Vaccine-induced immune thrombocytopaenia and thrombosis (VITT) after COVID-19 vaccination

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SUMMARY

COVID-19 represents a global health emergency, causing significant morbidity and mortality. Multiple vaccines have been distributed worldwide to control the spread of this pandemic. Several reports of thrombosis and thrombocytopaenia have been described after vaccination. These have been termed vaccine-induced immune thrombocytopaenia and thrombosis (VITT). We report a fatal case of VITT after receiving the first dose of Ad26.COV2.S vaccine. A man in his 30s developed thrombocytopaenia, massive haemoperitoneum due to spleen rupture and extensive portal and femoral vein thrombosis. The patient rapidly developed multiple organ failure and died. We attributed this condition to the vaccine due to the temporal relationship, presence of thrombosis and thrombocytopaenia, high levels of platelet factor 4 antibodies and exclusion of other diagnoses. Healthcare providers should be aware of such rare but fatal complications of COVID-19 immunisation, as early diagnosis of VITT may improve prognosis by allowing timely appropriate treatment.

BACKGROUND

SARS-CoV-2 causes COVID-19. COVID-19 is a contemporary pandemic disease. In an attempt to respond to this global health threat, multiple vaccines have been produced and distributed worldwide.[1]

Reviews showed that these vaccines have an acceptable safety and effective profile.[2] However, there have been several reports of unusual thrombotic events combined with thrombocytopaenia days after vaccination.[3 4]

These clinical occurrences have been termed vaccine-induced thrombocytopaenia and thrombosis (VITT), similar to those associated with autoimmune heparin-induced thrombocytopaenia (HIT) but triggered by COVID-19 vaccination.[1] Two adenovirus vector COVID-19 vaccines have been associated with VITT: ChAdOx1 nCoV-19 and Ad26.OCV2.S.[5] The exact incidence of VITT is still unknown, although it appears to be rare.[1 6] There are already some reports of fatal VITT.[7]

The pathophysiology of VITT is still not completely understood but involves an increase in antibodies to platelet factor 4 (PF-4), not heparin dependent, triggering massive platelet activation, aggregation and consumption.[6 8 9]

The main laboratory findings are thrombocytopaenia, highly elevated D-dimers, reduced fibrinogen, and positive PF-4 antibodies identified by ELISA.[1] Treatment includes intravenous Ig and anticoagulation while avoiding platelet transfusion.[3]

We describe a fatal case of VITT with severe thrombocytopaenia after receiving the first dose of the Ad26.COV2.S vaccine.

Clinicians should be familiar with the clinical presentation, pathophysiology, diagnostic criteria and management of this rare but potentially fatal side effect of COVID-19 vaccination. In the largest published cohort study of 220 patients the estimated mortality rate associated with VITT was 22%.[7] Also, a recent metanalysis, which included 664 patients, reported a mortality rate up to 29%.[10] There is no statistically significant difference in mortality between the different COVID-19 vaccines.[5] Early diagnosis and treatment may help provide patients with a more favourable outcome.

CASE PRESENTATION

A caucasian man in his 30s presented to the emergency department with progressively worsening abdominal pain for the last 48 hours. There were no allergies, history of trauma, recent surgery or immobilisation.

On physical examination, the patient was conscious and collaborative. His Glasgow Coma Scale was 15. He was pale, cold and peripheral perfusion was poor. The blood pressure was 101/60 mm Hg, pulse 150 beats per minute (bpm) in sinus rhythm. The peripheral oxygen saturation was 92% on room air. Abdominal palpation revealed diffuse abdominal pain.

Laboratory tests revealed severe thrombocytopaenia with a platelet count of 13×10^9/L (reference range, 130–400$\times10^9$/L), elevated D-dimers (38.15 µg/mL—reference value <0.23 µg/mL) and acute liver failure (Aspartate transaminase (AST) 398 UI/L and Alanine aminotransferase (ALT) 1131 UI/L, reference value <40 UI/L and <50 UI/L, respectively) were found on admission to the hospital. Haemoglobin, white cell count, plasmatic fibrinogen levels and coagulation profile were unremarkable. The blood smear showed platelet aggregation.

Ultrasonography and CT scan of the abdomen and pelvis showed a massive haemoperitoneum secondary to splenic and hepatic rupture and extensive portal and right femoral vein thrombosis (figure 1). Urgent laparotomy confirmed haemoperitoneum, and 3000 mL of blood were drained from the peritoneal cavity. Splenectomy and peritoneal lavage were also performed. Postoperatively the patient was transferred to the intensive care unit. His clinical condition further deteriorated with progressive haemorrhagic shock evolving into intravascular disseminated coagulation, managed with a total of four units of packed red blood cells, three units of fresh-frozen plasma, ten units of platelets, one unit of cryoprecipitate, three units of fibrinogen concentrate and 1 g of tranexamic acid.

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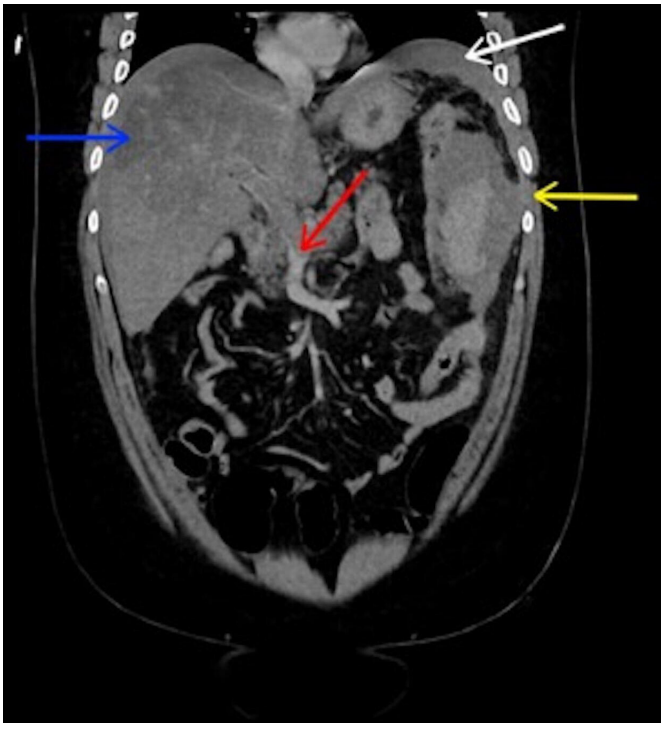

Figure 1 Contrast-enhanced CT scan of the abdomen and pelvis in coronal view showing portal vein thrombosis (red arrow), haemoperitoneum (white arrow), heterogeneous spleen (yellow arrow) and liver with multiple areas of parenchymal devascularisation and haemorrhage (blue arrow).

A closer review of the patient's medical history revealed that he had received the first dose of Ad26.COV2.S COVID-19 vaccine 10 days before hospital admission. Apart from obesity and smoking history, there were no other previous medical conditions and no long-term medication. Further investigation ruled out possible underlying causes of thromboembolic events and a history of recent heparin therapy was absent. The patient had no clinical or epidemiological history consistent with SARS-CoV2 infection, and screening for COVID-19 was negative.

As we suspected VITT as the most likely diagnosis, an assay test for detecting PF-4 complex antibodies was performed. Prompt treatment was started with Ig (intravenous 1 g/kg body weight), glucocorticoids (methylprednisolone 1 mg/kg body weight) and anticoagulation with bivalirudin 250 mg.

One week postmortem, the result of the levels of PF-4 antibodies returned as positive (by ELISA—8.46, with a reference value <1.00) supporting VITT as the most probable diagnosis.

DIFFERENTIAL DIAGNOSIS

Other causes of thrombosis were considered, such as thrombotic thrombocytopaenic purpura (TTP). Diagnosis of TTP typically correlates with severely reduced ADAMTS13 activity. In this case, ADAMTS13 activity was not evaluated, but the absence of schistocytes or microangiopathic haemolytic anaemia on the blood film ruled out the possibility of TTP. Underlying haematological malignancies were excluded. There was no history of trauma or surgery.

Classic HIT is characterised by decreased platelet count with arterial or venous thrombosis following heparin administration with a tendency to improve once heparin is withdrawn. The presence of PF-4 antibodies supports the presumptive diagnosis of HIT, however, the absence of recent heparin exposure makes the occurrence of this syndrome unlikely.

Other causes for thrombocytopaenic thrombosis as thrombophilia were ruled out, the lupus-anticoagulant, antibodies to cardiolipin, and β2-glycoprotein revealed normal laboratory results. Autoimmune testing for complement levels (C3 and C4), antinuclear antibodies, extractable nuclear antibodies, antineutrophil cytoplasmatic antibodies, rheumatoid antibody, antidouble stranded-DNA antibodies and cryoglobulins were within the normal range.

Blood and urine cultures were negative. Testing for hepatitis B and C, HIV, cytomegalovirus, syphilis, Herpes simplex and SARS-CoV-2 RT-PCR (reverse transcription-PCR) revealed negative results.

OUTCOME AND FOLLOW-UP

The patient rapidly developed multiple organ failure with acute kidney injury and fulminant hepatic failure leading to his death 48 hours after admission.

DISCUSSION

As illustrated in this case, VITT is a potentially life-threatening disorder, and the clinician must be wary of the diagnosis.

This syndrome mainly occurs in healthy young adults (<55 years), 5–30 days after receiving the COVID-19 vaccine.[3 9] Signs and symptoms are dependent on the location of the thrombosis. Persistent headaches, focal neurological symptoms and seizures can indicate cerebral venous sinus thrombosis (CVST) or arterial stroke; shortness of breath and chest pain can manifest pulmonary embolism or cardiac infarction; abdominal pain suggests a portal vein thrombosis, and lower extremities swelling and erythema may be indicative of deep vein thrombosis.[8]

This severe condition is characterised by an unusual location of thrombosis, including CVST, portal, splanchnic and hepatic vein thrombosis. More typical thrombotic sites such as deep vein thrombosis and pulmonary embolism have also been reported.[4 11]

Complete blood count, coagulation profile, D-dimer, fibrinogen and anti-PF4 IgG (ELISA method) antibody levels should be checked. Moreover, an appropriate imaging modality such as a CT scan or colour Doppler ultrasound should be performed in accordance with symptoms to search for thrombosis at unusual sites.

This diagnosis is confirmed by a positive PF-4 ELISA in the appropriate clinical context of post-COVID-19 vaccine thrombosis and/or thrombocytopaenia (including lack of proximate heparin exposure to explain the positive ELISA), typically with an OD >2.00, or by a positive functional assay (SRA, or PF4-enhanced SRA, or another PF4-dependent functional assay).[12] The clinical diagnosis of VITT can be established according to five criteria, which are: the onset of symptoms 5–30 days after COVID-19 vaccination, the presence of thrombosis, thrombocytopaenia (platelet count $<150\times10^9$/L), a D-dimer level greater than 4000 µg/L, and the presence of antibodies to PF4 detected by ELISA. Our patient had a D-dimer level between 2000 and 4000 µg/L, which together with all the other criteria, made VITT a highly probable diagnosis.[7]

Our patient had no prior risk factors for thrombosis other than obesity and smoking. His initial symptom of abdominal pain and the investigation finding highlights the need for early awareness and recognition of VITT after administration of the Ad26.COV2.S vaccine.

The management of patients with confirmed or suspected VITT consists of full therapeutic anticoagulation, ideally on a non-heparin regimen, as this might cause further coagulopathy. It has not been fully established whether heparin exacerbates the clinical presentation, but for now, anticoagulation therapy should involve non-heparin-based treatments, such as fondaparinux, argatroban or

bivalirudin.[3 13 14] Alternatively, the use of direct oral anticoagulants can be considered. Platelets should not be transfused due to continuous autoimmune destruction with further coagulation cascade activation, except in the setting of life-threatening bleeding, as occurred in our patient. In VITT, administration of intravenous Ig (1–2 g/kg/day for 2 days) and high-dose glucocorticoids may improve the platelets count.[12] The intravenous Ig blocks platelet receptors and may down-regulate platelets activation, resulting in a rapid rise in the platelet count.[15] Transfusion to correct hypofibrinogenaemia is also recommended for those with a fibrinogen concentration of less than 1–5 g/L.[14] Plasma exchange can be used in refractory disease with severe thrombocytopaenia with multiple thrombosis. In case of bleeding complications, cryoprecipitate or fresh frozen plasma may be used to correct coagulopathy.[3]

In our case, intravenous Ig 1 g/kg was administered. Despite the initial improvement on the thrombocytopaenia, the condition progressed to a fulminant hepatic failure with consumptive coagulopathy, severe thrombocytopaenia and bleeding diathesis.

VITT is a rare syndrome, but it is associated with high mortality and morbidity. Severe thrombocytopaenia, cerebral venous sinus thrombosis, intracranial haemorrhage and laboratory markers of severe coagulation activation are related to increased mortality. Prognosis may be improved with earlier recognition hence the importance of clinical suspicion in this setting.

Besides potential side effects, vaccination remains the most effective way to reduce severe or fatal disease in COVID-19.

Learning points

- This case should alert healthcare providers to the possibility of fatal complications of vaccine-induced immune thrombocytopaenia and thrombosis (VITT) after COVID-19 vaccination estimated to occur in up to 29% of patients with VITT.
- The high mortality rate associated with VITT may decrease with earlier recognition and improved intervention.
- The risk of VITT remains far lower than severe COVID-19, therefore, the benefit of vaccination still exceeds the risks.

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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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