CASE REPORT

Lower limb arterial thrombosis followed by sub-massive pulmonary thromboembolism after Sinopharm BBIBP-CorV COVID-19 vaccination

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ABSTRACT

The global COVID-19 vaccination had an undeniable influence on the pandemic management, despite of having reported rare but life-threatening side-effects of vaccines. Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a rare autoimmune complication determined by thrombocytopenia and thrombosis propensity in the circulatory system. The activation of antibodies against platelet factor-4 (PF-4) which mimics the heparin-induced thrombocytopenia (HIT) characteristic is the main known pathogenicity of the disease. Herein, we reported a case of VITT in a middle-aged woman with no previous history of thrombophilia or other medical conditions who presented with thrombosis of the left superficial femoral artery 3-days after receiving the second dose of inactivated BBIBP-CorV (Sinopharm) vaccine. The patient underwent bypass vascular surgery and received none-heparin anti-coagulation consistent with high-dose intravenous immunoglobin. Eight days after the discharge, she was subsequently referred to our center with the presentation of sub-massive pulmonary thromboembolism in spite of receiving the prophylactic anticoagulants during follow-up period. Details on side-effects of COVID-19 vaccines, specifically the inactivated ones are yet to be fully ascertained. Clinicians should consider the history of COVID-19 vaccines in thromboembolism patients who do not have well-acknowledged risk factors. Further studies about the necessity of prophylactic anticoagulants and clinical judgment for receiving other vaccines in such patients are required.

KEYWORDS: VITT; Thrombosis; pulmonary thromboembolism; Sinopharm; vaccine; COVID-19

INTRODUCTION

The most effective strategy in controlling waves of afflictions during the COVID-19 pandemic was a widespread global vaccination. Statistical models estimated that vaccines against SARS-CoV-2 pneumonia prevented at least 20 million mortalities in the first year of vaccine initiation [1]. Undeniably, Vaccines also imply complications that are mostly mild, self-limited, with no further sequels. Nevertheless, a rare but life-threatening complication of vaccine-induced immune thrombotic thrombocytopenia (VITT) following COVID-19 vaccines has been reported in few receivers [2]. VITT is an autoimmune disorder determined by the platelet activation following groups of antibodies which leads to thrombosis propensity in both venous and arterial circulation [3]. Herein, we presented an Iranian middle-aged woman with arterial thrombosis 3-days after receiving Sinopharm vaccine which was ultimately diagnosed as VITT and complicated with submassive pulmonary thrombo-embolism a few days later.

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CASE REPORT

A 46-year-old woman with no evidence of hereditary or acquired thrombophilia or other medical conditions has been referred to our hospital (Masih Daneshvari Hospital, Tehran, Iran) with sudden and extreme pain in her left calf 12 hours before referral. She had a history of receiving a second dose of the BBIBP-CorV (Sinopharm) vaccine 3-days before. She claimed she had no symptoms after receiving the first dosage of the Sinopharm vaccine except mild pain in the injection site which has been improved by non-steroidal anti-inflammatory drugs (NSAIDs) and the second dose of

Sinopharm was administered based on the previous schedule 21 days later. On examination, her calf was extremely painful, pulselessness, pale, and hypothermic. Because of the suspicion of arterial thrombosis, Doppler ultrasound was performed and a complete thrombosis was found in the distal region of the left superficial femoral artery, with extension to the popliteal artery. Her initial laboratorial findings revealed a normocytic normochromic red blood cell (hemoglobin=12.9 mg/dl, MCV=87 FL), leukocytosis (white blood count=17.1 $\times 10^9$/L), and thrombocytopenia (platelet=67.5 $\times 10^9$/L) (Figure 1). On more evaluation, plasma D-dimer=67 mg/L, prothrombin time (PT) = 16 sec, activated partial thromboplastin time (APTT)= 30-sec, fibrinogen=206 mg/dl, and fibrinogen degradation product (FDP) = 33 ug/ml were obtained. Since VITT was strongly suggested by the pulmonology and hematology team, platelet factor-4 antibody (anti-PF4) using Enzyme-linked immunosorbent assay (ELISA) was conducted which confirmed the diagnosis. Further, she had a negative real-time polymerase chain reaction test (rt-PCR) for both O-micron and Delta variants of COVID-19. For her arterial thrombosis, the patient underwent emergency bypass vascular surgery of the popliteal and femoral arteries which was successful. During hospitalization, she was treated with Dabigatran as non-heparin anticoagulant (NHA), systemic antibiotics (due to surgical site infection), and high-dose intravenous immunoglobin (IVIG) (1gr/kg for 3 consecutive days). She was ultimately discharged 11-days after surgery with the administration of antibiotics, Aspirin, and prophylactic NHA. On her follow-up consultation 3-day after discharge, she was clinically stable with normalized laboratory tests. 5-days later she was referred to our emergency department (ED) with sudden dyspnea, and chest pain which occurred 6-hours before. In electrocardiography, signs of right bundle branch block with sinus tachycardia were revealed. Transthoracic echocardiography showed right ventricle enlargement and severe dysfunction consistent with McConnell's sign. She was admitted to the cardiac care unit (CCU) due to her unstable vital signs and strong suspicion of pulmonary thromboembolism (PTE). CT-Angiography revealed submassive emboli in the pulmonary artery extended to the left and right main branchial (Figure 1). The PTE management initiated with fibrinolytic and NHA agents. After 6-days of hospitalization, the patient was discharged in stable condition. Of note, during the episode of PTE, she had normal levels of platelet (Figure 1) and an ELISA essay for anti-PD4 was negative. She received prophylactic NHA (Dabigatran) for 6 months after discharge and was closely followed up during this time as no more pathological conditions occurred.

DISCUSSION

The vaccines against SARS-CoV2 infection had an unprecedentedly impact on the management of the lethal pandemic [1,4]. In Iran, till July 2022, 69.1% of the population have received at least 2 dosages of vaccines which approximately 90% of these have been conducted with the un-activated vaccine of Sinopharm [5,6]. The national vaccination policy has reduced rate of mortality from 650cases/day in July 2021 to 1case/day in July 2022 in Iran [5,7]. Notwithstanding, most of the authorized vaccines for COVID-19 are still amongst the phase 3 of the clinical trials which have not accomplished the phase 4 and subsequently restrict our knowledge regarding serious or long-term vaccine side-effect [1,8]. Whilst most of the vaccine complications are

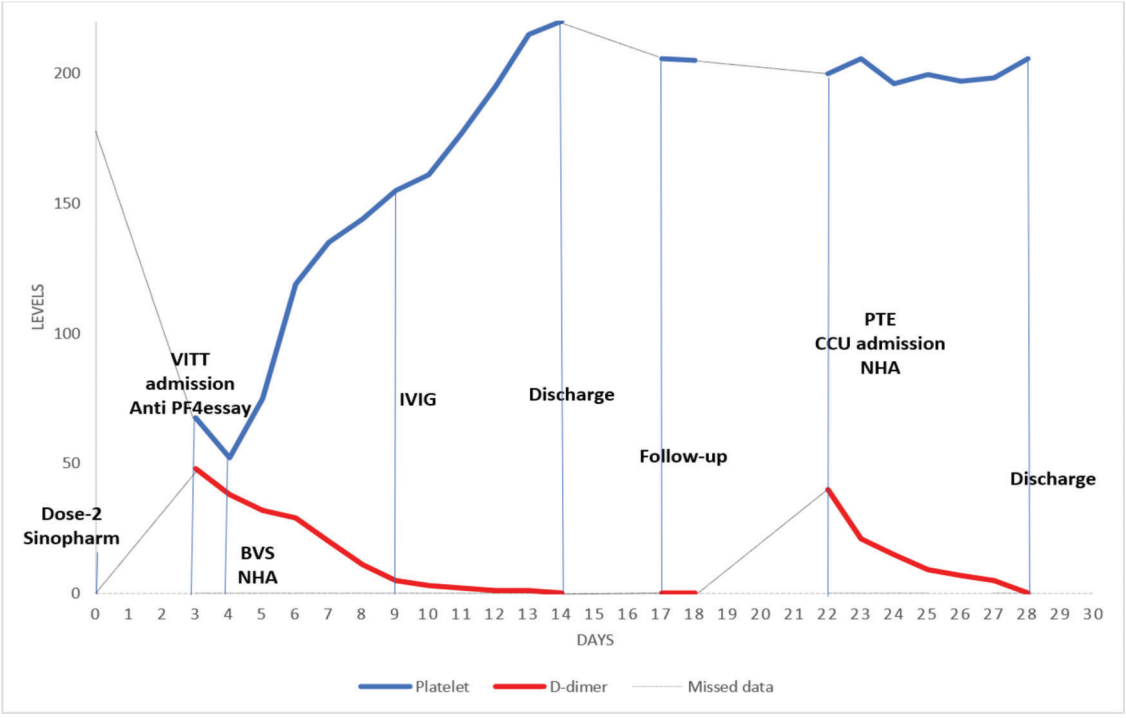

Fig. 1. Trendline of the platelet and D-dimer levels. The black line (missed date) is drawn to keep the integrity of the chart. VITT=vaccine induced thrombotic thrombocytopenia; PF4= platelet factor 4; BVS= bypass vascular surgery; NHA= none-Heparin anticoagulants; IVIG= intravenous immunoglobin, CCU= cardiac care unit.

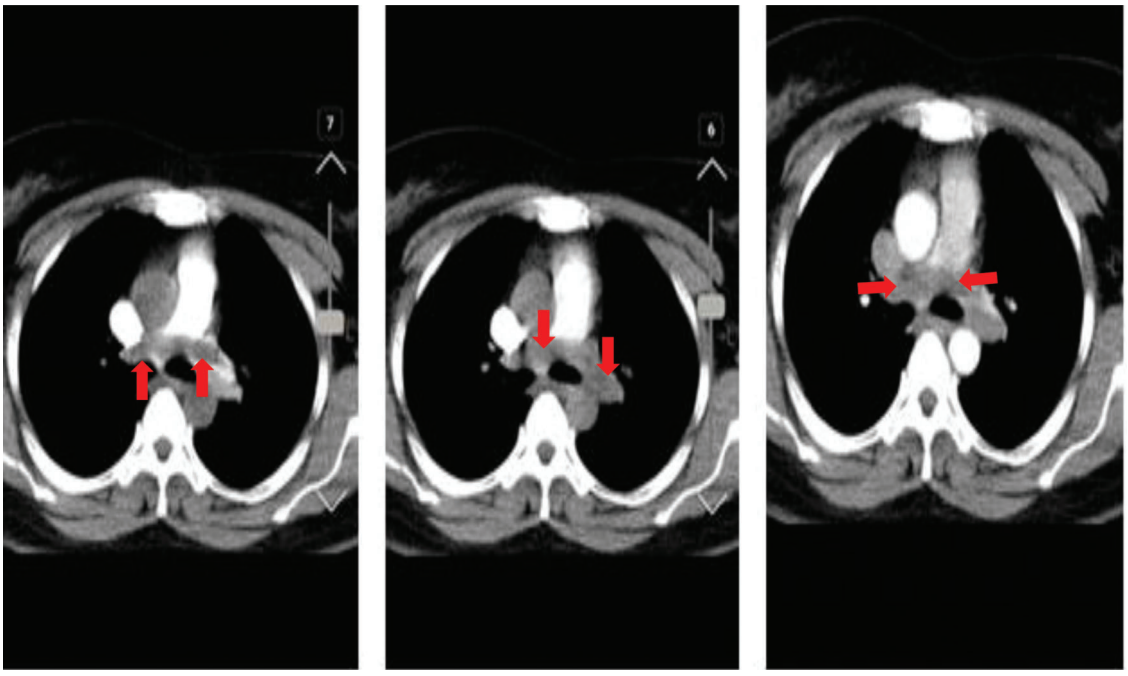

Fig. 2. submissive emboli in the pulmonary artery extended to left and right main branch mentioned by red arrow.

mainly a result of incubation processes and human immune system response interactions which are mild and self-limited, some cases faced with more challenging side-effects such as thromboembolic events [1,5,9]. In a vast study in courtiers of European Union on complication of viral-vector vaccine (AstraZeneca), a total of 250 VITT cases were detected whom majority of them (67%) were diagnosed with cerebral venous sinus thrombosis (CVST). Further, an unusual thrombosis event within the inferior ophthalmic vein 2 weeks after administration of AstraZeneca has been recently described by Mcdonell et al. [10]. The VITT phenomenon followed by administration of inactivated vaccines is more scarce comparing to other types of vaccines, which has been reported in two essays until July 2022: first, a 78-years old Pakistani man with history of diabetes mellitus who was presented with swelling of the left leg and sudden dyspnea and diagnosed as a deep vein thrombosis (DVT) and PTE co-occurrence. He had history of receiving Sinopharm vaccine 2 weeks before the thromboembolic event and was thoroughly healed by fibrinolytic and NHA management [11]; and second, a 85-years old Iranian man with history of mild chronic heart ischemia and daily Aspirin consumption who had episodes of syncope 5-days after receiving second dose of Sinopharm vaccine and diagnosed as CVST. The patient was successfully managed by NHA, high dose of IVIG, and systemic corticosteroids [12]. To our knowledge, our case is the third report of VITT following inactivated vaccine specifically in a condition of experiencing two consecutive thromboembolic events. Notwithstanding, it is yet to be clarified whether the PTE phenomenon in our patient was the thrombosis sequels of COVID-19 vaccine, or the clinical status difficulties such as vascular surgery or insufficient therapeutic and prophylactic anticoagulation, per se, were responsible. Our patient had accomplished criteria of ASH in fully diagnosis of VITT [3] as she had 1. thrombotic event, 2. moderate thrombocytopenia, 3. remarkably elevated D-dimer and fibrinogen levels, and 4. positive anti PF4 utilizing ELISA. Of interest, our patient had a routine check-up a week before the receiving the second dose of vaccine as normal platelet count was reported (243×10^9/L); This shows the fact that she had not previous thrombocytopenia. Our patient undergone emergency bypass vascular surgery due to high risk of lower limb amputation as the complete obstruction of superficial femoral artery was occurred. Based on surgical consultation, her initial platelet count was appropriate for the lower extremity operation (platelet $> 50 \times 10^9$/L) [13] and platelet transfusion was inhibited due to immune pathogenicity of the VITT that anti-PF4 antibodies could affect transfused platelets [14]. Further we avoided to use unfractionated heparin for our patients as the previous studies confirmed that immune complexes of the plasma found by functional cytometry in VITT cases strongly mimic the characteristics of heparin induced thrombocytopenia (HIT) immunogenicity, and administration of heparin could deteriorates VITT [14]. We also administered high-dose of IVIG for our patient which leaded to better improvement of platelet counts with higher slope of increment (Figure 2). Previous study supported that IVIG could boost the platelet count, lower the inflammatory factors, and blockade the receptors that could have role in demolition of the platelets in VITT cases who received Oxford-AstraZeneca vaccine [15].

CONCLUSION

As conclusion, given the fact that Sinopharm vaccine is conducted more in countries with lower rate of follow-up and surveillance, it is difficult to clarify the complications of inactivated SARS-CoV2 vaccine. Hence, it is suggested clinicians have caution about COVID-19 vaccine history in patients presenting with thromboembolic events and do not have obvious risk factors. Finally, further studies are required to evaluate the re-occurrence risk of thromboembolic events, the requirement of prophylactic anticoagulation for rest of

life, and clinical judgments on receiving other vaccines in such patients.

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The authors of this study did not receive grant or other financial supports from any company or institution.

Conflicts of interest

The authors of this study declare no conflict.

Ethical consideration

The patient of this study was informed about this survey and she was thoroughly agreed about sharing the previous medical records and disease procedure. Also, a written informed contest was obtained. Further, our study was reviewed and accepted by the ethical commitment of Shahid Beheshti University of Medical Sciences (ethical number: SBMU.IR.REP.1401.4)

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