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CASE REPORT

Semi-selective plasma filtration applied to the treatment of acquired thrombotic thrombocytopenic purpura following *bnt162b2* administration

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Abstract
Following the widespread use of anti SARS-CoV-2 vaccines, there have been reports of thrombocytopenia developing after the administration of different types of vaccine. We report a case of a 63-year-old male who developed neurological symptoms after receiving the second dose of the bnt162b2 vaccine. Blood tests performed upon admission to the Emergency Department revealed severe thrombocytopenia and microangiopathic hemolytic anemia. ADAMTS13 activity was undetectable and antibody titer was high. Due to the rapid neurological deterioration, steroid therapy with prednisone was started at an initial dose of 1 mg/kg/day. Rituximab therapy was started to prevent the formation of new antibodies. Given the slow response to this therapy, we added Caplacizumab, (a monoclonal antibody anti-Von Willebrand factor) in order to inhibit platelet hyperaggregation, combined with standard plasma exchange. The patient experienced repeated episodes of intolerance to fresh frozen plasma (FFP). Switching from plasma exchange to plasma filtration, remission was attained in this unusual case of vaccine-related thrombocytopenia with microangiopathic hemolytic anemia.

Keywords Caplacizumab · Anti SARS-CoV-2-vaccination · Microangiopathic hemolytic anemia · Plasma filtration

Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease characterized by microangiopathic hemolytic anemia, thrombocytopenia and thrombosis with consequent ischemic organ damage [1, 2]. The hallmark of TTP is the deficient activity of ADAMTS13 (*disintegrin and metalloprotease with thrombospondin-1-like domains*), a von Willebrand factor (vWF)-cleaving protease. TTP is classified into two types: congenital, characterized by the mutation of a gene that codes for ADATMS13, and acquired thrombotic thrombocytopenic purpura (aTTP), sustained by the presence of autoantibodies against the ADAMTS13 protease [3].

A small number of patients with thrombocytopenia following the administration of the various types of COVID vaccines has recently been reported in the literature. This occurrence shares similarities with previously described cases following other types of vaccinations, for example the pneumococcal vaccine [4].

Case presentation

In April 2021, a 63-year-old male presented to the Emergency Department with dyspnea and mental confusion. The previous day he had experienced an episode of buccal deviation that spontaneously resolved. His past medical history was unremarkable. He had completed the SARS-CoV-2 vaccination schedule with *bnt162b2* in the previous weeks. Blood tests revealed severe anemia (6.8 g/dl) and thrombocytopenia (51,000/mm3) associated with increased LDH (852 IU/l), reduced haptoglobin (< 20 mg/dl), hyperbilirubinemia (3.58 mg/dl) and high D-dimer (4.77 mcg/ml). ADAMTS13 activity was 0% with high antibody titer

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(122 IU/ml), confirming the diagnostic suspicion of thrombotic thrombocytopenic purpura. Despite starting fresh plasma infusion, the patient developed neurological symptoms (dysarthria and paresthesia in the right upper limb), which spontaneously regressed: brain CT scan was negative for acute lesions. Further investigation included epiaortic ultrasound, which excluded hemodynamically significant stenosis, and chest computerized tomography (CT) scan, which resulted negative for neoplastic lesions. In the following days the patient presented sudden worsening of neurological conditions, requiring orotracheal intubation and hospitalization in the Intensive Care Unit. Plasma exchange was not immediately performed because the patient had been previously referred to the Emergency Department of a spoke Hospital where the procedure was not available. The patient was then referred to our tertiary hospital and due to the worsening of his general conditions, a cycle of daily plasma exchange (PE) was started (Fig. 1). The role of the COVID vaccination in the development of our case of iPTT raised doubts regarding the nature of the disorder.

Given the onset of fever during the fourth session of PE, infectious disease screening was repeated and resulted negative. Therefore, a hypersensitivity reaction was hypothesized. We then cautiously opted for semi-selective plasma filtration (PF), aimed at removing antibodies, combined with 600 ml infusions of fresh plasma, aimed at replacing ADAMTS13, which was administered very slowly in order to anticipate possible infusion reactions. We used the Evaflux 3A plasma fractionator filter, which removes substances with a molecular weight cut-off of approximately 67 KDa, thus eliminating autoantibodies. We performed PF twice a week for a total of nine procedures, processing 1.5 to 2 times the estimated plasma volume. To ensure the replacement of functional ADAMTS13, fresh frozen plasma (FFP) was infused at low flow after each apheresis session. The method used to sterilize FFP is based on the "solvent/detergent method" that targets nucleic acids (DNA, RNA). Almost all pathogens require nucleic acids in order to reproduce and to cause clinically significant infection. As a result, it is able to inactivate viruses, bacteria, and parasites that use nucleic acids to replicate.

At the same time, oral glucocorticoid therapy was started: the initial dose was 1 mg/kg/day (75 mg/day in our patient), with progressive tapering. Due to the persistence of extremely low platelet counts and disabling neurological symptoms, therapy with Caplacizumab, a humanized monoclonal antibody anti-von Willebrand factor, was started. This therapy aims to block platelet aggregation and reduce organ injury caused by ischemia.

Platelet count normalized within a few days: considering the excellent response observed in the first 10 days of therapy, we decided to discontinue administration of Caplacizumab and to carefully monitor blood tests. Two days after drug discontinuation, platelet, hemoglobin and haptoglobin

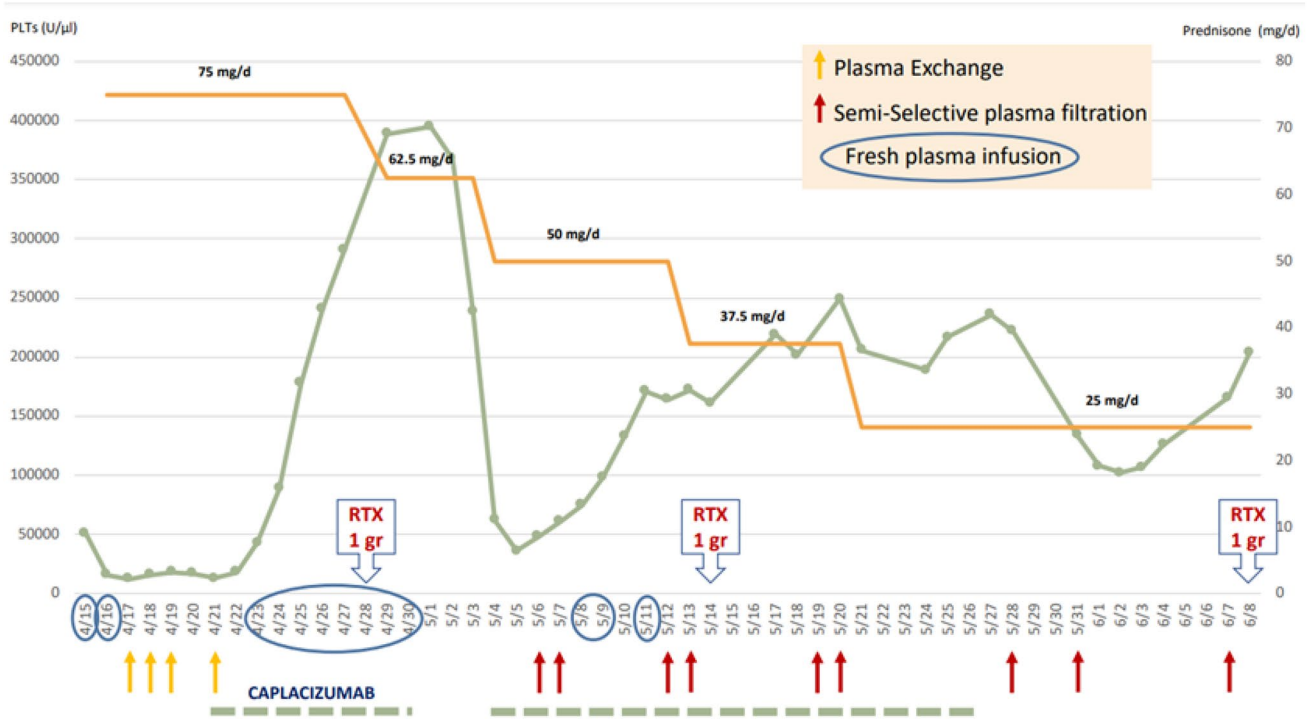

Fig. 1 Platelet trend and treatments performed. *RTX* rituximab

values again decreased, together with an increase in LDH. Hence, we resumed Caplacizumab administration which was continued for 33 days. At the same time, two doses of Rituximab 1 g were given 2 weeks apart. A third dose of Rituximab was administered at week 6 to replace the portion removed by PF. A total of 13 PF sessions were performed in order to obtain a negative antibody titer and normalization of ADAMTS13 values.

Approximately two months after admission to the hospital, the patient's conditions significantly improved and it was possible to discharge him.

Discussion

We present the case of a 63-year-old male patient with no past medical history who developed aTTP three weeks after the second dose of *bnt162b2* administration.

To the best of our knowledge, the number of reported cases of de novo TTP following mRNA Pfizer COVID-19 vaccination remains limited [5]. The clinical presentation, characterized by the presence of microangiopathic hemolytic anemia and thrombocytopenia was highly suggestive of aTTP. Diagnostic investigations did not point to other possible secondary causes.

In the differential diagnosis of post-vaccination forms of thrombocytopenia reported in the literature, three pathogenic entities have been highlighted: vaccine-induced immune thrombotic thrombocytopenia (VITT), immune thrombocytopenic purpura (ITP) and aTTP.

VITT is characterized by the presence of anti-platelet antibodies (PF4), as is observed in cases of heparin-induced thrombocytopenia (HIT) [6, 7]. Autoantibodies against several platelet surface glycoproteins, especially GpIIb/IIIa [8] may be found in ITP, while, aTTP is characterized by the presence of autoantibodies directed against the ADAMTS13 protease. Our patient belongs to this latter category: other cases with similar presentation have recently been reported in the literature. [3, 9].

According to the most recent guidelines, treatment is based on the association of various therapeutic approaches. The main goals are to reduce inflammation, block platelet aggregation, replace ADAMTS13 and stop the formation of new ADAMTS13. With these targets in mind, therapeutic strategies include the use of steroids and plasmapheresis [10], associated with the administration of Rituximab and Caplacizumab [11].

Recently, Caplacizumab, an anti-vWF humanized immunoglobulin that acts by blocking platelet aggregation to reduce organ injury caused by ischemia, has been approved for use in the European Union for the "treatment of adults experiencing an episode of aTTP, in conjunction with plasma exchange and immunosuppression" [12]. The most recent International Society on Thrombosis and Haemostasis (ISTH) guidelines suggest the use of Caplacizumab both in the first episode and in relapses of iTTP [11]. However, this is a conditional recommendation in the context of moderate certainty of evidence. This recommendation is based on the results of two RCTs, which showed a significant reduction in the number of exacerbations in the Caplacizumab group [13, 14].

The aim of therapeutic apheresis is to remove circulating autoantibodies while ensuring supplementation of the deficient ADAMTS13 factor. The administration of Rituximab, which leads to a depletion of CD20 B-cells, aims to inhibit the formation of new autoantibodies. Lastly, the rationale for the use of Caplacizumab is to replace the functionality of the deficient Von Willebrand factor and inhibit platelet hyperaggregation.

Conventional plasmapheresis could not be used in this patient due to intolerance to plasma infusion. Using a semi-selective technique combined with drug therapy aimed at blocking antibody production and platelet aggregation made it possible to circumvent the obstacle and was associated with a favorable putcome.

Two months after the start of therapy, the patient attained a complete clinical and laboratory remission, allowing progressive tapering and finally discontinuation of treatment.

To our knowledge, this is one of the few reported cases of aTTP secondary to vaccination against SARS-CoV-19 [15, 16], and the first one successfully treated with Rituximab and Caplacizumab in combination with semi-selective apheresis.

The timing of onset supports the role of the vaccine in pathogenesis. Data available in the literature are increasing, but further studies are needed to clarify the mechanisms of post-vaccine thrombotic microangiopathy.

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Declarations

Conflict of interest None.

Ethical statement The study has been conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

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