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A Case of VAXZEVRYA Vaccine-Associated Thrombotic Thrombocytopenia Syndrome: Chess Match between Pathophysiology and Therapy

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Abstract

Background: Cerebral Venous Sinus Thrombosis (CVST) and Extracranial Thrombosis (ECT) with thrombocytopenia have been described in Europe following receipt of the VAXZEVRYA (Oxford/AstraZeneca) vaccination.

Objectives: To describe a case of VAXZEVRYA Vaccine-associated Thrombotic Thrombocytopenia syndrome (VITT), to analyze the mechanisms that determines this syndrome and the possible therapeutic strategies.

Patients: We report a case of a 75-year-old Caucasian woman, admitted to Fano, internal medicine unit hospital, who developed CVST and portal vein thrombosis, associated with thrombocytopenia following VAXZEVRYA vaccination. We demonstrated the presence of autoantibodies anti-platelet factor 4 (anti-PF4), with a weak functional ability of activate platelets. She received non-heparin anticoagulation treatment, intravenous immunoglobulins at high dosage, dexamethasone and fresh frozen plasma.

Results and Conclusion: This case report surely contains the greatest difficulties that a clinic may ever encounter in the management of anticoagulant therapy with severe thrombocytopenia and hemorrhaging complications. More data on the pathogenesis of VITT are needed to optimize the treatment of this rare but often clinically severe thrombotic syndrome associated with VAXZEVRYA vaccination.

Case Description

This case report concerns a 75-year-old woman who underwent VAXZEVRYA vaccination: Seven days after the vaccination developed fever and after a further three days reported the onset of purpura in the lower limbs, so she referred to our hospital.

In her medical history arterial hypertension on treatment was present and a recently diagnosed polymyalgia rheumatica treated with a course of steroid therapy. No family history of bleeding or thrombotic disorders was reported.

Blood tests were performed demonstrating severe thrombocytopenia with a nadir value of

23.000 × 10^3/μL, confirmed at the platelet count in sodium citrate-anticoagulated whole blood; no other blood count abnormalities were identified. Coagulation tests revealed INR prolongation (1.3); elevated D-dimer (maximum value of 53800 ng/ml), fibrinogen consumption (lowest value: 99 mg/d) and slight reduction of Anti-thrombin III to 75%. Serial nasopharyngeal swabs for SARS-CoV-2 resulted negative.

A total body tomography with iodine-based contrast revealed: 1) at abdominal level, a portal thrombosis in the abdomen; 2) in the brain, opacification defects in correspondence of the transverse and sigmoid sinus left as from thrombosis, in addition to thin hematoma subdural along the left tentorium. No pulmonary embolism was found. Doppler ultrasound of the lower limbs and neck vessels did not reveal the presence of venous thrombosis in the explored areas.

The patient was treated with intravenous immunoglobulins at high dosage (1 g/kg for two consecutive days), Dexamethasone 12 mg/die, fresh frozen plasma at the dosage of 10 ml/kg and Fondaparinux 2.5 mg/die, posology subsequently increased to 7.5 mg/die, anticoagulant dosage, when the platelet count rose >50,000/mmc.

Several analyzes were performed to investigate the thrombotic thrombocytopenia: no presence of schistocytes on peripheral blood smear was found, no deficiency of plasma ADAMTS13 activity or detectable autoantibodies against ADAMTS13, no lupus anticoagulant antibodies, Anticardiolipin antibodies, anti-beta 2-GPI, Complement determinations (C3 and C4 levels) were found to be within the normal limits, AntiNuclear Antibody (ANA) and Extractable Nuclear Antigen Antibodies (ENA) resulted negatives and serological markers of hepatitis B and C, Cytomegalovirus and Epstein-Barr virus did not show the presence of an active viral infection. Blood tests for anti-PF4 antibodies with Enzyme-Linked Immunosorbent Assay (ELISA) resulted weakly positive.

To confirm the diagnosis, samples for Platelet Factor 4 (PF4) antibody testing were sent to the core laboratory of hemostasis and thrombosis of Azienda Ospedaliero-Universitaria Careggi, Florence. The analysis was performed with two different techniques: Enzyme-Linked Immunosorbent Assay (ELISA) tested positive for anti-PF4/hep IgG with 3128 Optical Density (OD) readings (n.v. OD > 0.400); on the other hand, chemiluminescence immunoassay for anti-PF4/hep IgG gave negative results (0.06 U/ml with n.v. <1 U/ml). At the first evaluation in a functional assay, the antibodies showed a platelet-activating ability, after addition of PF4 addition, only in 1/5 donors: The concomitant treatment with high-dose IVIG may explain this result, considering the capability of IVIG to compete with anti PF4 Ab and reduce the platelet activation effect. A subsequent control, after one week, confirmed both results.

Despite the progressive normalization of coagulation tests and the increase in the platelets count, on the tenth day of hospitalization, the patient developed right lateral hemianopsia and aphasia with right facio-brachial weakness. Magnetic resonance angiography confirmed the thrombosis of the transverse sinus and the left sigmoid sinus with contextual subdural hematoma and showed left temporo-parieto-occipital subcortical and cortical bleeding, bilateral hemoventricle, edema and compression on the left ventricle and midline shift of 7 mm (Figure 1). For subsequent worsening of the Cognitive Status (GCS 5) and temporoparietal hemorrhage on CT imaging (Figure 2), she was transferred to neurosurgical ward where she underwent evacuation of the hematoma and decompressive craniotomy (Figure 3). The patient continued dexamethasone therapy at the dose 16 mg daily and fondaparinux at 2.5 mg/day with stable level of platelets around 100.000/mmc and resolution of portal thrombosis at Doppler ultrasound. Unfortunately, after two weeks the patient developed right acute subdural hematoma that was evacuated, but the prognosis remained severe.

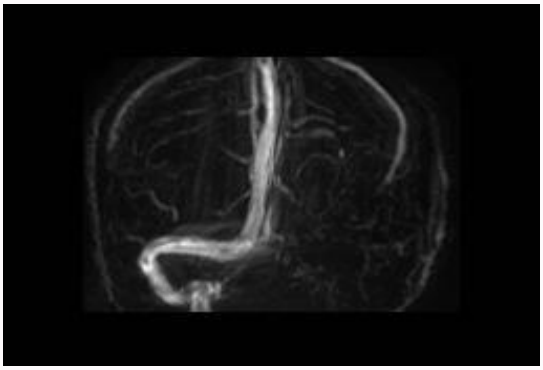

Figure 1: Selected coronal from a MR phase contrast venography confirms extensive venous thrombosis of straight sinus and left transverse sinus, showing the absence of normal signal intensity in sinus.

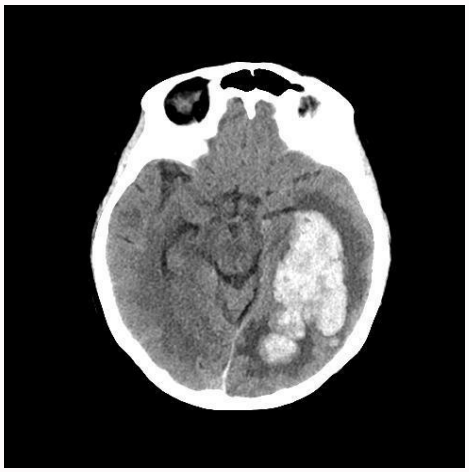

Figure 2: Axial CT scan 4 days later demonstrates brain herniation due to dimensional increase of the left parieto-occipital hematoma, with effacement of the basal cisterns and transtentorial herniation that required emergency evacuation.

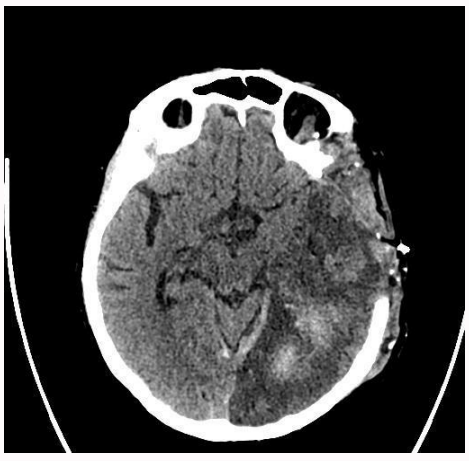

Figure 3: CT scan after evacuation, showing dimensional reduction of hematoma and of the mass effect.

Discussion

The VITT syndrome is a very rare but potential life-threading condition with a mortality rate more than 30% [1].

Greifswald and coll recently proposed a pathogenic mechanism for this syndrome, resembling Heparin-Induced Thrombocytopenia (HIT) [2]. Accordingly, they also renamed this syndrome as "Vaccine-induced Immune Thrombotic Thrombocytopenia (VITT) [3]. The pro-thrombotic thrombocytopenic disorder appears to be provoked by IgG auto-antibodies directed against the molecular complex heparin/PF4. This complex activates platelets through the receptor J receptor IIA (FCγRIIA) [4-6]. Time gap between vaccine administration and symptoms onset is 5 to 16 days after the inoculum, similar to that described for HIT [7]. Interestingly, this adverse reaction develops in patients not exposed to heparin, neither before nor after dose administration [8,9].

How vaccines specifically trigger VITT, remain speculative and require further research. It has been proposed that vaccine-induced cytokine stimulation could enhance autoantibodies production. Spike protein or free DNA contained in the preparations could play a pivotal role [2,10]. The vector in Astrazeneca vaccine is the adenovirus which may be involved in interactions between the platelets/PF4 and vaccine [11,12]. Moreover, it is noteworthy that many critical aspects still need clarification. In particular the atypical localization of thrombotic events, preferably in cerebral sinuses and splanchnic veins, opposed to leg veins, awaits a clear explanation. These venous territories drain the microbial rich area of nose and intestine, enabling admission of viral products and toxins to the endothelial networks [12].

As the autoimmune complexes actives platelets through FCγRIIA, doses of intravenous immunoglobulins have been recommended together with non-heparin anticoagulants (i.e., fondaparinux) according to the level of platelets [13-15]. Steroid may also be helpful, although the best dosage is controversial. Plasma exchange could be considered in IVIG refractory patients with severe disease characterized by extensive thrombosis and platelet ≤ 3 0.000/mmc [13].

This case report surely contains the greatest difficulties that a clinic may ever encounter in management of anticoagulant therapy since we have had to face a new disease, a disease which we don't completely understand in terms of pathogenetic mechanism. Moreover, we have also had to anticoagulate the patients even with severe thrombocytopenia and possible hemorrhaging complications, which did actually occur.

Therefore, on one hand, platelet hyperactivation and the immune mechanism that causes thrombocytopenia have to be "switched off" while on the other hand we must treat the thrombosis in order to break the vicious circle that causes cerebral venous hypertension and bleeding.

We have played a chess match with high dosage of gamma globulins, reasonably low doses of steroids and non-heparin anticoagulants based on the level of platelets.

Acknowledgment

Giancarlo Titolo recognized and reported the adverse vaccine reaction in the emergency department. Giulia Rossetti, Vanessa Nunziata, Pietro Sodani, Samuele Bedetta and Anna Maria Di Carlo managed the patient according to the most recent available evidence. Rossella Marcucci performed the laboratory analyzes. Michele Tempesta, Alberto Rebonato, Elena Marini, Giuseppe Visani and Martina Chiarucci managed the cerebral hemorrhage following thrombosis. Filippo Saltamartini, Maria Capalbo and Gabriele Frausini coordinated patient and laboratory data management between the different hospitals.

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