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VACCINE-INDUCTED THROMBOTIC THROMBOCYTOPENIA AND COVID-19 VACCINES: CASE SERIES

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ABSTRACT

Vaccine-induced thrombotic thrombocytopenia (VITT) is a condition similar to heparin-induced thrombocytopenia (HIT), but it is associated with prior administration of COVID-19 vaccines without prior exposure to heparin. The incidence of VITT is not certain, but it appears to be extremely rare. Reports of unusual and severe thrombotic events, including cerebral and splanchnic venous thrombosis and other autoimmune adverse reactions, such as immune thrombocytopenia or thrombotic microangiopathies in connection with some of the SARS-CoV-2 vaccines, have caused a great deal of concern within the population and the medical community. We would like to present 4 clinical cases of VITT, hospitalized and treated in intensive care unit (ICU) of University clinic of cardiology in Skopje.

Keywords: vaccine-induced thrombotic thrombocytopenia, COVID-19

INTRODUCTION

Vaccine-induced thrombotic thrombocytopenia (VITT), also known as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) or thrombosis with thrombocytopenia syndrome (TTS). This condition is similar to heparin-induced thrombocytopenia (HIT) but is associated with prior administration of COVID-19 vaccines without prior exposure to heparin [1].

The incidence of VITT is not certain, but it appears to be extremely rare. A recent report in JACC found that cerebral vein thrombosis occurred in 3.6 per million people after the AstraZeneca COVID-19 vaccine and 0.9 per million people after Johnson & Johnson vaccine . For comparison, the rate of cerebral vein thrombosis is estimated at 207 per million in patients hospitalized with COVID-19 and 2.4 per million in the general population. The risk of death and serious outcomes of COVID-19 (including thrombosis) far outweigh the small risk of VITT [2].

Reports of unusual and severe thrombotic events, including cerebral and splanchnic venous thrombosis and other autoimmune adverse reactions, such as immune thrombocytopenia or thrombotic microangiopathies, in connection with some of the SARS-CoV-2 vaccines, have caused a great deal of concern within the population and the medical community [3, 4].The suspected mechanism is through antibodies directed against the platelet factor 4 (PF4)-heparin

complex which activate platelets, similar to HIT antibodies, which can be detected by using the HIT ELISA-test [4]. Anti-PF4 antibodies cause "pancellular" activation, meaning that, besides activating platelets and coagulation reactions, the antibodies activate monocytes, neutrophils, and endothelial cells. Activation of these other cell types further contributes to high thrombosis risk.

Thrombosis in VITT can occur in typical sites such as pulmonary embolism (PE) or deep vein thrombosis (DVT) in the leg. However, a distinctive feature of the syndrome is thrombosis in unusual sites including the splanchnic (splenic, portal, mesenteric) veins, adrenal veins (risk for adrenal failure), and the cerebral and ophthalmic veins [5]. Arterial thrombosis, including ischemic stroke (often, middle cerebral artery) and peripheral arterial occlusion has also occurred .

Diagnostic criteria for VITT are the following: recent vaccination (< 30 days) with prolonged period of being unwell (> 48h), thrombocytopenia (< 150), very high D-dimmers (> 2000), low/normal fibrinogen, with signs of headache, blurring vision, abdominal pain, nausea/vomiting, chest pain, leg swelling, and bleeding/petechia. Initial work-up consist of CBC with platelet count, fibrinogen and D-dimmer, imaging for thrombosis based on signs and symptoms, PF4-ELISA (HIT assay). The most important imaging techniques which can visualize the site of thrombosis are: CT angiography, MRI, and Doppler ultrasound [6].

The time frame of reported events is between 4-42 days following the vaccine (median 14 days). There is no evidence that patients with a history of thrombosis, thrombophilia, or prior HIT are at increased risk for VITT. Demographic and clinical risk factors for the development of VITT are uncertain. Most patients who developed VITT were younger (age < 60 years) women, although both men and women have been diagnosed with VITT [7].

A recent study was performed in England, in order to assess the association between Covid-19 vaccines and risk of thrombocytopenia and thromboembolic events among adults. Patient level data were obtained for approximately 30 million people vaccinated in England between 1 December 2020 and 24 April 2021. 29,121,633 people were vaccinated with first doses (19,608,008 with Oxford-AstraZeneca (ChAdOx1 nCoV-19) and 9,513,625 with Pfizer-BioNTech (BNT162b2 mRNA)) and 1,758,095 people had a positive SARS-CoV-2 test. The primary outcomes were hospital admission or death associated with thrombocytopenia, venous thromboembolism, and arterial thromboembolism within 28 days of three exposures: first dose of the ChAdOx1 nCoV-19 vaccine; first dose of the BNT162b2 mRNA vaccine; and a SARS-CoV-2 positive test. Secondary outcomes were subsets of the primary outcomes: cerebral venous sinus thrombosis (CVST), ischemic stroke, myocardial infarction, and other rare arterial thrombotic events. Increased risks of hematological and vascular events that led to hospital admission or death were observed for short time intervals after the first doses of the ChAdOx1 nCoV-19 and BNT162b2 mRNA vaccines. The risks of most of these events were substantially higher and more prolonged after SARS-CoV-2 infection than after vaccination within the same population [8].

We would like to present 4 clinical cases of VITT, hospitalized and treated in the ICU of the University clinic of cardiology in Skopje, during the summer months.

CASE 1

A 75-year old woman presented in the emergency room (ER) with progressive dyspnoea, fatigue, over the course of the week prior to arrival at the ER. She had a previous history of pulmonary thromboembolism (PTE) 25 years ago, due to prolonged immobilization of a fractured right fibula, hypothyroidism and hypertension (HTN). She was revaccinated with the Astra Zeneca Covid-19 vaccine one month prior. A bedside echocardiography revealed a D-shape of left ventricle, mildly dilated right ventricle with initial signs of overload, normal systolic function, mild tricuspid regurgitation without pulmonary hypertension (SPAP 33 mmHg). A CT pulmonary angiography (CTPA) revealed thrombus in right distal pulmonary artery with extension in upper lobe artery with distal embolization in apical subsegmental branch, massive emboli in the lower lobe artery and mid lobe artery with subsegmental extensions. The left pulmonary artery presented eccentric thrombus, with extension in upper lobe artery and emboli in all segmental branches in lower lobe (Figures 1, 2). Atelectatic and small infarct zones present in both right and left lung. A duplex ultrasound of the leg veins revealed left femoro-popliteal thrombosis. Initial antithrombotic treatment with low-molecular

weight heparin (LMWH) was started, until aPTT reached the therapeutic range and anti-factor Xa level reached 1IU. Hereafter we switched to direct oral anticoagulant (DOAC) Apixaban 2 x 10 mg 7 days, followed by 2 x 5 mg. The initial level of D-dimmers was 35712ng/ml and during therapy dropped to 12044 ng/ml. Laboratory findings were consistent with mild anemia (Hgb 119 g/l), infection (WBC 11.4) and normal PLT (220). Before discharge, tests for thrombophilia were done and acquired thrombophilia with positive lupus anticoagulant (LA) was found. Therefore, a life-long anticoagulant regiment was the recommended therapeutic option and secondary prevention of VTE.

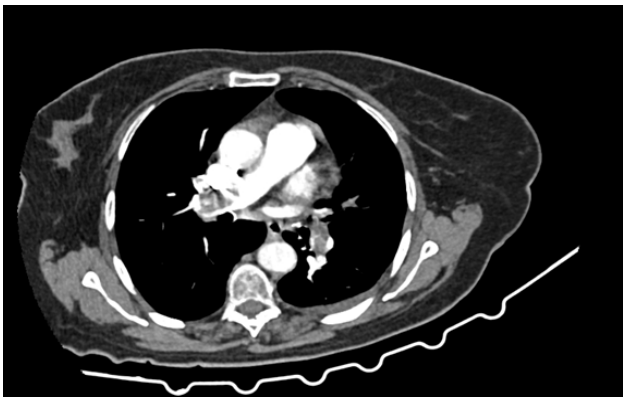


Figure 1. *CTPA showing eccentric thrombus in left pulmonary artery, extended in upper lobe artery and segmental branches*

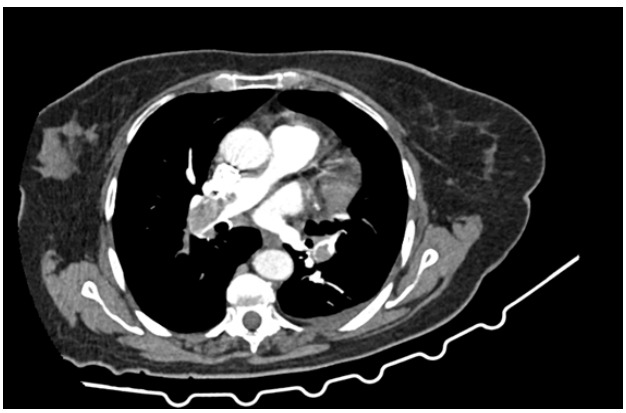


Figure 2. *CTPA showing thrombus in the right distal pulmonary artery with extension in upper lobe artery*

CASE 2

A 64-year old man arrived who was having exertional dyspnoea 4 hours before hospital admission. This exertional dyspnoea persisted at rest. Previous history of type 2 Diabetes mellitus (T2DM), HTN, physically active, mountaineer, revaccinated with Pfizer-BioNTech Covid-19 vaccine 5 days prior to arrival. An urgent CT pulmonary angiography showed thrombosis of right pulmonary artery (PA), and he was therefore admitted to the ICU (Figure 3). A bed-side echocardiography showed an enlarged right ventricle with reduced systolic function, positive Mc-Connell's sign, and no PAH, normal size and function of left ventricle. A compressive ultrasound (CUS) of leg veins showed that it was normal. There were hematologic abnormalities consistent with low PLT 162, high D-dimmers 2772 ng/ml, normal CBC and WBC. An anticoagulant treatment with LMWH was started. After 5 days, because of new onset of coronary ischemia (negative T-waves in precordial leads, increase of hsTr I 633 ng/l), coronary angiography was performed with a finding of significant LAD stenosis of 90%, followed by percutaneous coronary intervention (PCI) with stent implantation. He was discharged with triple antithrombotic therapy (Acetylsalicylic acid 100 mg, Clopidogrel 75mg, Rivaroxaban 20mg) with indication for ASA discontinuation after 1 month.



Figure 3. *CTPA showing thrombus in right pulmonary artery*

CASE 3

A 64-year old woman with complaints of palpitations and malaise arrived one week prior. She was transferred from the general hospital in Prilep on suspicion of pericardial effusion. She had a previous history of HTN and vaccination with Astra Zeneca COVID-19 vaccine one month prior to arrival. She was dyspnoic upon admission with a Sa02 of 62%, pCo2 33.5 mmHg, pO2 29.5 mmHg , pH 7.493 (arterial sample). CBC showed high WBC 14.5 and CRP 177.53 mg/l, reduced PLT 138, high D-dim-

mers 5148 ng/ml. Echocardiography revealed normal size and function of left ventricle, with dominant enlarged right ventricle with reduced systolic function, positive Mc Connell's sign, severe tricuspid regurgitation with PAH (SPAP 74 mmHg), pericardial effusion. Because of high suspicion of PTE, an urgent CT pulmonary angiography was performed, with a finding of massive pulmonary embolism in the right PA with extension in lobar, segmental, and subsegmental branches, with a zone of infarction in the upper right lobe and a zone of consolidation in the right medial lobe. There was a massive pericardial effusion with diameter 28 mm. A CUS of the leg vein returned normal. An anticoagulant treatment with LMWH was started immediately after admission to the ICU, antibiotics, and other supportive therapy (beta blockers, ACE-inhibitors, proton pump inhibitors, fluids etc.). She was discharged after 20 days with significant improvement in right ventricular function, reduced SPAP and pericardial effusion. DOAC (Apixaban 2 x 10 mg 7 days, followed by 2 x 5 mg) was the preferred oral anticoagulant therapy.



Figure 4. *CTPA showing right and left lobar, segmental thrombosis and pericardial effusion*

DISCUSSION

An 42-year old man was admitted to the ER with complaints of pain and swelling of left leg 1 day prior, but discomfort in his left leg persisted for 1 month before arrival. He has no previous history, except revaccination with the Pfizer COVID-19 vaccine, 40 days prior. Initial CBC was normal, except low PLT 177, high D-dimmers 4623 ng/ml. A duplex ultrasound was performed with a signs of extended ileo-femoro-popliteal vein thrombosis and intensive anticoagulant regimen with 30,000 IU Heparin/24h was started, with aPTT 3-4 times prolonged. A CT phlebography revealed a dilated left femoral vein, with thrombus which extended proximal in left iliacal vein and IVC (inferior vena cava) before inflow of left renal vein, and distal extension in left popliteal vein (Figure 5). Because of a high thrombogenic potential, an urgent indication of IVC filter was recommended and performed by the interventional radiologist at the City General hospital, "8th of September", in Skopje, after failed thromboaspiration (Figure 6) . Control duplex ultrasound showed partial reduction of thrombus in iliac and femoral vein, with a significant reduction in the popliteal vein. The patient was discharged after 16 days with LMWH (2 x 8000 IU Enoxaparin) for the next 10 days, up to control examination.



Figure 5. *CT phlebography: thrombus in left iliac vein extended in inferior vena cava*

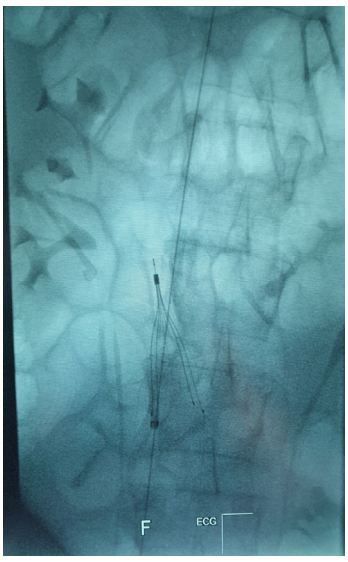


Figure 6. *Inferior vena cava filter*

MANAGEMENT STRATEGY

In patients presenting with thrombocytopenia, documented or suspected thrombosis, and a positive or pending PF4 ELISA 4-42 days post-vaccination, rapid initiation of treatment is recommended, analogous to treatment of severe HIT, including: intravenous immune globulins (IVIG) 1 g/kg daily for two days; non-heparin anticoagulation, chosen based on the clinical status and organ function of the patient: parenteral direct thrombin inhibitors (argatroban or bivalirudin), or direct oral anticoagulants without lead-in heparin phase, or fondaparinux, or danaparoid, if the platelet count is >50 x 10/l and no serious bleeding. Corticosteroids can be administered along with IVIG in some cases. Aspirin should be avoided (no efficiency in preventing HIT antibodies from activating platelets and could increase the risk of bleeding), also platelet transfusions. Some patients with serious bleeding or need for surgical intervention may benefit from platelet transfusion. Additional therapies include: plasma exchange if the platelet count <30 x 10/l, after IVIG and steroids, in patients with severe disease (9).

At this time, the duration of therapy in patients with VITT is not known. Those with documented thrombosis should receive a therapeutic dose for a minimum of three months via oral anticoagulation, as for any provoked venous thromboembolism (VTE).

DISCUSSION

From the onset of the COVID-19 pandemic in December 2019 to mid-October 2021, more than 240 million cases and 4.9 million deaths have been reported to the World Health Organization. The comes with the disruption of economic and social activity, as well as devastating material, physical, and psychological consequences. Reports of unusual and severe thrombotic events in connection with some of the SARS-CoV-2 vaccine have caused a great deal of concern within the population and the medical community. These thrombotic events are extremely rare but have serious consequences. These adverse events must be put into perspective with an objective analysis of the facts and the issues of the vaccination strategy during this SARS-Cov-2 pandemic.

Healthcare professionals remain the most pertinent advisors and influencers regarding vaccination decisions; they have to be supported in order to provide reliable and credible information on vaccines. Patients should be reassured that the benefits of vaccination against COVID-19 far outweigh any potential risk. All patients should be encouraged to get vaccinated against COVID-19 as soon as possible (10).

Up to now, the situation of the COVID-19 pandemic is still unpredictable. There is no effective vaccine or specific anti-viral drug to treat COVID-19 patients. Combination therapies have shown promising clinical improvement, even though without specific treatment and efficient vaccines for COVID-19, the most effective way to prevent from being infected is protection, precautions and preventive measures (11).

According to recent data provided by the EMA (European Medical Agency) and the CDC (Center for Disease Control) , VITT is an extremely rare event in the context of COVID-19 vaccinations, but it can be associated with severe morbidity and mortality. Data is emerging regarding details on the clinical presentation and mechanisms leading to the disease, including PF4/heparin associated antibodies and potentially other immune complexes related to platelet activation. These cases should be early recognized, diagnosed, and properly treated. Recommendations for the clinical and laboratory diagnosis and management of COVID-19 vaccination related complications are provided by the ISTH (International Society of Thrombosis and Hemostasis). Clinicians and laboratories should perform initial testing to access the possibility of VITT. Unfortunately, in North Macedonia, a PF4-ELISA assay is not available. It is important to mention that current recommendations provided in this article are made based on expert consensus on limited data. An update will be needed once more data is available (12).

CONCLUSION

So far in our clinical practice, the incidence of COVID-19 related vascular events that have led to hospital admission and death is much higher compared to the same thrombotic compli-

cations induced by COVID-19 vaccines. Finally, the apparent risk of VITT with a COVID-19 vaccine is greatly outweighed by the risk of complications from COVID-19 infection, including hospitalization, thrombosis and death.

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Резиме

ТРОМБОТИЧНА ТРОМБОЦИТОПЕНИЈА ИНДУЦИРАНА СО ВАКЦИНА И ВАКЦИНИТЕ ЗА КОВИД-19: СЕРИЈА СЛУЧАИ

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Тромбоцитната тромбоцитопенија индуцирана со вакцина (ВИТТ) е состојба слична на тромбоцитопенијата индуцирана од хепарин (ХИТ), но е поврзана со претходна администрација на вакцини против КОВИД-19 без претходна изложеност на хепарин. Инциденцата на ВИТТ не е сигурна, но се чини дека е исклучително ретка. Извештаите за невообичаени и тешки тромботични настани, вклучувајќи церебрална и спланхнична венска тромбоза и други автоимуни несакани реакции, како што се имунолошката тромбоцитопенија или тромботичните микроангиопатии во врска со некои од вакцините САРС-КоВ-2, предизвикаа голема загриженост кај населението и кај медицинската заедница. Во овој труд ви презентираме четири клинички случаи на ВИТТ, хоспитализирани и лекувани во единицата за интензивна коронарна нега на Универзитетската клиника за кардиологија во Скопје.

Клучни зборови: тромбоцитна тромбоцитопенија индуцирана со вакцина, вакцини против КОВИД-19