and editing. **Ghazi Abdullah Damanhouri:** Conceptualization; supervision.

FUNDING INFORMATION

No external funding was received.

CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest regarding the publication of this paper.

DATA AVAILABILITY STATEMENT

The data supporting this case report are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Hatem Mahmoud Alahwal https://orcid.org/0000-0003-3961-0765
Abdullah Talal Almohammadi https://orcid.org/0000-0002-1489-459X
Adel Fahad Al-Marzouki https://orcid.org/0009-0003-7066-1939
Ahmed Saleh Barefah https://orcid.org/0000-0003-2009-3817
Salem Mohammad Bahashwan https://orcid.org/0000-0002-5635-230X
Osman Omer Radhwi https://orcid.org/0000-0002-1578-3998
Ghazi Abdullah Damanhouri https://orcid.org/0000-0001-7127-2597

REFERENCES

1. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: a critical review of published reports. *Am J Hematol* [Internet]. 2010;85(3):174-180. doi:10.1002/ajh.21616
2. Clinical updates in adult immune thrombocytopenia|Elsevier Enhanced Reader [Internet]. 2022 https://reader.elsevier.com/reader/sd/pii/S0006497120333541?token=15798BE439D656460021D89790C8118330D4074C8EDCB2A92F976DD27CA7CC38EC67717C6B25B4A6F2CFF04962846D68&originRegion=eu-west-1&originCreation=20220809170411
3. Thrombocytopenia in Patients with Chronic Hepatitis C Virus Infection—PMC [Internet]. 2022. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5333732/
4. The Role of Cytomegalovirus in Immune Thrombocytopenia Purpura|Blood|American Society of Hematology [Internet]. 2022 https://ashpublications.org/blood/article/110/11/2101/56101/The-Role-of-Cytomegalovirus-in-Immune
5. Nascimento FG, Tanaka PY. Thrombocytopenia in HIV-infected patients. *Indian J Hematol Blood Transfus* [Internet].

2012;28(2):109-111. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3332279/
6. Black C, Kaye JA, Jick H. MMR vaccine and idiopathic thrombocytopaenic purpura. *Br J Clin Pharmacol* [Internet]. 2003;55(1):107-111. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884189/
7. Shah SRA, Dolkar S, Mathew J, Vishnu P. COVID-19 vaccination associated severe immune thrombocytopenia. *Exp Hematol Oncol*. 2021;10(1):42.
8. Kim G, Choi EJ, Park HS, Lee JH, Lee JH, Lee KH. A case report of immune thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *J Korean Med Sci*. 2021;36(43):e306.
9. Welsh KJ, Baumblatt J, Chege W, Goud R, Nair N. Thrombocytopenia including immune thrombocytopenia after receipt of mRNA COVID-19 vaccines reported to the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*. 2021;39(25):3329-3332.
10. Uaprasert N, Panrong K, Tungjitviboonkun S, et al. ChAdOx1 nCoV-19 vaccine-associated thrombocytopenia: three cases of immune thrombocytopenia after 107720 doses of ChAdOx1 vaccination in Thailand. *Blood Coagul Fibrinolysis*. 2022;33(1):67-70.
11. Thomas W, Albano A, Kirkel D, Rouhizad N, Arinze F. Immune thrombocytopenic purpura following administration of mRNA-based SARS-CoV-2 and MMR vaccinations: a cautionary tale. *Case Rep Infect Dis*. 2021;2021:2704249.
12. Lee EJ, 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(10):1564-1574.
13. Koch M, Fuld S, Middeke JM, Fantana J, von Bonin S, Beyer-Westendorf J. Secondary immune thrombocytopenia (ITP) associated with ChAdOx1 Covid-19 vaccination—a case report. *TH Open*. 2021;5(3):e315-e318.
14. Helms JM, Ansteatt KT, Roberts JC, et al. Severe, refractory immune thrombocytopenia occurring after SARS-CoV-2 vaccine. *J Blood Med*. 2021;12:221-224.
15. David P, Dotan A, Mahroum N, Shoenfeld Y. Immune thrombocytopenic purpura (ITP) triggered by COVID-19 infection and vaccination. *Isr Med Assoc J*. 2021;23(6):378-380.
16. Chong KM, Yang CY, Lin CC, Lien WC. Severe immune thrombocytopenia following COVID-19 vaccination (Moderna) and immune checkpoint inhibitor. *Am J Emerg Med*. 2022;56:395.e1-395.e3.
17. Immune thrombocytopenia secondary to COVID-19: a systematic review|SpringerLink [Internet]. 2022. doi:10.1007/s42399-020-00521-8
18. ASH-ITP-Pocket-Guide-FOR-WEB-1204.pdf [Internet]. 2022 https://www.hematology.org/-/media/Hematology/Files/Education/Clinicians/Guidelines-Quality/Documents/ASH-ITP-Pocket-Guide-FOR-WEB-1204.pdf
19. Song F, Al-Samkari H. Management of Adult Patients with immune thrombocytopenia (ITP): a review on current guidance and experience from clinical practice. *J Blood Med* [Internet]. 2021;12:653-664. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8323851/
20. COVID-19 and ITP—Hematology.org [Internet]. 2022 https://www.hematology.org:443/covid-19/covid-19-and-itp
21. Kenney A, Adhikari A. Immune thrombocytopenia in a 68-year-old woman after COVID-19 vaccination. *Clin Case Rep*. 2021;9(8):e04689.
22. Gordon SF, Clothier HJ, Morgan H, et al. Immune thrombocytopenia following immunisation with Vaxzevria ChadOx1-S (AstraZeneca) vaccine, Victoria, Australia. *Vaccine*. 2021;39(48):7052-7057.
23. Jasaraj RB, Shrestha DB, Gaire S, Kassem M. Immune thrombocytopenic purpura following Pfizer-BioNTech COVID-19 vaccine in an elderly female. *Cureus*. 2021;13(8):e16871.
24. Ghosh AK, Bhushan S, Lopez LDR, Sampat D, Salah Z, Hatoum CA. BNT162b2 COVID-19 vaccine induced immune thrombocytopenic purpura. *Case Rep MedCase Rep Med*. 2022;2022:5603919.
25. Nutalapati S, Gupta G, Hildebrandt GC. Rapid response to mycophenolate mofetil in combination with romiplostim in a case of severe refractory immune thrombocytopenia post COVID-19 vaccination. *Clin Case Rep*. 2021;9(11):e05035.
26. Ogai A, Yoshida R, Yuasa C, Chin K, Fujimaki K, Nakajima H. Acute immune thrombocytopenia following SARS-CoV-2 vaccination in chronic ITP patients and a healthy individual. *Int J Hematol*. 2022;115(2):293-295.
27. Shonai T, Kimura F, Watanabe J. Severe immune thrombocytopenia after COVID-19 vaccination: two case reports and a literature review. *Intern Med*. 2022;61(10):1581-1585.
28. Sivaramakrishnan P, Mishra M. Vaccination-associated immune thrombocytopenia possibly due to ChAdOx1 nCoV-19 (Covishield) coronavirus vaccine. *BMJ Case Rep*. 2022;15(3):e249237.
29. Cooper KM, Switzer B. Severe immune thrombocytopenic purpura after SARS-CoV-2 vaccine. *Arch Clin Cases*. 2021;8(2):31-36.
30. King ER, Towner E. A case of immune thrombocytopenia after BNT162b2 mRNA COVID-19 vaccination. *Am J Case Rep*. 2021;22:e931478.
31. Battegay R, Istampoulouoglou I, Holbro A, et al. Immune thrombocytopenia associated with COVID-19 mRNA vaccine tozinameran—a clinical case and global pharmacovigilance data. *Swiss Med Wkly*. 2021;151:w30084.
32. Liao PW, Teng CLJ, Chou CW. Immune thrombocytopenia induced by the chimpanzee adenovirus-vectored vaccine against SARS-CoV-2 infection. *Vaccines (Basel)*. 2021;9(12):1486.
33. Al-Ahmad M, Al Rasheed M, Shalaby N, Rodriguez-Bouza T, Altourah L. Immune thrombocytopenia (ITP): relapse versus de novo after COVID-19 vaccination. *Clin Appl Thromb Hemost*. 2022;28:10760296211073920.
34. Baba Y, Sakai H, Kabasawa N, Harada H. Successful treatment of immune thrombocytopenic purpura with intracranial hemorrhaging and duodenal bleeding following SARS-CoV-2 vaccination. *Intern Med*. 2022;61(12):1891-1895.
35. Malayala SV, Papudesi BN, Sharma R, Vusqa UT, Raza A. A case of idiopathic thrombocytopenic purpura after booster dose of BNT162b2 (Pfizer-Biontech) COVID-19 vaccine. *Cureus*. 2021;13(10):e18985.
36. Bae DH, Kim M, Lee DI, et al. Simultaneous occurrence of immune-mediated thrombocytopenia and myocarditis after mRNA-1273 COVID-19 vaccination: a case report. *J Korean Med Sci*. 2022;37(21):e169.

37. Malayala SV, Mohan G, Vasireddy D, Atluri P. Purpuric rash and thrombocytopenia after the mRNA-1273 (Moderna) COVID-19 vaccine. *Cureus* [Internet]. 2022;13(3):e14099 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7996471/
38. Akiyama H, Kakiuchi S, Rikitake J, et al. Immune thrombocytopenia associated with Pfizer-BioNTech's BNT162b2 mRNA COVID-19 vaccine. *IDCases*. 2021;25:e01245.
39. Idogun PO, Ward MC, Teklie Y, Wiese-Rometsch W, Baker J. Newly diagnosed idiopathic thrombocytopenia post COVID-19 vaccine administration. *Cureus*. 2021;13(5):e14853.
40. Fueyo-Rodriguez O, Valente-Acosta B, Jimenez-Soto R, et al. Secondary immune thrombocytopenia supposedly attributable to COVID-19 vaccination. *BMJ Case Rep*. 2021;14(5):e242220.
41. Saito K, Ichikawa S, Hatta S, Katsuoka Y, Harigae H, Izumi T. Vincristine therapy for severe and refractory immune thrombocytopenia following COVID-19 vaccination. *Ann Hematol* [Internet]. 2022;101(4):885-887. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8485970/
42. Koilpillai S, Dominguez B, Khan A, Carlan S. Severe case of refractory immune thrombocytopenic purpura requiring splenectomy after the COVID-19 vaccine. *BMJ Case Rep [Internet]*. 2022;15(6):e250153. doi:10.1136/bcr-2022-250153
43. Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. *Br J Haematol* [Internet]. 2021;195(3):365-370. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8239625/
44. Portuguese AJ, Sunga C, Kruse-Jarres R, Gernsheimer T, Abkowitz J. Autoimmune- and complement-mediated hematologic condition recrudescence following SARS-CoV-2 vaccination. *Blood Adv*. 2021;5(13):2794-2798.
45. tjordan_drupal. FDA reports increased risk of immune thrombocytopenia after J&J vaccine|AHA News [Internet]. 2022 https://www.aha.org/news/headline/2022-01-12-fda-reports-increased-risk-immune-thrombocytopenia-after-jj-vaccine
46. Simpson CR, Shi T, Vasileiou E, et al. First-dose ChAdOx1 and BNT162b2 COVID-19 vaccines and thrombocytopenic, thromboembolic and hemorrhagic events in Scotland. *Nat Med* [Internet]. 2021;27(7):1290-1297. https://www.nature.com/articles/s41591-021-01408-4

How to cite this article: Alahwal HM, Alsharif MH, Alsharif MH, et al. COVID-19-induced immune thrombocytopenia management approach: A case report and literature review. *Clin Case Rep*. 2024;12:e9070. doi:10.1002/ccr3.9070