

Thrombotic thrombocytopenic purpura after ChAdOx1 nCoV-19 vaccine

Hui Ping Lee ^{1,2}, Veena Selvaratnam,³ Jay Suriar Rajasuriar⁴

¹College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

²Medicine, Queen Elizabeth Hospital Birmingham, Birmingham, UK

³Haematology, Hospital Ampang, Ampang, Malaysia

⁴Haematology, Gleneagles Hospital Kuala Lumpur, Kuala Lumpur, Wilayah Persekutuan, Malaysia

Correspondence to

Hui Ping Lee;
leehp1998@gmail.com

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SUMMARY

A 50-year-old Indian woman presented with acute dysphasia, left upper limb numbness and thrombocytopenia 12 days after receiving the ChAdOx1 nCoV-19 vaccine (AstraZeneca/Vaxzevria). MRI of the brain was unremarkable. Microangiopathic haemolytic anaemia with thrombocytopenia was noted on her peripheral blood film. A diagnosis of thrombotic thrombocytopenic purpura (TTP) was confirmed through the findings of absent ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity and markedly raised titre of ADAMTS13 autoantibodies. Prompt treatment with plasma exchange, adjunctive steroids and rituximab was commenced. A remission of TTP was achieved and she was discharged 3 weeks after admission. While other immune-mediated conditions have been documented after receipt of the vaccine, this report highlights the first case of immune-mediated TTP diagnosed after administration of the ChAdOx1 nCoV-19 vaccine.

BACKGROUND

To date, the European Medicines Agency has authorised the use of four COVID-19 vaccines: Comirnaty (Pfizer/BioNTech), Spikevax (Moderna), Vaxzevria (AstraZeneca) and COVID-19 Vaccine Janssen (Johnson and Johnson).¹ The ChAdOx1 nCoV-19 vaccine (AstraZeneca/Vaxzevria) was proven to be effective and to have an acceptable safety profile in clinical trials.² Since April 2021, a newly recognised immune mediated syndrome—vaccine-induced immune thrombotic thrombocytopenia (VITT) or thrombosis with thrombocytopenia syndrome—has been documented in several individuals after administration of the vaccine.^{3,4}

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening thrombotic microangiopathy. This report highlights the first case of immune-mediated TTP diagnosed after administration of the ChAdOx1 nCoV-19 vaccine (Vaxzevria).

CASE PRESENTATION

A 50-year-old Indian woman presented to the emergency department with dysphasia and acute numbness of her left upper limb lasting 15 min. These symptoms had resolved by the time she presented and neurological examination was unremarkable. A bruise was noted on her left anterior chest wall with petechiae on her right shoulder. The patient had received her first dose of ChAdOx1 nCoV-19 vaccine (Vaxzevria) 12 days prior to admission, during which she experienced postvaccination symptoms of fever, headaches and muscle aches

over a period of 5 days. The patient had a medical history of well-controlled hypertension.

Routine blood tests revealed anaemia (haemoglobin 99 g/L, normal range 120–160 g/L) and a low platelet count ($33 \times 10^9/L$, normal range $150\text{--}400 \times 10^9/L$). These early findings led to an initial suspicion of VITT with cerebral thrombosis.

Further tests showed increases in total bilirubin ($29.5 \mu\text{mol/L}$, normal range $<22 \mu\text{mol/L}$; direct bilirubin $11.4 \mu\text{mol/L}$, indirect bilirubin $18.1 \mu\text{mol/L}$) and lactate dehydrogenase (LDH) (359 U/L , normal range $81\text{--}234 \text{ U/L}$). D-dimer was moderately raised (950 mcg/mL). The direct anti-globulin test was negative, whereas prothrombin and activated partial thromboplastin times were normal with normal serum fibrinogen of 3.48 g/L . An elevated reticulocyte count (6.9%) was noted on admission. Antinuclear antibody (ANA) and lupus anticoagulant were negative. Chest radiograph, echocardiogram and MRI of the brain were unremarkable. A COVID-19 reverse transcription-PCR test via a nasopharyngeal swab was negative.

Her blood film confirmed thrombocytopenia with subtle microangiopathic haemolytic anaemia characterised by schistocytes and mild polychromasia (figure 1). This led to a revision of her diagnosis to TTP. The diagnosis of immune-mediated TTP was later confirmed by absent ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity (0%) and a high titre of ADAMTS13 autoantibodies ($>94.93 \text{ u/mL}$) (Technozym ADAMTS-13 Activity ELISA and ADAMTS-13 Inhibitor Assay, Diapharma, West Chester, Ohio, USA). Heparin PF4-dependent antibodies, which are found in almost all patients with VITT, were negative (MBS 3803480 ELISA, MyBioSource, San Diego, USA).

Treatment was commenced in the intensive care unit with a total of 14 daily plasma exchanges (PEXs), along with intravenous methylprednisolone 10 mg/hg/day . The exchange fluid used was fresh frozen plasma and the procedures were well tolerated. An initial decline in platelet count was noted after six sessions of PEX. This was managed with a repeat pulse of intravenous methylprednisolone 500 mg over 3 days, with an optimisation of exchange volume to one plasma volume and initiation of 4 weekly doses of intravenous rituximab 375 mg/m^2 . She received thromboprophylaxis with fondaparinux when platelets were $>50 \times 10^9/L$. Aspirin was commenced when platelet counts were $>100 \times 10^9/L$.



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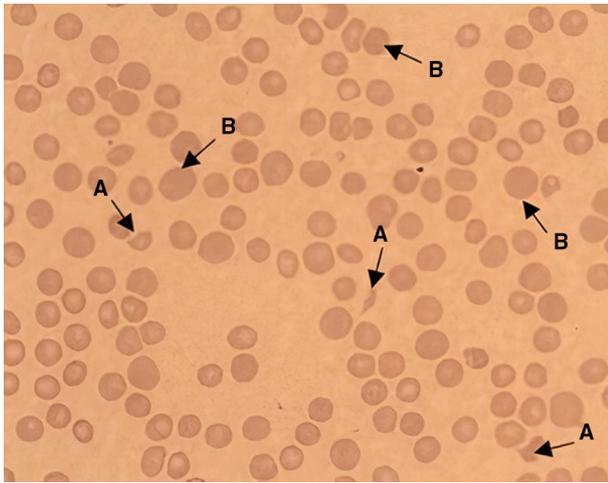


Figure 1 Peripheral blood film showed schistocytes (A) and polychromatic cells (B).

OUTCOME AND FOLLOW-UP

Normalisation of LDH was achieved 4 days after initiation of PEX, whereas a decrease in total bilirubin to 19.6 $\mu\text{mol/L}$ was seen on day 8 of treatment. On day 13 of PEX, normalisation of the platelet count was observed, confirmed on her blood film. The changes in platelet and LDH levels throughout the course of PEX treatment are shown in [figure 2](#). After ceasing PEX, the patient continued to maintain normal platelet counts. She was discharged 3 weeks after admission to hospital on tapering doses of oral prednisolone and aspirin for a month post discharge. Follow-up at 3 weeks post discharge demonstrated complete resolution of symptoms, with a platelet count of $260 \times 10^9/\text{L}$. The patient will continue to be monitored for a relapse in TTP and repeat ADAMTS13 activity and autoantibody assays will be performed after cessation of steroid therapy.

DISCUSSION

The patient presented with focal neurological symptoms 12 days after vaccination with the ChAdOx1 nCoV-19 vaccine. Greinacher *et al* and Schultz *et al* previously described cases of VITT mimicking heparin-induced thrombocytopenia, occurring after the

administration of ChAdOx1 nCoV-19 vaccine.^{3,4} However, a diagnosis of VITT was excluded in this patient due to the absence of thrombosis and antibodies to PF4–polyanion complexes. In addition, markedly elevated D-dimer levels and depleted fibrinogen, expected in VITT, were not present. Moreover, the presence of microangiopathic haemolytic anaemia in the presence of thrombocytopenia and markers of haemolysis strongly raised suspicion of TTP, as these are constant features observed in TTP. The possibility of connective tissue disease with ischaemic manifestations such as systemic lupus erythematosus and antiphospholipid syndrome was excluded by absence of ANA, hypocomplementemia and a negative lupus anticoagulant. A diagnosis of immune TTP was subsequently confirmed by a severe deficiency in the von Willebrand factor cleaving protease, ADAMTS13, in addition to the presence of antibodies against the enzyme.

Without appropriate treatment with timely PEX, TTP is associated with a mortality risk of 80%–90%. Factors including old age, raised LDH levels (10 times the normal upper limit) indicating organ ischaemia and increased cardiac troponin levels ($>0.25 \text{ ng/mL}$) are associated with a higher risk of mortality in spite of adequate management.⁵ The presence of neurological deficits such as in this patient, raising concerns of a cerebrovascular accident, also further increases the patient's mortality risk.

TTP is a medical emergency and treatment should be commenced immediately on recognition, usually in the setting of intensive care. Management primarily involves daily PEX until a normalisation in platelet count and LDH levels are observed. PEX removes ultralarge von Willebrand multimers and the pathogenic autoantibodies and provides replacement of normal ADAMTS13. The use of adjunctive treatment such as steroids and rituximab is indicated in the acute treatment of TTP, by inhibiting the production of ADAMTS13 autoantibodies.⁶

To our knowledge, this is the first reported case of TTP diagnosed after the ChAdOx1 nCoV-19 vaccine. The overlap in clinical features with the VITT may result in diagnostic confusion and inappropriate delay in PEX, which is a second-line treatment of VITT after failure of intravenous immune globulin. Timely examination of a blood film in all cases of suspected of VITT is therefore mandatory. The presence of microangiopathic haemolysis has been described in a patient with confirmed VITT and its presence does not necessarily exclude VITT in appropriate circumstances.⁷

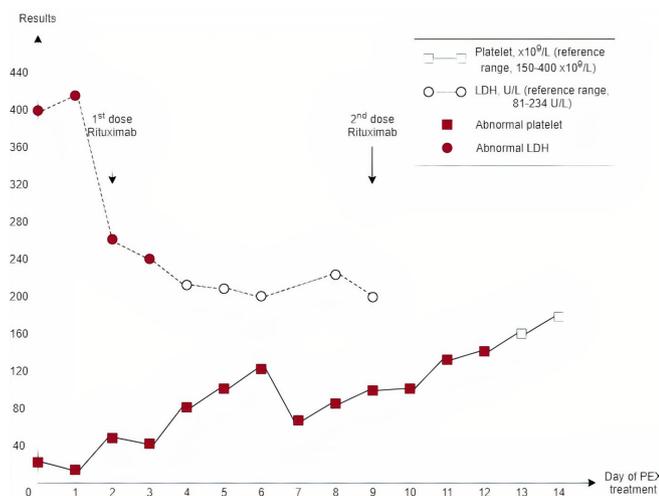


Figure 2 Graph showing the changes in platelet and LDH levels throughout the course of PEX treatment. LDH, lactate dehydrogenase; PEX, plasma exchange.

Patient's perspective

This was a very emotional journey, as I was diagnosed with a condition which I had not heard of. I am grateful to the healthcare members, as everyone was very friendly and helpful in aiding my journey to recovery.

Learning points

- ▶ A broad differential should be considered in patients presenting with neurological symptoms, especially in the absence of findings on neuroimaging.
- ▶ As part of the process of assessing possible vaccine-induced immune thrombotic thrombocytopenia, examination of a peripheral blood smear is necessary to exclude microangiopathic haemolytic anaemia.
- ▶ Prompt treatment involving plasma exchange and steroids with a consideration of rituximab should be commenced on diagnosing thrombotic thrombocytopenic purpura.

Another individual was recently described to experience a relapse of TTP 6 days after receiving the second dose of Pfizer-BioNTech COVID-19 vaccine.⁸ However, our patient differs from the previous reported case as she does not have a prior history of TTP. TTP has also been reported to develop after several other types of vaccines, particularly influenza vaccines.⁹ The association between microangiopathic thrombotic disorders and vaccinations remains unclear; however, vaccines have been hypothesised to play a role in triggering certain autoimmune diseases.¹⁰ Further research is required to establish the relationship between thrombotic microangiopathies and the administration of vaccinations against COVID-19.

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ORCID iD

Hui Ping Lee <http://orcid.org/0000-0002-0713-7021>

REFERENCES

- 1 European Medicines Agency. COVID-19 vaccines: authorised. Available: <https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/vaccines-covid-19/covid-19-vaccines-authorised> [Accessed 26 Jul 2021].
- 2 Voysey M, Clemens SAC, Madhi SA, *et al*. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99–111.
- 3 Greinacher A, Thiele T, Warkentin TE, *et al*. Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination. *N Engl J Med* 2021;384:2092–101.
- 4 Schultz NH, Sørvoll IH, Michelsen AE, *et al*. Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination. *N Engl J Med* 2021;384:2124–30.
- 5 Benhamou Y, Assié C, Boelle P-Y, *et al*. Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA reference center experience. *Haematologica* 2012;97:1181–6.
- 6 Joly BS, Coppo P, Veyradier A. Thrombotic thrombocytopenic purpura. *Blood* 2017;129:2836–46.
- 7 Tiede A, Sachs UJ, Czwalińska A, *et al*. Prothrombotic immune thrombocytopenia after COVID-19 vaccination. *Blood* 2021;138:350–3.
- 8 Sissa C, Al-Khaffaf A, Frattini F, *et al*. Relapse of thrombotic thrombocytopenic purpura after COVID-19 vaccine. *Transfus Apher Sci* 2021;60:103145.
- 9 Yavaşoğlu İrfan. Vaccination and thrombotic thrombocytopenic purpura. *Turk J Haematol* 2020;37:218–9.
- 10 Toussiot Éric, Bereau M. Vaccination and induction of autoimmune diseases. *Inflamm Allergy Drug Targets* 2015;14:94–8.

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