Um Caso Raro de Trombocitopenia Trombótica Induzida pela Vacina Após uma Vacina de mRNA COVID

A Rare Case of Vaccine-Induced Immune Thrombotic Thrombocytopenia After mRNA COVID Vaccine

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Resumo:

A trombocitopenia trombótica imune induzida pela vacina (VITT) é uma complicação primariamente associada às vacinas COVID-19 de vetor adenovírus. Dados emergentes são consistentes com a possibilidade desta entidade ser observada no contexto de vacinas de mRNA.

Apresentamos o caso de um homem de 62 anos, internado devido a múltiplos eventos trombóticos arteriais e venosos com trombocitopenia grave, coagulopatia e D-dímeros elevados, dias após a administração de uma vacina de mRNA contra a COVID-19. Após exclusão de outras etiologias e na presença de anticorpos anti-PF4, considerou-se o diagnóstico de VITT. O doente melhorou após o tratamento com imunoglobulina intravenosa, metilprednisolona e argatroban, seguido de prednisolona oral e apixabano. Apesar da anticoagulação, houve progressão do processo trombótico e a terapêutica anticoagulante foi alterada para heparina não fraccionada e posteriormente para varfarina.

Apesar das *guidelines*, o conhecimento crescente da patogénese da VITT sugere que a heparina não agrava o curso da doença.

Palavras-chave: COVID-19; Púrpura Trombocitopénica Idiopática/induzida quimicamente; SARS-CoV-2; Trombocitopenia/induzida quimicamente; Vacinas contra a COVID-19/efeitos adversos; Vacinas de mRNA.

Abstract:

Vaccine-induced immune thrombotic thrombocytopenia (VITT) is primarily a complication of adenoviral vector-based COVID-19 vaccination. Emerging data are consistent with the possibility that rare cases of VITT may be seen in the setting of an mRNA vaccine.

We present a case of a 62-year-old man, admitted due to multiple arterial and venous thrombotic events with severe thrombocytopenia, coagulopathy and elevated D-dimer, some days after administration of mRNA COVID-19 vaccine. After the exclusion of other etiologies and in the presence of detectable antibodies against anti-PF4 (ELISA only), the diagnosis of VITT was made. The patient improved after starting treatment with intravenous immunoglobulin, methylprednisolone, and argatroban, followed by oral prednisolone and apixaban. Despite anticoagulation a progression of a deep vein thrombosis happened, and anticoagulation therapy was changed to unfractionated heparin and then to warfarin.

Despite the guidelines, increasing knowledge of VITT pathogenesis suggests that heparin does not worsen the course of the disease.

Keywords: COVID-19; COVID-19 Vaccines/adverse effects; mRNA Vaccines; SARS-CoV-2; Purpura, Thrombocytopenic, Idiopathic/chemically induced; Thrombocytopenia/ chemically induced.

Introduction

In response to the COVID-19 pandemic, there has been an effort to develop novel vaccines that minimize SARS-CoV-2 morbidity and mortality.[1] Two vaccine types were developed: viral vectors and messenger RNA (mRNA). To date, in Europe, four vaccines have been authorized: two mRNA vaccines: Comirnaty (Pfizer/Biontech) and mRNA-1273 (Moderna); two adenoviral vector vaccines: COVID-19 vaccine Janssen (Johnson and Johnson's), and Vaxzveria (AstraZeneca).

These vaccines are generally safe and effective, with the most common side effect being local pain. Attention to hematologic complications has largely focused on rare but severe cases of vaccine-induced immune thrombotic thrombocytopenia (VITT).[2]

VITT is a rare but life-threatening disorder first recognized as a complication of adenoviral vector-based COVID-19 vaccination. More recently, cases of mRNA vaccines associated with VITT have been documented. This condition is characterized by arterial and venous thrombosis, and thrombocytopenia mediated by anti-platelet factor 4 (PF4) antibodies. The pathophysiology of VITT is not yet fully understood but it seems to be similar to that of heparin-induced thrombocytopenia. The most frequently reported sites

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of thrombosis are the cerebral venous sinus, splanchnic vein, pulmonary embolism, deep vein of the legs, ischemic stroke, acute limb ischemia, and myocardial infarction.[1,3] VITT is diagnosed when the following five criteria are met: COVID-19 vaccination 5 to 30 days before symptom onset; venous or arterial thrombosis usually in atypical locations; thrombocytopenia (platelet counts <150 000/L), positive anti-PF4 (ELISA only), and elevated D-dimer (>4000 µg/L).[4] Intravenous immunoglobulin (IVIg) and non-heparin-based anticoagulation remain the mainstay of treatment, in many cases, along with steroids. The first publication advised to not use heparin, nevertheless, further studies are needed.[1] The anticoagulation should be continued for at least 3 months and until anti-PF4 antibodies (ELISA only) are no longer detected.[5]

Herein, we describe a rare case of VITT associated with the Moderna vaccine, an mRNA vaccine.

Case Report

A 62-year-old Caucasian man, with arterial hypertension, dyslipidemia and past smoking history of 26 pack-year, was admitted due to multiple arterial and venous thrombotic events with severe thrombocytopenia and coagulopathy.

On January 2nd, 2022, the patient developed a mild COVID-19 infection and three days later, he received the vaccine against SARS-CoV-2 (Moderna). After 10 days, the patient went to the emergency room twice, with upper abdominal pain. Initially, blood tests showed mild thrombocytopenia (101 000/L). An abdominal computed tomography (CT) scan was performed and showed bilateral adrenal hematomas. The patient refused hospitalization but returned due to pain in the right lower limb, along with edema, pallor and coldness.

Objectively he was conscious, hypotensive and tachycardic (blood pressure: 91/68 mmHg, pulse rate: 106 bpm), without signs of respiratory distress, and cardiopulmonary auscultation was unchanged. He presented abdominal pain on palpation, without peritoneal irritation. Petechiae, ecchymoses and nail hemorrhage were noted. His right lower limb was cold, pale and swollen, with numbness in the forefoot and fingers with distal pulses absence.

The analytical study showed severe thrombocytopenia (15 000/L), coagulopathy (activated partial thromboplastin time (aPTT) 52.4"; prothrombin time (PT) 16.7"; fibrinogen 102 mg/dL) and increased D-dimers (199.7 µg/mL), acute kidney injury at KDIGO stage 3 (creatinine 2.29 mg/dL, urea 98 mg/dL) and an elevated C-reactive protein (144 mg/L). Furthermore, he had cytocholestasis (aspartate aminotransferase 80 U/L, alanine aminotransferase 37 U/L, gamma-glutamyl transferase 112 U/L, alkaline phosphatase 167 U/L) and hyperbilirubinemia (total bilirubin 1.59 mg/dL and direct bilirubin 0.51 mg/dL), high troponin (896 ng/L) and muscle enzymes (creatine kinase 969 U/L and myoglobin 1118 ng/mL) with normal B--Type natriuretic peptide.

Electrocardiogram showed sinus tachycardia (105 bpm) and thoraco-abdominopelvic CT scan revealed bilateral pulmonary thromboembolism, multiples hypodense atheromatous plaques distributed along the aorta, little ischemic lesion in the upper right rim and spleen, and hematomas in both adrenal glands; evidence of left popliteal and femoral venous thrombosis; in the right lower limb, in the arterial phase, the absence of opacification of the arterial territory distally to the beginning of the popliteal artery and, in the venous phase, a filling defect extending from the superficial femoral artery to the popliteal artery could be observed.

The patient was admitted to the intensive care unit and an extensive etiological investigation was conducted. No changes in blood count, other than thrombocytopenia were documented, peripheral blood smear and haptoglobin were normal, as well as protein electrophoresis. Coombs test was negative, without antithrombin III deficiency and normal protein C and erythrocyte sedimentation rate, thyroid function and urine analysis were normal. Antinuclear antibody was borderline (1:100, speckled pattern) with positive anti-PF4 antibodies (ELISA only). Lupus anticoagulant (LA) and IgG anticardiolipin antibody (ACL) were initially positive but proved negative after the acute phase of the disease. The serology for human immunodeficiency virus, hepatitis B and C were all negative, as well as blood and urine cultures. Polymerase chain reaction for SARS-CoV-2 was negative but antibody IgG anti-SARS-CoV-2 was positive, which is suggestive of a recent infection. The patient performed echocardiography with preserved biventricular function and no images suggestive of intracavitary masses.

The temporal relationship between symptoms onset and vaccination, along with anti-PF4 positive antibodies, favored the diagnosis of VITT. However, at this point, a catastrophic antiphospholipid syndrome could not be completely excluded. Therapy was started with IVIg (400 mg/kg/day) for five days, combined with intravenous methylprednisolone (1 g/day) for three days, followed by oral prednisolone, 1 mg/kg/day, with progressive tapering. He started anticoagulation with argatroban (1 µg/kg/minute, titrating to aPTT target 70"). After three weeks, the patient underwent a transtibial amputation, due to irreversible ischemia of the right lower limb.

In addition, the patient displayed persistent hyponatremia and hyperkalemia, associated with a normal-low blood pressure profile. Based on observations and findings of hematomas in adrenal glands, a diagnosis of adrenal insufficiency was suspected. Mineralocorticoid supplementation with fludrocortisone 0.1 mg daily was started, after measuring renin and aldosterone. The patient showed clinical and biochemical improvement, and the available results later confirmed the diagnosis.

After the beginning of therapy, there was a gradual improvement in platelet count and coagulation parameters, including D-dimers. He was discharged from the hospital, after a switch from argatroban to apixaban, keeping a close watch on the internal medicine consultation.

After two weeks, the patient was readmitted due to bilateral thrombosis of the femoral vein that had extended to the inferior vena cava at the infrarenal level, despite anticoagulation with apixaban at therapeutic levels. No other clinical or analytical changes were seen, namely thrombocytopenia, or an increase in D-dimers. The anticoagulation therapy was changed, initially to unfractionated heparin with tight analytical control, and later to warfarin.

During the first year after diagnosis, the patient maintained anticoagulation with warfarin without recurrence of thrombosis or bleeding events. Platelet count and D-dimers are normal, and LA and ACL were consistently negative. Anti-PF4 antibodies (ELISA only) remained positive, determining our decision to extend the anticoagulation duration.

Discussion

VITT was first reported in February 2021, and is strongly associated with adenovirus-based vaccines. The condition is thought to be a class effect, but recent reports of its rare occurrence after the mRNA vaccine have emerged.[6]

The diagnosis of VITT is not obvious and the differential diagnosis is crucial which includes essentially: COVID-19-associated coagulopathy, antiphospholipid syndrome (APS), thrombotic thrombocytopenic purpura (TTP), heparin-Induced thrombocytopenia (HIT) and immune thrombocytopenic purpura (ITP).[7]

In our case, HIT and ITP are unlikely due to the absence of previous heparin exposure, and the presence of thrombotic events, respectively. The absence of schistocytes or microangiopathic hemolytic anemia on blood smear, excluded the possibility of TTP. Although initially LA and ACL revealed positive, some weeks later they proved negative, excluding APS.

In severe COVID-19, thrombosis and thrombocytopenia are present, but fibrinogen levels are usually elevated, or normal, severe thrombocytopenia is uncommon, and the PT is typically normal. In our case, the patient had a COVID-19 infection before vaccination, it was a mild infection and the typical analytical findings were not present, which makes this hypothesis unlikely.

After exclusion of other etiologies, the occurrence of both severe thrombocytopenia and thrombosis in the presence of detectable antibodies against anti-PF4 (ELISA only), as well as marked elevation of D-dimer occurring within 10 days of vaccination, fulfills all five diagnostic criteria for VITT.

The American Society of Hematology suggests for treatment of VITT, immunoglobulin, anticoagulation with non-heparin drugs, and corticosteroids if necessary.[5] Our patient improved after treatment with IVIg, intravenous methylprednisolone and argatroban, followed by oral prednisolone and apixaban.

However, some weeks later the patient presented with a progression of previous thrombosis, despite anticoagulation with apixaban. Despite the risk of worsening the thrombosis scenario, anticoagulation therapy was changed to unfractionated heparin with close monitoring and then to warfarin, without complications.

Despite the guidelines, it has not been conclusively confirmed that heparin exacerbates VITT.6 Some studies seem to show that heparin is a reasonable choice in VITT.[8,9] Our case is one of those examples, although more studies and case reports are needed.

The incidence of mRNA vaccine-associated VITT is extremely infrequent. Herein, we present a rare case of VITT in a patient after mRNA-1273 vaccine. This report highlights the need for understanding the mechanism of VITT, its treatment and closely monitoring signs and symptoms of patients after vaccination. ■

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FC, EF, IHR, FC, MC – Elaboração, revisão e finalização do artigo. Todos os autores aprovaram a versão final a ser publicada.

Contributorship Statement

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