A case of ChAdOx1 vaccine-induced thrombocytopenia and thrombosis syndrome leading to bilateral adrenal haemorrhage and adrenal insufficiency

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Summary

Vaccine-induced thrombosis and thrombocytopenia (VITT) after vaccination against SARS-CoV-2 with the adenoviral vector-based vaccines ChAdOx1 and Ad26.COV2.S has been associated with adrenal pathology, such as bilateral adrenal vein thrombosis, adrenal cortex haemorrhage and adrenal insufficiency in 6% of patients. We report the case of a 23-year-old woman who presented at 8 days after ChAdOx1 vaccination with a low platelet count of 43 × 10^9/L, raised d-dimers >100 000 ng/mL and multiple lobar and segmental pulmonary emboli. Anti-platelet factor 4 antibodies were detected confirming definite VITT in accordance with the UK diagnostic criteria. At 16 days post-vaccine, further imaging showed bilateral adrenal haemorrhage, non-occlusive splenic vein thrombosis and right ventricular thrombosis. Her cortisol level was <25 nmol/L. She was treated with anticoagulation, plasmapheresis, immunosuppression and steroid replacement. She had high anti-spike titre and positive anti-nucleocapsid titres for SARS-CoV-2. She developed seizures secondary to posterior reversible encephalopathy, requiring intensive care. After 4 weeks in hospital, she was discharged on warfarin, hydrocortisone and fludrocortisone replacement. Short synacthen tests 3 and 9 months later showed no recovery of adrenal function, although magnetic resonance imaging of the adrenal glands showed resolving adrenal haemorrhage. Adrenal insufficiency secondary to bilateral adrenal vein thrombosis and adrenal haemorrhage should be suspected in patients with VITT and treated promptly. Adrenal vein thrombosis can occur either as the initial presentation of VITT or days to weeks after the development of thrombosis in other sites. Further studies are required to provide insight on adrenal function recovery after VITT.

Learning points:

- Adrenal insufficiency secondary to bilateral adrenal vein thrombosis and adrenal cortex haemorrhage should be suspected in patients with vaccine-induced thrombosis and thrombocytopenia (VITT) and treated promptly.
- Adrenal vein thrombosis can occur as the initial presentation of VITT or even days to weeks later after the development of thrombosis in other more classic sites (e.g. pulmonary or cerebral vasculature).
- Completion of vaccination schedule against SARS-CoV-2 post-VITT using an mRNA-based vaccine should be recommended to patients post-VITT as mRNA-based vaccines have not been associated with VITT but confer protection against SARS-CoV-2.
- There is paucity of data regarding the potential for recovery of adrenal function after bilateral adrenal haemorrhage in the context of VITT, and thus, more studies are needed to inform clinical practice.
- The need for disease registries for rare conditions, such as VITT, is crucial as direct cooperation and sharing of information by clinicians might enable quicker identification of disease patterns than would have been possible via established reporting tools of adverse events.
Background

Vaccine-induced thrombosis and thrombocytopenia (VITT) refers to a markedly prothrombotic syndrome associated with low platelets occurring 5–30 days after vaccination against SARS-CoV-2 with the adenoviral vector-based vaccines ChAdOx1 and Ad26.COV2.S (1). Similar to heparin-induced thrombocytopenia and thrombosis (HITT), platelet-activating antibodies are implicated in the pathogenesis of VITT via interactions with platelet factor-4 (PF-4) (1). Thrombosis might involve the pulmonary or cerebral vasculature as well as unusual anatomical sites, such as the adrenal veins, splenic and mesenteric veins (2).

The causal association between SARS-CoV-2 vaccination and adrenal insufficiency is of clinical interest for the acute physician and endocrinology specialist caring for patients presenting with VITT after SARS-CoV-2 vaccination. Adrenal vein thrombosis and haemorrhage should be considered and treated promptly in patients presenting with non-specific symptoms after SARS-CoV-2 vaccination, such as lethargy, dizziness, abdominal pain, hypotension and tachycardia, as this constellation of symptoms could signify adrenal crisis.

We report a case of VITT after the first dose of SARS-CoV-2 vaccination with the ChAdOx1 vaccine. The patient developed thrombosis with multiorgan involvement, including bilateral adrenal vein thrombosis, leading to adrenal haemorrhage and acute primary adrenal insufficiency. No recovery of adrenal function was noted at 9 months follow-up, and the patient remained on glucocorticoid and mineralocorticoid replacement.

Case presentation

A 23-year-old woman presented to her local hospital with acute pleuritic chest pain, fever and headaches at day 8 after the first vaccination dose against SARS-CoV-2 with the ChAdOx1 vaccine. Her medical history was significant for a BMI 35 kg/m². Family history identified venous thromboembolism in aunt, cousin and great-grandparents but not in any first-degree relative. She was a non-smoker, consumed alcohol socially and was not using any recreational substances. Her initial diagnosis was multiple lobar and segmental pulmonary emboli with associated thrombocytopenia. She was clinically well and was discharged home on apixaban.

The following day the patient returned to her local hospital with worsening respiratory symptoms. She was admitted to hospital for treatment of pulmonary emboli, lower respiratory tract infection and thrombocytopenia. In view of new-onset seizures, the patient required admission to the intensive care unit and was transferred to Oxford University Hospitals NHS Trust for further management.

Investigation

On initial presentation, the patient’s platelet count was $43 \times 10^9/L$ (150–450 x $10^9/L$) and d-Dimers were $>100000$ ng/mL (<500). Inflammatory markers and urea and electrolytes were within normal range (Table 1). Computed tomography-pulmonary angiogram (CT-PA) showed multiple lobar and segmental pulmonary emboli. CT venogram ruled out cerebral thrombosis.

In view of clinical deterioration and new haemodynamic instability, CT-PA was repeated at day 16 post-vaccination, showing possible bilateral adrenal haemorrhage, pulmonary embolism, consolidation and bilateral parapneumonic effusions, not suspicious for empyema. CT chest, abdomen and pelvis (CT CAP) the following day confirmed the presence of bilateral adrenal haemorrhage secondary to bilateral adrenal vein thrombosis and also revealed additional non-occlusive splenic vein thrombosis and right ventricular thrombosis. MRI of the adrenal glands was performed the same day confirming bilateral adrenal haemorrhage (Fig. 1A and B). The radiological finding of bilateral adrenal haemorrhage was consistent with the clinical picture of adrenal insufficiency leading to new clinical deterioration and haemodynamic instability. This correlated with random cortisol level that day which was <25 nmol/L (6:00–10:00 h: 133–537).

In addition to thrombocytopenia, the blood film showed fragmented red blood cells at day 17 which were not present at initial presentation at day 8 post-vaccination. The differential diagnosis of microangiopathic haemolytic anaemia included thrombotic thrombocytopenic purpura (TTP) and catastrophic antiphospholipid syndrome (CAPS). Thus, the patient was treated empirically for TTP/CAPS. HIT AcuStar was negative. One week later, the ADAMTS13 result was reported as negative. Anti-PF4 antibodies were confirmed by ELISA. The aforementioned laboratory results, along with reports published at that time by the Medicines and Healthcare products Regulatory Agency and the European Medicines Agency on VITT related to the adenoviral vector-based vaccines, pointed to the differential diagnosis towards the diagnosis of VITT (3).

An MRI brain was undertaken due to new-onset seizures and showed bilateral cortical and juxtacortical signal changes in the frontal and parietal cortex and bilateral cerebellar hemispheres. CT venogram ruled out cerebral...
thrombosis. On repeat MRI 1 month later, these changes had resolved completely, pointing towards a diagnosis of posterior reversible encephalopathy syndrome, rather than embolic phenomena or stroke.

**Treatment**

On first presentation, the patient was prescribed apixaban for pulmonary emboli and discharged home. Over the course of a week, she developed fulminant VITT. Bilateral adrenal haemorrhage with clinical features consistent with adrenal crisis was diagnosed at day 16 post-vaccination. Intravenous hydrocortisone, fluids and heparin were administered in the High Dependency Unit of the local hospital. After developing seizures secondary to posterior reversible encephalopathy, she required admission to the intensive care unit for mechanical ventilation for 2 days and thus the patient was transferred to our hospital.

In view of the possibility of cross-reactivity of the antibodies that activate platelets in HITT and VITT, the intravenous heparin infusion was switched to argatroban, a direct thrombin inhibitor. Subsequently, the argatroban was switched to fondaparinux and then to warfarin on discharge, aiming for INR 2–3. The patient underwent five cycles of plasma exchange. In terms of adrenal insufficiency treatment, intravenous hydrocortisone 50 mg four times a day was initially administered for 2 days. Then, hydrocortisone was switched to 1 g of methylprednisolone once a day in order to induce immunosuppression as a treatment for VITT. After 3 days, intravenous methylprednisolone was switched to oral prednisolone in view of clinical improvement. The starting dose of prednisolone was 60 mg once a day, which was gradually tapered down to hydrocortisone 20/10/10 mg in a weeks’ time. Fludrocortisone 50 µg once a day was also added. Two days later, hydrocortisone was tapered down to 10/5/5 mg a day maintenance dose.

Despite the high anti-spike titre and positive anti-nucleocapsid titre for SARS-CoV-2, which were indicative of concurrent COVID-19 infection, there was no evidence of COVID pneumonitis and thus no antiviral treatment was indicated.

Finally, in view of complete adrenal insufficiency, she was discharged on hydrocortisone 10/5/5 mg and fludrocortisone 50 µg daily. She received steroid education and an emergency hydrocortisone injection, along with a steroid emergency card. In the outpatient setting, she had postural hypotension and fludrocortisone was initiated and up-titrated to 200 µg once a day with good symptomatic effect. She still remains on anticoagulation treatment with warfarin.

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**Table 1** Haematology and biochemistry investigations.

|                     | Day 8 post-vaccination/initial presentation at hospital | Day 17 post-vaccination adrenal haemorrhage | 9 months follow-up | Units (normal range) |
|---------------------|---------------------------------------------------------|---------------------------------------------|-------------------|----------------------|
| White cell count    | 8.7                                                     | 17.4                                        | 9.8               | 10^9/L (4–11)        |
| Haemoglobin         | 127                                                     | 102                                         | 91                | g/L (115–165)        |
| Platelets           | 43                                                      | 63                                          | 394               | 10^9/L (150–450)     |
| Neutrophils         | 5.8                                                     | 11.8                                        | 6.3               | 10^9/L (2–7)         |
| Lymphocytes         | 2.3                                                     | 4.1                                         | 3.0               | 10^9/L (1–4)         |
| Eosinophils         | 0.1                                                     | 0.2                                         | 0.0               | 10^9/L (0.0–0.4)     |
| Na                  | 138                                                     | 132                                         | 141               | mmo/L (133–146)      |
| K                   | 3.9                                                     | 4.0                                         | 4.0               | mmo/L (3.5–5.3)      |
| Urea                | 2.4                                                     | 4.3                                         | 2.5               | mmo/L (2.5–7.8)      |
| Creatinine          | 64                                                      | 72                                          | 75                | mmo/L (45–84)        |
| d-Dimers            | >100 000                                                | -                                           | -                 | ng/mL (<500)         |
| Cortisol            | -                                                       | <25                                         | -                 | nmol/L (6:00–10:00 h: 133–537) |

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**Figure 1**

MRI of adrenal glands. (A and B) Bilateral ill-defined lesions measuring about 4.8 cm on the right and about 3 cm on the left representing bilateral adrenal haemorrhages. (C and D) Interval decrease in size of both adrenal glands, which remain enlarged and of abnormal morphology, at 3 months follow-up. The findings are consistent with resolving adrenal hemorrhages.
Outcome and follow-up

The patient was followed-up by the endocrinology and haematology teams. Short synacthen tests (SST) at 3 and 9 months after presentation demonstrated a flat response (0' cortisol 37 nmol/L and 30' cortisol 43 nmol/L; at 9 months 0' 41 nmol/L and 30' 53 nmol/L) and ongoing adrenal insufficiency (Table 2). Persistent lack of adrenal response during repeat SST is indicative of persistent adrenal insufficiency. However, repeat assessment of adrenal function was scheduled in 6 months' time.

MRI of the adrenal glands 3 months after initial presentation showed resolving bilateral adrenal haemorrhage, albeit with some reduction of the adrenal gland size (Fig. 1C and D). Repeat CTPA at 3 months interval showed resolution of pulmonary emboli and right ventricular thrombosis.

As the patient only received one dose of SARS-CoV-2 vaccine, completing her vaccination was crucial to ensure immunisation against SARS-CoV-2. Vaccination with an mRNA-based vaccine was deemed to be safe (4). After discussing the risks and benefits with the patient, a plan was made to proceed with the second dose, as the pathogenesis of VITT is unrelated to mRNA-based vaccines.

Discussion

The rollout of national vaccination programmes against SARS-CoV-2 has been the most important countermeasure against the COVID-19 virus globally. Despite the overall safety and efficacy of the adenoviral vector-based vaccines ChAdOx1 and Ad26.COV2.S, the very rare, yet potentially life-threatening, complication of VITT has been described (1). Reporting of adverse events following immunisation is of clinical and public health importance. Identification of adrenal thrombosis leading to adrenal insufficiency was identified early in the post-vaccination surveillance period due to daily meetings of the Expert Haematology panel in the UK where cases were discussed, especially in the context of a rapid vaccination programme rollout during the COVID-19 pandemic.

Adrenal insufficiency secondary to bilateral adrenal vein thrombosis and adrenal haemorrhage after vaccination against SARS-CoV-2 with the adenoviral vector-based vaccines has been reported previously (2). Unlike thrombosis involving more classical sites such as cerebral and pulmonary vasculature, adrenal vein thrombosis is a rare manifestation of VITT. In a recent case series of 294 patients in the UK, adrenal vein thrombosis accounted for approximately 6% of cases of VITT (2). Despite its rarity, if unreconised, adrenal insufficiency related to VITT can be potentially life threatening.

The patient was dependent on hydrocortisone and fludrocortisone replacement therapy on discharge. Repeat SSTs showed no recovery of the adrenal function at 9 months follow-up.

To the best of our knowledge, this case provides the longest follow-up period reported in regards to recovery of adrenal function post-VITT. It is noteworthy that VITT resembles HITT in terms of pathogenesis and clinical presentation with a prominent role of circulating PF-4 antibodies leading to thrombocytopenia and thrombosis. As such, lessons can be learned from studies investigating adrenal recovery post bilateral adrenal haemorrhage secondary to HITT. Although partial or complete recovery of adrenal function after adrenal haemorrhage secondary to HITT has been described, it is uncommon (5). Additionally, in the context of bilateral adrenal vein thrombosis secondary to antiphospholipid syndrome, post-operative hypotension and trauma, partial or complete recovery of adrenal function has only rarely been reported (6, 7). In these studies, the majority of patients end up with atrophic adrenal glands after 5–10 years of follow-up.

There is paucity of data on the percentage of patients recovering adrenal function after adrenal haemorrhage due to vaccination against SARS-CoV-2. Furthermore, there is paucity of data as to whether any favourable or non-favourable factors exist that could potentially affect the recovery of adrenal function. Patient age and gender, earlier initiation of anticoagulation and status of prothrombotic mutations on genetic screening could potentially affect adrenal recovery.

The use of adenoviral vector-based vaccines has largely been superseded by use of mRNA-based vaccines and as such fewer number of VITT cases are likely to be reported in the future.

Adenoviral vector-based vaccines have largely been superseded by mRNA-based vaccines. This is expected to substantially reduce the incidence of VITT associated with adenoviral vector-based vaccines in the future. However, the establishment of a central UK registry for centres to report potential future VITT cases is advised.
The clinical presentation of adrenal insufficiency in the context of VITT might be variable. Adrenal insufficiency presenting as acute abdominal pain and Addisonian features has been described as the initial presentation of VITT (8, 9). However, bilateral adrenal vein thrombosis and adrenal insufficiency can follow days to weeks after initial presentation with thrombosis at other sites (10). Thus, clinicians should have a high index of suspicion for thrombosis development at new sites and should consider close follow-up and monitoring of patients post-VITT. Finally, as patients with adrenal insufficiency can often present with non-specific symptoms, a low threshold for empirical treatment with glucocorticoids is warranted if adrenal insufficiency post-VITT is suspected.

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**Patient's perspective**

While I remember very little of my stay in hospital, I do remember some symptoms that could be put down to the adrenal insufficiency. When I was in hospital, I lost about 12 kg over a 12-day period, extreme fatigue, muscle weakness, low mood and I would get lightheaded when I would sit or stand. While these might not all have been caused by my adrenal issues, they are some of the few issues I dealt with in, around and just after my diagnosis.

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**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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**Patient consent**

Written informed consent was obtained from the patient/patient’s mother for publication of this case report.

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**Author contribution statement**

A P conceived the study and assigned A E to draft the manuscript. A P, D K and S P critically revised the manuscript, providing their expert input. All authors have seen and approved the final manuscript for submission.

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