CEREBRAL VENOUS SINUS THROMBOSIS RELATED TO VACCINE-INDUCED IMMUNE THROMBOTIC THROMBOCYTOPENIA: FIRST REPORTED CASE IN VIETNAM

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Vaccination remains one of the most important public health interventions to control and mitigate the impacts of COVID-19 worldwide. A number of post-vaccination reactions have caused concern and are the cause of vaccine hesitancy. Vaccine-induced immune thrombotic thrombopenia (VITT) has been reported in several countries such as Norway at a rate of 1 per 26000 doses of the ChAdOx1 nCoV vaccine (AstraZeneca), 15 per 8 million doses of Ad26.COV2.S (Janssen; Johnson & Johnson) vaccines in the US. In Vietnam, 11.5 million doses of AstraZeneca vaccine have been administered since the commencement of a nation-wide vaccination program five months ago. We report the first case of cerebral venous thrombosis related to VITT which was promptly diagnosed and successfully treated with rivaroxaban alone. Thus, VITT is very rare in Vietnamese people vaccinated with the AstraZeneca vaccine in the prevention of COVD-19 infection.

Keywords: Vaccine-induced immune thrombotic thrombopenia, viral vector vaccine, cerebral venous thrombosis, COVID-19, Vietnam.

I. INTRODUCTION

In response to the COVID-19 pandemic, several vaccines were developed to protect the community against severe acute respiratory syndrome caused by the novel coronavirus (SARS-CoV-2).[1] The ChAdOx1 nCoV vaccine (AstraZeneca) was one of the earliest vaccines to be used widely.[2] It was a replication-deficient chimpanzee adenoviral vector containing the sequence for SARS-CoV-2 structural surface glycoprotein antigen.[2,3] In a multinational phase III randomized trial, this vaccine had 70.4 percent efficacy (95% CI: 54.8 - 80.6) in preventing symptomatic COVID-19 at or after 14 days following the second dose.[4] It also demonstrated efficacy against new variants of concerns such as B.1.351.[3]

In early-phase trials, post vaccination side-effects fatigue, headache, and fever were relatively common which were severe in up to 8 percent of recipients.[4] Some rare cases of thrombosis associated with thrombocytopenia were reported.[4] Many of these cases have been associated with autoantibodies directed against the platelet factor 4 (PF4) antigen, similar to those found in patients with autoimmune heparin-induced thrombocytopenia (HIT).[5,6] Thrombosis in the vaccine-induced immune thrombotic thrombopenia can appear in common sites such as pulmonary embolism (PE) or deep vein thrombosis (DVT); however it can occur in unusual area including the splanchnic veins, adrenal, cerebral and ophthalmic veins. Arterial

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thrombosis such as ischemic stroke, peripheral arterial occlusion has also been reported, often in individuals with venous thrombosis.[6-8] Cerebral venous thrombosis (CVT) is a rare and serious event and accounts for 0.5% of all stroke cases.[9] Among approximately 34 million vaccine recipients in the United Kingdom and European Economic Area, there were 169 cases of CVT (0.0005%).[10] The available data suggest that CVT is uncommon.[11] We report a case of CVT-associated VITT observed in a young male.

II. CASE REPORT

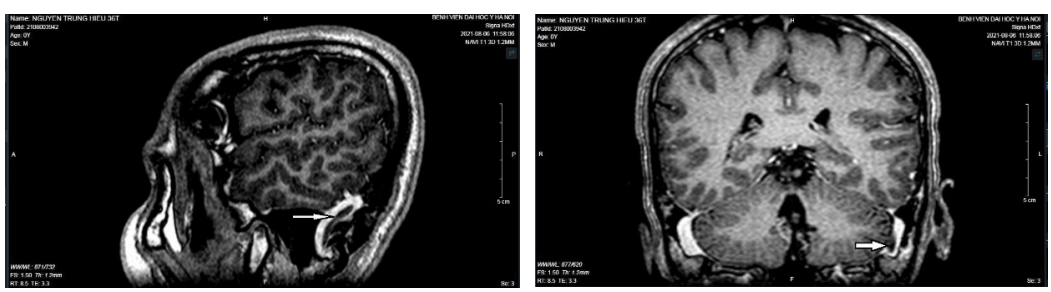
A 36-years-old man developed a persistent headache nine days after vaccination. He received his first dose of intramuscular the ChAdOx1 nCoV vaccine (AstraZeneca) on July, 27, 2021. The lot number of this vaccine was A1018, made in Thailand. The next day, he had mild fever, lethargy and local pain at the injection site. These symptoms improved and resolved within a day. On August 5th, 2021, he experienced acute severe headache and nausea. He did not experience visual loss or neck stiffness. On arrival to the Emergency Department, he was alert and orientated with a pulse of 70 beats per minute, blood pressure 117/74 mmHg, oxygen saturations 99% and temperature of 37.1°C. He did not have motor deficit, Babinski sign was negative and normal pupillary reflex. Cervical range of movement were normal with no pain on flexion and no tenderness point. The results of some blood tests were showed in table 1. A non-contrast computed tomography was performed which was normal.

Table 1. Haematology test results over course of hospitalisation

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Red Blood Cell (T/L)	4.58	4.83	4.36	4.52	4.41	4.39	4.31	4.82
Hematocrit	0.4	0.43	0.38	0.4	0.39	0.39	0.38	0.43
White Blood Cell (G/L)	6.10	6.64	4.35	5.3	7.85	5.20	8.94	7.32
NE/ LY (%)	81.4/ 10.6	58.6/ 26.9	54.2/ 29	70.7/ 21	62.1/ 22.6	54.1/ 31.1	66/ 14.2	67.6/ 21.3
Platelet (G/L)	78	61	48	47	55	59	66	142
Urea/ creatinine (mmol/L)/µmol/L	4.7/ 67							3.8/ 69
GOT/ GPT (U/L)	16/15							64/ 189
Prothrombin%/ INR	90/ 1.04			61/ 1.28	108/ 0.93			
APTT (s)	32			35.6	29.4			
Fibrinogen	1.58			1.35	1.58			
D-Dimer (ng/mL)	41519			4297			2733	1117

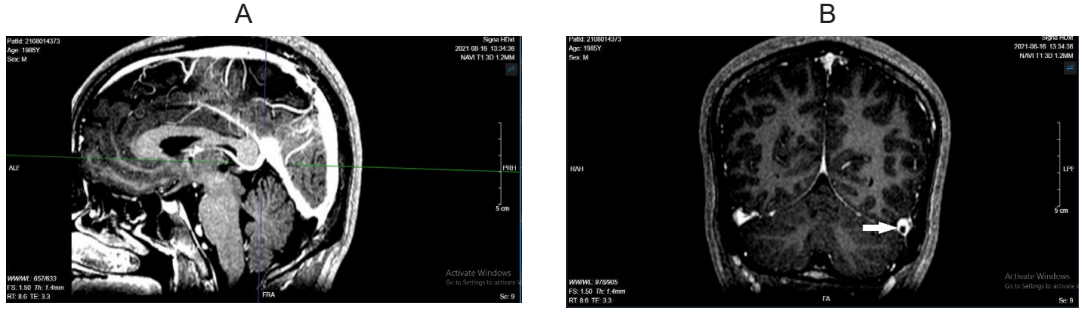
	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
CRPhs (mg/dL)	2.13			0.7				
Protein C (%)	97							
Protein S (%)	68.1							
Antithrombin III (%)	102							
RT-PCR SARS CoV2	Negative							Negative

The patient responded poorly with first line analgesic agents. Of note, the platelet was 79 G/L (normal: 150 - 450 G/L) and D-Dimer was 41519 ng/mL (normal < 500 ng/mL). Cerebral Magnetic Resonance Imaging (MRI) was performed the next morning demonstrating spontaneous hypersignal on T1-weighted and T2 FLAIR-weighted images in the straight sinus, the left sigma sinus and the lateral sinuses. MRI with gadolinium injection showed the rail sign and empty delta sign, which further strengthen the diagnosis. Anti-Platelet Factor 4 antibodies (anti-PF4) IgM test was positive and the diagnosis of vaccine-induced immune thrombotic thrombocytopenia was performed. He was anticoagulated with rivaroxaban in the regime: 15mg, PO, twice a day in 21 days followed by 20mg, PO, once a day for the next three months. The patient had a good improvement and no need for further analgesic. He was discharged from the hospital on August 11th, 2021 with routine follow up.



A. Left sigma sinus 1 B. Left sigma sinus 2

Picture 1. The First Cerebral MRI with gadolininum injection of the patient (August 6th, 2021)



A B

C D

Picture 2. Cerebral MRI with gadolininum injection on August 16th, 2021

III. DISCUSSION

This case described the first reported case of CVT with thrombocytopenia following ChAdOx1 (AstraZeneca) vaccination in Vietnam after 11.5 million doses. The rate was approximately 0.000009%. The incidence of VITT is unknown but appears to be exceedingly rare.[5,7] The highest incidence was reported from Norway, in which five cases were reported from among approximately 130,000 individuals vaccinated with ChAdOx1 nCoV-19 (0.0007%).[7] The low rate may be due to decreased recognition and case reporting, but pharmacovigilance for these outcomes has been thorough, suggesting that case ascertainment is high. Such a low incidence rate supports ongoing vaccination efforts.

Headache and vomiting presentation at the 9th day after ChAdOx1 nCoV-19 vaccination were the first data for us to consider of CVT related to VITT; coupled with an elevated thrombopenia and blood D-dimer level, we decided to perform a cerebral venous MRI to confirm the diagnosis of CVT. According to an Expert Hematology Panel, VITT is diagnosed when all five of the following criteria are met: 1) Onset of symptoms 5 - 30 days after vaccination against SARS-CoV2; 2) Presence of thrombosis; 3) Thrombocytopenia (platelet count < 150 G/L); 4) D-dimer level > 4000 ng/mL 5) Positive anti-PF4 antibodies on ELISA. Our case met all of the criteria to perform a definite diagnosis.[6]

The most common thrombotic site at presentation was the cerebral vein, identified in approximately 50% of patients with VITT. Some other common sites were splanchnic vein, pulmonary arteries, deep veins of the leg, adrenal vessels, renal vessels, and arteries of cerebral, the arm or leg with lower rate.[6] Anti-PF4 antibodies cause “pancellular” activation, meaning that, besides activating platelets and coagulation reactions, these antibodies activate monocytes, neutrophils, and endothelial cells.[5,10,12] Activation of these cell types further contributes to high thrombosis risk. Anti-PF4 antibodies in these disorders are able to activate platelets and cause thrombosis.[12] However, PF4 autoimmunity was restricted to discrete venous drainage basins rather than being generalized. Splanchnic and cavernous sinus venous drainage territories share common features with draining gut and respiratory barrier tissues, including the presence of angiotensin-converting enzyme 2 (ACE2) receptor that allows SARS-CoV-2 cell entry.[13,14] The site-specific factor which underlined disease topography and localization was important and could be explained this typically location with an extension due to the local endothelial-heparin-PF4 interaction.[12]

Some patients with CVT may present as intracerebral hemorrhage. The intracranial hemorrhage was common in patients with low platelet counts, usually lower than 34 G/L.[6] Multivariate analysis identified baseline platelet count and the presence of intracranial hemorrhage as being independently associated with death; the observed incidence of death was 73% among patients with both a platelet count below 30 G/L and an intracranial hemorrhage.[6] Therapeutic anticoagulation in this instance was necessary as one of the primary treatments for VITT, but imaging was required to rule out intracranial hemorrhage.

Early reports in which patients were treated with heparins described clinical worsening, including death, and early recommendations were to avoid heparin because of the resemblance of VITT to HIT.[7] It may be reasonable to avoid heparin in cases of diagnostic uncertainty in which HIT (including

delayed or spontaneous HIT) remains possible in the differential diagnosis. The choice of anticoagulant depends on the patient's clinical status (consciousness and ability to eat/drink). Anticoagulants in order of preference are: a direct oral anticoagulant (apixaban, edoxaban, rivaroxaban, or dabigatran), fondaparinux. In our case, the patient was conscious and had good adherence to medication, so we chose rivaroxaban even though the results of the anti-PF4 test were not available at that time. The platelet counts of this patient have increased and the symptom began to resolve from the fifth treatment day. No bleeding event occurred. The patients did not need intravenous immune globulin (IVIG) or therapeutic plasma exchange which are expensive treatment options in Vietnam.

IV. CONCLUSION

The first reported case of cerebral venous thrombosis with thrombocytopenia following ChAdOx1 (AstraZeneca) was presented here after 11.5 million doses of vaccination in Vietnam. The patient was succesfully treated only by rivaroxaban.

Declaration of Conflicting Interests

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Ethical Approval

The clinical case was presented anonymously with the informed consent of the patient. This manuscript is for scientific purposes only.

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