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Letter to the Editors-in-Chief

Double high-dose immunoglobulin for ChAdOx1 nCov-19 vaccine-induced immune thrombotic thrombocytopenia☆

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1. Introduction

The ChAdOx1 nCoV-19 vaccine (AstraZeneca) is one of the major vaccines against coronavirus disease 2019 (COVID-19). Until May 26, 2021, more than 53 million people world-wide have received the ChAdOx1 nCoV-19 vaccine following regulatory approval by the European Medicines Agency [1]. A rare but severe side effect of the ChAdOx1 nCoV-19 vaccine is vaccine-induced immune thrombotic thrombocytopenia (VITT) [1].

VITT usually develops five to 28 days after ChAdOx1 nCoV-19 vaccine administration. The pathophysiology of VITT is similar to autoimmune heparin-induced thrombocytopenia, including generation of platelet-activating antibodies that recognize platelet factor 4 (PF4), thrombocytopenia, and thrombosis. VITT's most common symptoms include headache, nausea, blurry vision, abdominal pain, dyspnea, and limb pain/pallor/swelling, indicating such thrombotic events as cerebral vein sinus thrombosis, splanchnic vein thrombosis, aortic/peripheral artery thrombosis, and venous thromboembolism [1]. Hematologic abnormalities include significant thrombocytopenia (platelet count less than 150×10^9/L), significantly elevated D-dimer and fibrin degradation product (FDP) levels, and reduced fibrinogen [1]. Moreover, patients usually test strongly positive in PF4-dependent enzyme-immunoassay (EIA) [1].

Five case series and five case reports have described a total of 52 cases of VITT (38 related to the ChAdOx1 nCoV-19 vaccine and 14 cases post Ad26.COV2.S vaccination) (Table 1) [1–4]. All the reported VITT cases were Caucasian, with 78.8% of cases female (11 males and 27 females in reports of ChAdOx1 nCoV-19 vaccine and 14 females in reports of Ad26.COV2.S vaccine) (Table 1) [1–4]. 93% of cases were younger than 50 years old (range, 20 to 65 years) (Table 1) [1–4]. The mortality rate with ChAdOx1 nCoV-19 VITT was 42.1% (16 of 38 patients died) [1–4]. In Taiwan, 378,000 persons received the ChAdOx1 nCoV-19 vaccine (by May 30, 2021). To our knowledge, no published literature has described VITT in Asia. We now report an Asian male with VITT who was successfully treated by early administration of "double" high-dose intravenous immunoglobulin (IVIG) with a satisfactory outcome (i.e., 2 g/kg on two consecutive days, rather than the conventional dosing of 1 g/kg for two consecutive days).

2. Case presentation

A 34-year-old healthy male (weight, 88 kg) without COVID-19 history received the first dose of ChAdOx1 nCoV-19 vaccine on May 12, 2021 (Day 0). He had a post-vaccination fever for three days, which spontaneously resolved. Beginning on day 5, the patient developed abdominal pain (pain score, 7 out of 10); beginning on day 7, he developed persistent and severe headache (pain score, 7 out of 10), leading to hospital referral on day 10. He did not receive heparin or dabigatran before hospitalization. He had no signs of neurological deficits, upper respiratory infection, or photophobia. Laboratory examination showed thrombocytopenia (platelet count, 34×10^9/L), greatly elevated D-Dimer (>10 mg/L), normal prothrombin time (12.8 s), mildly prolonged activated partial thromboplastin time (31.9 s), normal troponin-I (< 0.01 ng/mL), and normal procalcitonin (0.19 ng/dL) (Fig. 1). Computerized tomography (CT) of the brain revealed a lacunar infarct in the right semicentral ovale without hemorrhagic transformation. CT of abdomen did not identify intra-abdominal vessel thrombosis or hemorrhage.

After admission, dabigatran 150 mg twice daily was initially given as antithrombotic therapy. Laboratory results the next day (day 11) revealed persisting severe thrombocytopenia (platelet count, 25×10^9/L), severely decreased fibrinogen (0.6 g/L), significantly increased fibrin degradation products (>80 mg/L), and persistently elevated D-dimer levels (>10 mg/L). The following day (day 12), the platelet count was further decreased to 23×10^9/L (Fig. 1). At that time, a blood sample was sent for anti-PF4/polyanion antibodies for a potential diagnosis of VITT. Anti-PF4/polyanion ELISA (MyBioSource, San Diego, CA, USA) yielded a strong positive result of 1.214 optical density units (normal range ≤ 0.399), corresponding to an estimated antibody level of 87.00 ng/mL (Fig. 1), thereby confirming the clinical diagnosis of VITT.

☆ The study was approved by the Institutional Review Board at Chang Gung Memorial Hospital (#201901585A3).

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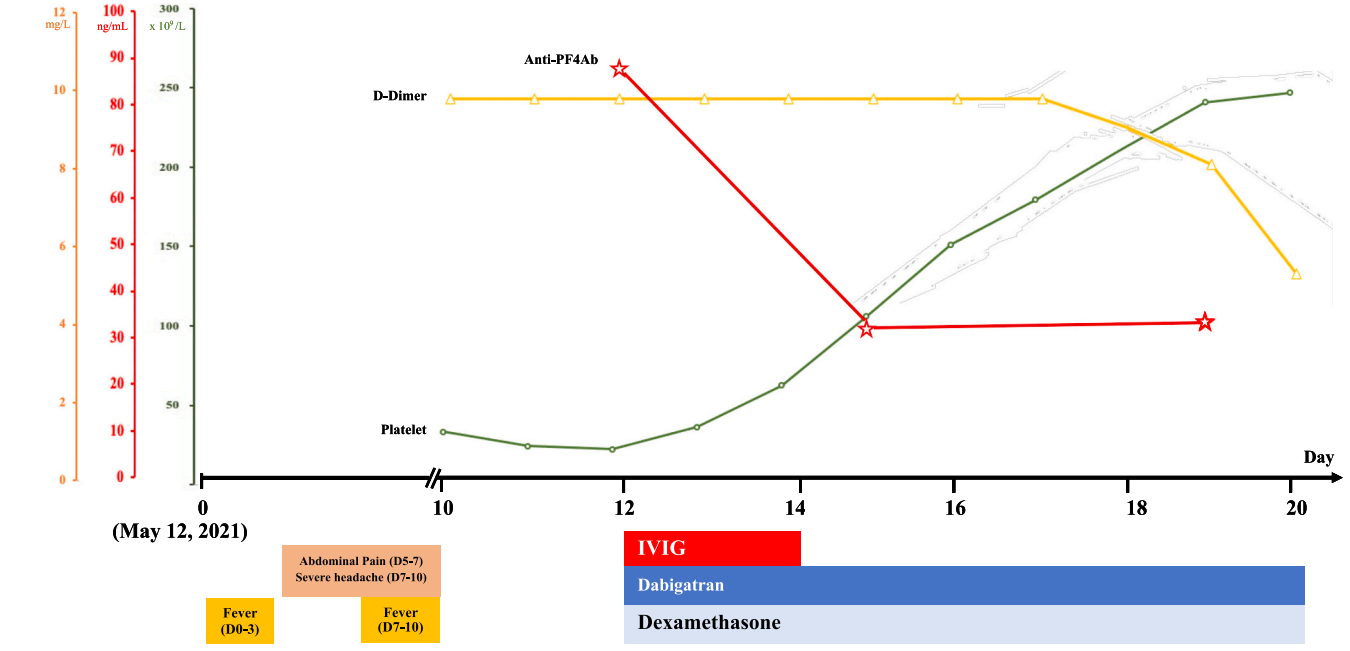
Table 1
Literature review of Covid-19 vaccine-induced immune thrombotic thrombocytopenia.

	No. of Cases	No. of	Thrombosis	Hemorrhagic	Treatments		
		Mortality (%)	Events (n)	Events (n)	Anticoagulants	Steroid	Immunoglobulin
Reports of ChAdOx1 nCoV-19 vaccine							
Thaler, J. 2021	1	0 (0%)	0	1	1	1	1
Greinacher, A. 2021	11	6 (54.5%)	10	1	1	0	0
Schultz, NH. 2021	5	3 (60.0%)	5	4	4	4	4
Scully, M. 2021	22	7 (31.8%)	22	5	Not provided	Not provided	Not provided
Subtotal	38	16 (42.1%)	37 (97.4%)	11 (28.9%)			
Reports of Ad26.COV2.S vaccine							
George, G. 2021	1	0 (0%)	1	0	1	0	1
See, I. 2021	12	3 (25.0%)[a]	12	7	12	0	7
Muir, K.-L. 2021	1	Critical[b]	1	1	1	0	1
Subtotal	14	3 (21.4%)[c]	14 (100%)	8 (57.1%)			
Total	52	19 (36.5%)[c]	51 (98.1%)	19 (36.5%)			
Current case	1	0	1	0	1	1	1

[a] The outcome evaluation was incomplete since three patients died, 3 patients remained in the intensive care unit, 2 patients were hospitalized in an ordinary ward, and 4 patients were discharged.
[b] The outcome evaluation was incomplete since the patient was still in critical condition.
[c] Incomplete statistic results due to incomplete outcome from two studies.



Day	10	11	12	13	14	15	16	17	18	19	20
Platelets (x 10^9 /L))	34	25	23	37	63	106	151	179		240	246
Anti-PF4Ab (ng /mL)			87.87			34.18				36.87	
D-Dimer (mg/L)	10	10	10	10	10	10	10	10		8.412	5.766
Fibrinogen (g /L)		0.6		0.6	0.49	0.47	0.82	0.93		1.2	
Prothrombin Time (sec)	12.8			13.9	15.2	15.9	13.5	12.7		11.7	11.4
Activated Partial Thromboplastin Time (sec)	31.9			30.2	29.3	28.9	25.6	24.7		23.6	23.4

Fig. 1. Clinical course of A 34-year-old male with vaccine-induced immune thrombotic thrombocytopenia, which was successfully treated by double high-dose intravenous immunoglobulin.

Double high-dose IVIG (Kiovig, Takeda Pharmaceuticals Australia; Sydney, Australia) was given, i.e., 2 g/kg/day for two consecutive days, with a total dose administered of 350 g.

Twelve hours after the first dose of IVIG, the platelet count rose to 37 $\times$ 10^9/L (Fig. 1). Thirty-six hours after starting IVIG therapy, the platelet count reached 63 $\times$ 10^9/L, fibrin degradation products decreased to 52.2 mg/L, but the D-dimer remained over 10 mg/L (Fig. 1). The platelet count continued to rise quickly, reaching 240 $\times$ 10^9/L by 7 days after starting IVIG, along with the decrease in the D-dimer (to 5.766 mg/L by day 20), along with recovering fibrinogen levels. Dabigatran 75 mg twice daily was administered for another month. The patient was discharged on day 20 without hemorrhagic or further thrombotic events.

3. Discussion

Heparin-induced thrombocytopenia (HIT) is an immune reaction characterized by IgG class antibodies that recognize PF4/heparin complexes, with strong platelet activation induced by the interaction of PF4/

polyanion/IgG immune complexes with FcγIIa receptors on platelets [5]. HIT can be divided into "typical" and "autoimmune" HIT, with the latter disorder indicating the presence of platelet-activating antibodies that recognize PF4 even in the absence of heparin [6,7]. Autoimmune HIT is characterized by unusually severe and persisting thrombocytopenia, a high frequency of overt disseminated intravascular coagulation (DIC), and unusually severe thrombotic events including in some cases disseminated microthrombosis. In a review of treatment of severe HIT (including autoimmune HIT) with high-dose IVIG, Warkentin found only one of 21 cases (4.8%) with severe hemorrhage (gastrointestinal bleeding) as a clinical feature of HIT [7]. In contrast, 19 of 52 VITT patients (36.5%) had hemorrhagic complications, although many bleeds represented hemorrhagic transformation of cerebral or splanchnic infarction [1–3]. Table 1 summarizes mortality, thrombosis and hemorrhagic events between ChAdOx1 nCoV-19 vaccine and Ad26.COV2.S vaccine [1].

The standard treatment of typical HIT is anticoagulation with factor Xa or thrombin inhibitors, such as fondaparinux or argatroban, respectively [6]. However, unlike in typical HIT, in patients with autoimmune HIT, the platelet count is less likely to recover quickly with factor Xa or thrombin inhibitor therapy [6]. Persistent thrombocytopenia and hypercoagulability can result in recurrent or progressive thrombosis, especially if anticoagulation is subtherapeutic as a result of "PTT confounding" [8] One approach to addressing this dilemma is to interrupt antibody-induced platelet activation by inhibiting activation through the platelet FcγIIa receptors [5]. This has led to increasing use of high-dose IVIG for treatment of autoimmune HIT, which is the rationale for treating the analogous disorder, VITT, also with high-dose IVIG [9]. As in autoimmune HIT, the recommended dose is one gram per kilogram per day for two consecutive days [6,7,9].

The mortality rate of 50% (2 of 4 cases) and hemorrhagic complication rate of 75% (3 of 4 cases) were strikingly high in the previous report of VITT patients treated with this standard dose of IVIG treatment (1 g/kg/day for two days) [2]. Schultz et al. described four VITT patients who received the standard dose of IVIG, and while three patients had platelet count recovery (of varying rapidity), one patient had only a minor, transient platelet count increase with subsequent recurrent thrombocytopenia [2]. These preliminary data suggest that the standard dose of IVIG for autoimmune HIT may be insufficient for patients with severe VITT. Since the effectiveness of IVIG for autoimmune HIT and for VITT is dose-dependent [6,7], higher dosing of IVIG therapy should be considered for patients with severe VITT.

Padmanabhan et al. found that IVIG dosage of 1 and 2 g per kilogram corresponds to in vitro immunoglobulin G (IgG) plasma concentrations of 23 mg/mL and 46 mg/mL, retrospectively [8]. Bakchoul et al. [10] and Arcinas et al. [11] found that IgG levels greater than 20 mg/mL were able to decrease antibody-induced platelet activation in the absence of heparin [9,10], whereas IgG levels greater than 30 mg/mL were able to inhibit platelet activation even with heparin present [8–10].

Schultz et al. found that serum collected from VITT patients showed spontaneous platelet activation without heparin [2]. Based on an effective dose of IVIG as one that should achieve a concentration of plasma IgG of at least 30 mg/mL, this supports an intravenous dosage of 2 g/kg/day for two days [8,10], i.e., twice the usual recommended dose. Our patient received this "double-dose" regimen, and showed excellent platelet recovery (platelet count rise to over 106×10^9/L) at approximately 72 h after starting IVIG therapy, with further rapid increase thereafter (Fig. 1). This rapid platelet count recovery rate was more significant than the patients in Schultz's study [2], as well as the patients reported by Bourguignon et al. [9].

VITT was first identified in Europe, and all reported cases to date have been Caucasian, a population who genetically may have a higher risk of thrombosis disorder than Asians [1]. Our patient is an Asian male with no previous history of autoimmune or thrombotic disease. Our case demonstrates the potential to develop VITT with severe thrombotic events even in an otherwise "low risk" patient population.

In summary, we have reported a case of VITT following ChAdOx1 nCoV-19 vaccination in an Asian male. Double high-dose IVIG of 2 g per kilogram for two consecutive days, i.e., a double-dose regimen, proved to be an effective treatment for this patient with severe VITT featuring cerebral thrombosis, severe thrombocytopenia, and hypercoagulability.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M. Makris, S. Pavord, W. Lester, M. Scully, B. Hunt, Vaccine-induced immune thrombocytopenia and thrombosis (VITT), Res Pract Thrombosis Haemostasis. (2021), https://doi.org/10.1002/rth2.12529.
[2] N.H. Schultz, I.H. Sørvoll, A.E. Michelsen, L.A. Munthe, F. Lund-Johansen, M. T. Ahlen, M. Wiedmann, A.-H. Aamodt, T.H. Skattør, G.E. Tjønnfjord, P.A. Holme, Thrombosis and thrombocytopenia after ChAdOx1 nCoV-19 vaccination, New Engl J Med. (2021), https://doi.org/10.1056/nejmoa2104882.
[3] A. Greinacher, T. Thiele, T.E. Warkentin, K. Weisser, P.A. Kyrle, S. Eichinger, Thrombotic thrombocytopenia after ChAdOx1 nCov-19 vaccination, New Engl J Med. (2021), https://doi.org/10.1056/nejmoa2104840.
[4] M. Scully, D. Singh, R. Lown, A. Poles, T. Solomon, M. Levi, D. Goldblatt, P. Kotoucek, W. Thomas, W. Lester, Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination, New Engl J Med. (2021), https://doi.org/10.1056/nejmoa2105385.
[5] G.M.Arepally A. Cuker B.H. Chong, Guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia, Blood Adv. 2 (2018) (2018) 3360–3392, https://doi.org/10.1182/bloodadvances.2018024489.
[6] J.A. Dougherty, R.L. Yarsley, Intravenous immune globulin (IVIG) for treatment of autoimmune heparin-induced thrombocytopenia: a systematic review, Ann. Pharmacother. 55 (2021) 198–215, https://doi.org/10.1177/1060028020943542.
[7] T.E. Warkentin, High-dose intravenous immunoglobulin for the treatment and prevention of heparin-induced thrombocytopenia: a review, Expert. Rev. Hematol. 12 (2019) 685–698, https://doi.org/10.1080/17474086.2019.1636645.
[8] A. Greinacher, K. Selleng, T.E. Warkentin, Autoimmune heparin-induced thrombocytopenia, J. Thromb. Haemost. 15 (2017) 2099–2114, https://doi.org/10.1111/jth.13813.
[9] A. Bourguignon, D.M. Arnold, T.E. Warkentin, J.W. Smith, T. Pannu, J.M. Shrum, Z.A.A.A. Maqrashi, A. Shroff, M.-C. Lessard, N. Blais, J.G. Kelton, I. Nazy, Adjunct immune globulin for vaccine-induced thrombotic thrombocytopenia, New Engl J Med. (2021), https://doi.org/10.1056/nejmoa2107051.
[10] T. Bakchoul, O. Borst, R. Riessen, J. Lucic, M. Gawaz, K. Althaus, P. Aidery, Autoimmune heparin-induced thrombocytopenia after transcatheter aortic valve implantation: successful treatment with adjunct high-dose intravenous immunoglobulin, Th Open. 03 (2019) e200–e202, https://doi.org/10.1055/s-0039-1692990.
[11] L.A. Arcinas, R.A. Manji, C. Hrymak, V. Dao, J.I. Sheppard, T.E. Warkentin, Autoimmune heparin-induced thrombocytopenia and venous limb gangrene after aortic dissection repair: in vitro and in vivo effects of intravenous immunoglobulin, Transfusion 59 (2019) 1924–1933, https://doi.org/10.1111/trf.15263.

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